

ORIGINAL ARTICLE

Design and rationale of the Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects with Psoriatic Arthritis (SEAM-PsA)

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ABSTRACT

Objective To evaluate the efficacy of etanercept and methotrexate as monotherapies and as combination therapy in subjects with active psoriatic arthritis (PsA).

Methods The Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects with Psoriatic Arthritis (SEAM-PsA) is an ongoing, global, double-blind, 48-week, randomised, controlled study. Subjects are randomised (1:1:1) to etanercept monotherapy, methotrexate monotherapy or etanercept-methotrexate combination therapy. Endpoints include rates of ACR20 response and Minimal Disease Activity, measures to characterise extra-articular manifestations (dactylitis, enthesitis, nail disease) and safety.

Conclusion SEAM-PsA will characterise the effects of etanercept with and without background methotrexate and methotrexate alone on PsA manifestations, and provide information of practical importance to clinicians on the optimal treatment of PsA.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease of the peripheral joints and axial skeleton with an estimated prevalence of 0.06%–0.25% in the US general population, and of 6%–41% in patients with psoriasis.¹ The clinical features of PsA are heterogeneous and include peripheral arthritis, axial disease, dactylitis, enthesitis, and skin and nail disease.² Despite long-term availability of tumour necrosis factor inhibitors (TNFi) for treatment of PsA, their optimal use as monotherapy or combination therapy with methotrexate has not been established. Additionally, most patients with PsA who have participated in clinical trials have established disease, and an understanding of how effective treatment early in the disease course may impact long-term outcomes is lacking.

Key messages

What is already known about this subject?

- Based on practices in treating patients with rheumatoid arthritis, combination therapy with the tumour necrosis factor inhibitor etanercept and methotrexate is common in patients with psoriatic arthritis (PsA), even though methotrexate is not approved for the treatment of PsA.

What does this study add?

- The Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects with Psoriatic Arthritis (SEAM-PsA) aims to examine the efficacy of etanercept or methotrexate as monotherapy and in combination in patients with PsA.

How might this impact on clinical practice?

- The results of SEAM-PsA are expected to inform clinicians about the comparative efficacy of these therapies and provide guidance on the optimal treatment of PsA.

In general, PsA is treated initially with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD), followed most commonly by the use of biological DMARDs (bDMARDs), including TNFi and interleukin (IL)-12/23 or IL-17 blockers. Methotrexate is the most common first-line csDMARD for PsA and is included in all treatment guidelines for PsA; however, methotrexate is not an approved drug for the treatment of PsA in the USA and in many other countries, nor is there substantive evidence for its efficacy in randomised clinical trials.^{3,4} Furthermore, physicians and patients have concerns about the use of methotrexate because of side effects and required lifestyle modifications. As a result, patients with PsA may

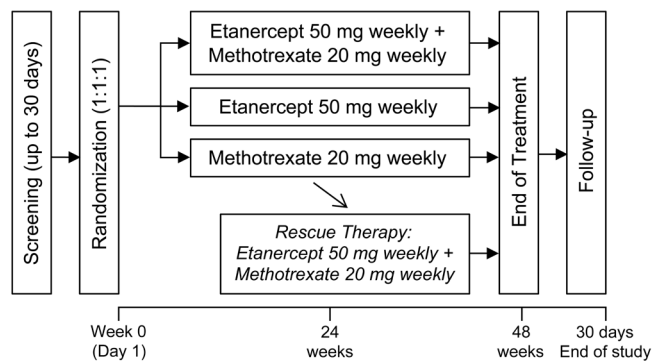


Figure 1 Study schema.

prefer bDMARD monotherapy rather than methotrexate monotherapy or combination therapy with bDMARDs.

In the Methotrexate in Psoriatic Arthritis (MIPA) study, methotrexate-naïve subjects received methotrexate (15 mg/week) or placebo for 6 months.³ In an intent-to-treat analysis, no statistically significant improvements in disease activity measures at 24 weeks were observed except for the Psoriatic Arthritis Response Criteria, although the rate of 20% improvement in American College of Rheumatology criteria (ACR20 response) was numerically higher for methotrexate than placebo and there was a suggestion of efficacy in a subgroup of subjects with poly-articular disease. A key limitation of the study was that a submaximal dose (15 mg) was used. In contrast, TNFi have been shown to be effective agents in PsA, improving joint symptoms and inhibiting the progression of structural damage.⁵ They also improve cutaneous and other extra-articular manifestations of PsA.⁵ In TNFi clinical trials, the presence or absence of methotrexate background therapy did not appear to affect outcomes, but most patients previously had an inadequate response to methotrexate, so these results did not truly address the utility of methotrexate background therapy.⁶

Registry studies have shown no consistent difference in response between patients who started a TNFi with or without methotrexate,^{7,8} but differences in survival (ie, the rate that a cohort discontinued use of an agent) appeared when analysing specific agents, suggesting longer survival when etanercept was used as monotherapy compared with infliximab. One contribution to this difference may be differences in immunogenicity with different agents.⁹ These results suggested that the combination therapy used in rheumatoid arthritis (RA) to provide superior efficacy to methotrexate or etanercept monotherapy may not have a similar impact on efficacy in PsA.¹⁰ Therefore, a gap exists in our understanding of the true effect of methotrexate monotherapy in PsA and the additional benefit of combining methotrexate with TNFi on which to base sound recommendations to patients.

METHODS

The Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects with Psoriatic Arthritis (SEAM-PsA) aims to address these key questions.

SEAM-PsA (ClinicalTrials.gov number NCT02376790) is a global, double-blind, randomised, controlled study that is currently enrolling adult subjects with active PsA with both skin and joint symptoms who are bDMARD naïve and methotrexate naïve.

The study comprises a 48-week treatment period and 30-day follow-up period (figure 1). Subjects are randomised to one of three arms (n=280 subjects per arm): etanercept 50 mg weekly administered subcutaneously plus methotrexate 20 mg weekly administered orally; etanercept 50 mg weekly subcutaneously plus oral placebo; or oral methotrexate 20 mg weekly plus subcutaneous placebo. At or after week 24, subjects with inadequate response receive rescue therapy with etanercept plus methotrexate.

The primary endpoint is the ACR20 response at week 24 and the key secondary endpoint is the Minimal Disease Activity (MDA) response at week 24. Other secondary endpoints include measures to characterise extra-articular manifestations in nails (modified Nail Psoriasis Severity Index (NAPSI)), dactylitis (Leeds dactylitis score), enthesitis (Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis score), composite measures shared with RA (Disease Activity Score based on 28 joints, Simplified Disease Activity Index, Clinical Disease Activity Index) and those specific to PsA (Psoriatic Arthritis Disease Activity Score), and safety (table 1). For those with psoriasis with affected baseline body surface area (BSA) $\geq 3\%$, static physician global assessment and BSA will be assessed. Patient-reported measures of Health Assessment Questionnaire Disability Index and Short-Form 36 at week 24 are also secondary endpoints. Measures of radiographic progression are included as exploratory endpoints, including the change from baseline and non-progression in the van der Heijde modified Total Sharp Score (mTSS) at weeks 24 and 48.

The design and sample size of SEAM-PsA were informed by four key studies of methotrexate and/or etanercept for PsA (table 2). There are no published studies of etanercept monotherapy compared with methotrexate monotherapy for the treatment of PsA. Therefore, assumed response rates are derived from separate studies. In the pivotal trial of etanercept for the treatment of PsA, the proportions of subjects with ACR20 responses were 50% in the etanercept arm and 14% in the placebo arm at week 24.^{6,11} Assuming the etanercept response in a methotrexate-naïve population would be better, a 60% response rate for the etanercept monotherapy arm is assumed. The MIPA trial showed an ACR20 response of 34% with methotrexate, although the dose used was suboptimal.³ Efficacy of methotrexate monotherapy based on ACR20 responses at 6 months was estimated to be 44% for SEAM-PsA, to account for the higher dose of methotrexate (20 mg/week) employed in this trial. The ACR20 response rate at week 24 for etanercept plus methotrexate combination therapy is assumed to be 5% higher than that for etanercept monotherapy (ie,

Table 1 Outcome measures

Outcome measures	Definition/description
Primary outcome measure	
ACR20	20% improvement in American College of Rheumatology response criteria; composite measure based on tender and swollen joint counts, patient's assessment of pain, patient and physician global assessment of disease activity, patient's assessment of physical function and acute-phase reactant value
Secondary outcomes	
Composite measures of disease activity	
MDA	Minimal Disease Activity; composite measure based on tender and swollen joint counts, Psoriasis Area and Severity Index or psoriasis-affected BSA; patient pain, patient global activity, HAQ and tender enthesal points
PASDAS	Psoriatic Arthritis Disease Activity Score; composite measure based on patient and physician assessments of disease activity, peripheral joint counts, dactylitis, enthesitis, acute-phase reactant value and SF-36 physical component score
DAS28	Disease Activity Score based on 28 joints; based on tender and swollen joint counts, patient assessment of general health and an acute-phase reactant value
SDAI	Simplified Disease Activity Index; based on swollen and tender joint counts, acute-phase reactant value, and patient and physician assessments of disease activity
CDAI	Clinical Disease Activity Index; based on swollen and tender joint counts, and patient and physician assessments of disease activity
Measures of non-arthritic PsA disease activity	
Leeds dactylitis score	Based on circumference and tenderness of affected digits
SPARCC	Spondyloarthritis Research Consortium of Canada; measures tenderness in 16 enthesal sites
NAPSI	Nail Psoriasis Severity Index; based on psoriasis in nail bed and matrix
BSA	Psoriasis-affected body surface area reported as a percentage
sPGA	Static physician global assessment; based on the severity of induration, erythema and scaling of psoriasis lesions
Patient-reported outcomes	
HAQ-DI	Health Assessment Questionnaire Disability Index; based on patient difficulties with eight quality-of-life categories
SF-36	Short Form (36) Health Survey; based on eight quality-of-life domains
Exploratory outcome	
mTSS	Modified Total Sharp Score; scoring system for X-rays of the hands and feet

65%) based on longitudinal observational studies assessing the role of TNFi and methotrexate combination therapy compared with TNFi monotherapy.^{7 8}

SEAM-PsA is powered to detect a treatment difference in ACR20 response at week 24 between the etanercept plus methotrexate therapy arm and the methotrexate

Table 2 Key studies and observations used in the design of SEAM-PsA

Study (Reference)	Observation
Methotrexate in Psoriatic Arthritis (MIPA) ³	Methotrexate monotherapy at 15 mg/week did not result in statistically significant improvements compared with placebo
Etanercept PsA pivotal phase 3 study ^{6 11}	Similar efficacy was demonstrated between etanercept monotherapy and combination therapy with etanercept plus methotrexate
Norwegian Disease-modifying Antirheumatic Drugs Longitudinal Observational Study (NOR-DMARD) ⁷ Corrona registry ⁸	Combination therapies that are efficacious in patients with RA do not provide similar efficacy in patients with PsA

PsA, psoriatic arthritis; RA, rheumatoid arthritis; SEAM-PsA, Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects with Psoriatic Arthritis.

monotherapy arm at a two-sided 0.025 significance level with >90% power.

DISCUSSION

The SEAM-PsA trial will address clinically important questions about the relative efficacy of methotrexate and etanercept and the combination using ACR20 as well as the MDA, representing a target level of disease activity. It will help address the management of treatment-naïve patients and provide data on a broad range of clinical outcomes associated with PsA. The study has been designed to evaluate efficacy of etanercept and/or methotrexate only; generalisability of the results to other TNFi bDMARDs must take into account the unique profiles of each agent, including the impact of immunogenicity.

There is a need for standardisation of measures to determine disease severity. SEAM-PsA will evaluate response to treatment based on the proportion of subjects achieving an ACR20 response (which is essentially a minimally important response) and MDA, a disease activity state that has been recently developed and validated for PsA that represents a significant response.^{12–13} MDA criteria provide a useful target for treat-to-target treatment strategies, and incorporate measures of joint and enthesal inflammation, skin disease, patient-reported outcomes and functional disability. Results from the TICOPA study¹⁴ and observational studies^{15–17} showed that MDA is achieved at most by 25% of patients treated with methotrexate, whereas patients treated with a TNFi achieved MDA at a frequency >60%. Post hoc analyses may include rates of very low disease activity, in which all seven conditions of MDA must be met.

This study will also characterise the response rates of etanercept and methotrexate as monotherapy or combination therapy for enthesitis, dactylitis and psoriatic nail changes. There is currently a paucity of data regarding the efficacy of methotrexate monotherapy for dactylitis and enthesitis in patients with PsA. A recent study showed that etanercept 50 mg weekly led to 72% improvement in NAPSI score.¹⁸ Another study showed that methotrexate monotherapy improved NAPSI score by 54% at 24 weeks.¹⁹ Measures to assess enthesitis in SEAM-PsA include the SPARCC and the Leeds Enthesitis Index; dactylitis will be measured using the Leeds dactylitis score.²⁰

The ability of a therapeutic agent to improve the signs and symptoms of PsA must be placed in the context of disease modification. Treatment with methotrexate has not been shown to affect radiographic progression in patients with PsA,¹⁴ whereas TNFi have consistently demonstrated improved radiographic outcomes.²¹ SEAM-PsA presents the opportunity to more precisely characterise the impact of methotrexate alone on radiographic progression relative to a TNFi. Radiographic progression is measured using the van der Heijde mTSS for PsA (exploratory endpoint). To maximise the ability to detect a potential difference in the radiographic

outcome measure between treatment arms, blinding was extended through 48 weeks.

In summary, SEAM-PsA will provide information on the potential role of methotrexate and etanercept as monotherapy in the treatment of PsA, and whether the combination of TNFi and methotrexate confers additional short-term benefits to TNFi alone. The results will provide guidance of great practical value for patients and their physicians.

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Ethics approval Institutional Review Board approval is obtained from each study site.

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Data sharing statement The study is ongoing and is not available.

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