SEquential Treatment of PSoriasis with Biologics

STEPS Study

Study protocol (Version 5.0)

Date: 28/07/2025

Introduction

Psoriasis affects up to 60 million people worldwide (1) and can lead to significant morbidity and a decline in quality of life (2, 3). Over the past two decades, rapid advances have been made in the understanding and treatment of this condition; multiple novel drugs have been approved (4). In the United Kingdom, there are currently 14 biologic and targeted synthetic therapies approved by National Institute for Health and Care Excellence (NICE) for use in psoriasis, within the classes anti-TNFα (TNFi), anti-interleukin-17 (IL-17i), anti-interleukin-12/23 (IL-12/23i), anti-interleukin-23 (IL-23i), PDE-4 inhibitors (PDE4i) and TYK2 inhibitors (TYK2i).

Randomised controlled trials have proven efficacy of biologics in psoriasis. However, in many trials, eligibility criteria include limitations on the number and class of prior biologic, for example in reSURFACE 1 and 2 evaluating tildrakizumab versus placebo or etanercept for psoriasis, exclusion criteria precluded previous use of IL-23i (p40/p19) or IL-17i (5). Within reported trials there are also limited sub-analyses of biologic experienced patients, assessing response stratified by number of previous lines of biologic treatment.

With real-world use, a significant percentage of patients on biologics for psoriasis stop treatment, and switch to another biologic, as a result of factors including inefficacy and adverse effects (6). Due to the chronicity of psoriasis, this can lead to a patient having multiple lines of treatment over time. Drug survival reduces with increasing lines of therapy, with previous biologic treatment shown to be a specific effect modifier for the risk of discontinuation associated with effectiveness in psoriasis (7). Drug survival is an important measure of real-world use, however is impacted by various factors including availability of a medication, patient and physician behavioural factors and adverse effects (8), and so is not a perfect substitute for efficacy.

A recent systematic literature review evaluating effectiveness of biologics beyond first line in psoriasis found that currently available evidence is mainly observational, and at high risk of bias (9). There was a scarcity of data available beyond second line, with data only available for 260 patients on 3rd/3rd+ line, and 152 patients on 4th/ 4th+ line. A meta-analysis of PASI75 response at 12-16 weeks did not find a serial reduction in response with sequential lines of treatment, however interpretation of this result is impeded by the limitations of the available data.

Further studies are required to gain understanding of response to later lines of biologic treatment in psoriasis, to assess if prior treatment has an impact on later efficacy response. The development of evidence of effectiveness beyond third line would also help inform healthcare

systems that currently ration the permitted number of lines of biologic per patient, and contribute to more informed discussions between patients and clinicians when switching biologic treatment.

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Study Aim

The aim of the study is to assess clinical response to sequential lines of biologic and targeted synthetic treatment in psoriasis.

Hypothesis

Our hypothesis is that the primary response (at 12-16 weeks) to sequential lines of biologic and targeted synthetic treatment in psoriasis does not reduce with increasing lines of treatment after 2nd line biologic or targeted synthetic treatment.

Objectives

i. To evaluate the proportion of patients achieving a PASI75 response to 3rd + line biologic or targeted synthetic therapy compared to 2nd line at 12-16 weeks and 6 months.
ii. To assess the proportion of patients achieving PASI75, PASI90 and PASI100 to 3rd, 4th, 5th and 6th + line biologic or targeted synthetic therapy compared to 2nd line, at 12-16 weeks and 6 months.
iii. To evaluate the likelihood of achieving PASI ≤2 to 3rd, 4th, 5th and 6th + line biologic or targeted synthetic therapy compared to 2nd line, at 12-16 weeks and 6 months.
iv. To evaluate the likelihood of achieving PASI75 to 2nd line TNFi, IL17i, IL23i, IL12/23i after;
    a. Primary inefficacy to 1st line TNFi
    b. Secondary inefficacy to 1st line TNFi
v. To determine whether primary or secondary inefficacy to 1st biologic or targeted synthetic therapy influences likelihood of response (PASI75 at 12-16 weeks) to subsequent lines of therapy

STUDY DESIGN

Retrospective observational cohort study

Inclusion criteria

- Age ≥18 years
- Diagnosis of chronic plaque psoriasis by a Dermatology consultant
- Prior treatment with biologic or targeted synthetic treatment (1 to 10 lines) for psoriasis in the United Kingdom

Exclusion criteria

- Age <18 years
- Diagnosis of other forms of psoriasis for example generalised pustular psoriasis

Methods

Data collection

Dermatology centres from around the United Kingdom who treat psoriasis patients with biologics will be recruited. Participating clinicians will be asked to submit data on patients treated with biologic and targeted synthetic therapy from a retrospective case note review. An online survey will be developed on the platform RedCAP (Research Electronic data Capture), to collect and store data. The data will be fully anonymous when inputted and will consist of retrospective information obtained during routine clinic appointments, with no additional appointments required for this study. Each patient will be given a study ID which will be kept with the corresponding patient identifying information at the study site, with no access to identifying information from the analysts.

Demographic data for each patient will be obtained at baseline, including the variables age, sex, ethnicity and comorbidities. A dataset of baseline, first follow up and 6-12 month follow up outcome measures (Psoriasis Area Severity Index (PASI), patient global assessment (PGA), Dermatology Life Quality Index (DLQI)) will be collected for each line of biologic treatment (Table 1). These measures will be used to calculate the percentage of patients achieving the predefined outcomes of interest (PASI75/90/100, PASI ≤2) and to assess for inter-line variability in response. In line with NICE guidance, it is likely that the PASI and DLQI will be the most consistently recorded data, but other domains of disease activity will be collected where available.

Table 1 Outcome measures to be assessed

Outcome measure	**Baseline**	**Baseline for each line**	**First follow up (12-16 weeks) for each line**	**6-12 months follow up for each line**
Age	x			
Sex	x			
Ethnicity	x			
Age at psoriasis diagnosis	x			
Comorbidities	x			
Diagnosed PsA	x			
Smoking status	x			
Height	x			
Psoriasis type				
Small or large chronic plaque	x			
Nail	x			
Scalp	x			
Palmoplantar	x			
Genital	x			
Previous systemic/ UV treatments	x			
Age at first biologic	x			
Concurrent systemic or UV treatment		x		
Weight/ BMI		x		x
PASI		x	x	x
DLQI		x	x	x
BSA %		x	x	x
Physician global assessment		x	x	x
Patient global assessment		x	x	x

Statistical analysis

Data analysis will be undertaken using SPSS and R. Demographic data will be analysed descriptively. Each patient will submit all treatment courses for analysis, for example, data from a

patient treated with 3 lines of biologic or and targeted synthetic medicine will be used in the first-, second- and third-line analyses.

This study aims to evaluate the proportion of patients achieving a relative PASI response (PASI75, 90 AND 100) across different lines of biologics. The primary response variable will be the binary PASI75 outcome. Explanatory variables include the line of therapy (categorised as 1st, 2nd-3rd or 4^{th}+ line), baseline PASI, age (categorised into 10-year intervals), disease duration (grouped into two-year intervals), sex, BMI and smoking status.

All statistical analyses will be performed using R. Logistic generalised estimating equations (GEEs) will be employed, utilising the R package 'gee' to account for repeated observations within individuals. An exchangeable correlation structure will be specified, assuming equal correlation among all pairs of observations within a given patient.

A complete case analysis will be conducted for model fitting, including only patients with available data for all explanatory variables at each line of therapy. This approach is valid under the assumption that data are missing at random (MAR), which is reasonable in this case given that missingness is likely due to differences in clinical practice and data collection systems. Patients with missing lines of therapy within their treatment sequence will be included in the analysis, as excluding lines beyond a missing entry would reduce the sample size and increase variance.

To assess the likelihood of achieving PASI75/90/100 AND PASI<2 across different lines of therapy, crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) will be estimated using logistic GEEs. Crude models adjust only for repeated measures, while adjusted models account for sex, age, baseline PASI, BMI and smoking status.

Recruitment approach

Each centre will submit detailed retrospective data collected as part of standard care on patients recruited from routine clinics. We will recommend that data is submitted on the most recent patients starting each line of biologic treatment for psoriasis, with 5 consecutive patients for each line of therapy (first through maximum) where available. We propose competitive recruitment with a maximum of 50 patients per centre until the sample size is met. We will aim to recruit 5-6 centres in case of under recruitment of patients.

Consent

Individual consent from patients is not required due to the nature of the data according to the HRA: this consists of retrospective data collected during standard patient care with no changes made to a patient's standard care.

Sample size and outcome rationale

A meta-analysis of the currently available evidence for effectiveness of biologics at achieving PASI75 at 12-16 weeks in different lines of therapy has shown a rate of 61%, 56.1%, 79% and 61.6% in 1st, 2nd, 3rd/3rd+ and 4th/4th+ lines respectively (Figure 1) (9). The primary question of this study is to compare 2nd line biologic response to 3rd+ line. The meta-analysis indicates that the likelihood of achieving PASI75 does not reduce with subsequent lines of treatment. The sample size is therefore based on a non-inferiority comparison of the proportion of patients achieving PASI75 to 2nd line (56.1%) versus 3rd/4th+ lines. At 5% significance, 80% power, assuming a 56% PASI75 in both and non-inferiority limit of 10%, a sample size of 305 treatment courses per group is required. In additional, 61 treatment courses in first line only will be collected for comparison. Therefore, a total sample size of 671 treatment courses will be sought. A treatment course is equivalent to one line of a biologic or targeted small molecule treatment in one patient. As all treatment courses per participant will be used for analysis, the number of patients required to be recruited is smaller than the sample size (Table 2).

Table 2. Number of recruited patients required to achieve treatment course sample size

Line of treatment	No treatment courses required per group	Number of patients required per line to achieve adequate treatment courses	Treatment courses total per line if number achieved	Treatment courses per group if number achieved
1st	61	61	366	366
2nd	305	61	305	205
3rd	305	61	244	610
4th		61	183	
5th		61	122	
6th+		61	61	
Total	**671**	**366**	**1281**	

Data storage, confidentiality and archiving

All information collected during the study will be kept strictly confidential. Information will be anonymous when inputted into the RedCAP system and will be held securely within the system at the University of Bath.

The study will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

- Each participant is to be allocated an anonymous patient ID; the local sites will hold the personal information of the corresponding patient. No personal identifying information will be available to the analysis team at any point of the study.
- Appropriate storage, restricted access and disposal arrangements for participant clinical details at the study sites.
- Sites are responsible for ensuring only the instructed identifiers (study ID) are present when submitting data into RedCAP and that any data/documentation is appropriately anonymised in accordance with the study procedures to conform with the 1998 Data Protection Act.

At the end of the study, personal data will be securely archived at the University of Bath (RedCAP) for 10 years. The archiving of all anonymised electronic data for a minimum of 10 years will be the responsibility of the Sponsor. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made. It is the responsibility of each centre to maintain their file of patient identifiers on site or at their designated archive facility for this period of time.

Timeline

Phase	**Timeline**
Set up: ethics and site initiation	February 2025- July 2025
Data collection	August 2025- November 2025
Analysis/ Write up	Dec 2025- April 2026

Ethical approval

This study will be conducted according to the principles of the Declaration of Helsinki, Good Clinical Practice (GCP), European Medicines Agency 2002 and current European Directives particularly 2001. We will obtain HRA ethical approval prior to the study initation and will register the study with the National Institute for Health and Care Research.

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