BMJ Open

Quality of life, treatment satisfaction and efficacy of non-biological systemic therapies in patients with plaque psoriasis: study protocol for a prospective observational study

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To cite: Fink C, Schank TE, Trenkler N, *et al*. Quality of life, treatment satisfaction and efficacy of non-biological systemic therapies in patients with plaque psoriasis: study protocol for a prospective observational study. *BMJ Open* 2017;**7**:e014279. doi:10.1136/bmjopen-2016-014279

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2016-014279).

Received 13 September 2016
Revised 28 April 2017
Accepted 2 May 2017

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ABSTRACT

Introduction Psoriasis vulgaris often leads to a significant impaired quality of life and dissatisfaction with the existing therapeutic approaches. However, patients' quality of life and treatment satisfaction are of utmost importance, since it is positively related to therapy adherence and encourages patient's compliance. The study described herein evaluates the quality of life, treatment satisfaction and efficacy during the initial 6 months of treatment with a non-biological systemic agent in a real-life clinical setting.

Methods and analysis This observational study compares quality of life, treatment satisfaction and the efficacy of non-biological systemic therapy between 60 patients suffering from plaque psoriasis receiving the non-biological systemic therapies with apremilast, methotrexate and fumaric acid esters.

Ethics and dissemination Ethics approval was provided by the ethics committee of the medical faculty of the University of Heidelberg. Ethics approval number is S-298/2015. The design and the final results of the study will be published and made available to the public.

Trial registration number German Clinical Trial Register (DRKS): DRKS00008721 (https://www.germanctr.de/).

Strengths and limitations of this study

- For the first time, quality of life, treatment satisfaction and efficacy of the commonly used non-biological systemic therapies with apremilast, methotrexate and fumaric acid esters will be evaluated in a real-life clinical setting.
- This is a non-commercial study.
- Limitations of this study are the non-randomised and single-site setting as well as the small sample size per group. Randomised controlled, multicenter trials with a high sample size generate the most reliable evidence of intervention efficacy. However, the protocol for an observational study described here is a necessary preliminary step in this challenging area of research.

INTRODUCTION

Background

Psoriasis is one of the most frequently occurring chronic inflammatory skin diseases, showing a prevalence of 1.5%–2% in western industrialised nations. Psoriasis vulgaris, also known as plaque-type psoriasis, is the most common clinical form of the disease. This particular type is characterised by sharply demarcated erythrosquamous plaques and is the focus of this study.[1 2] Concerning the treatment of psoriasis vulgaris, guidelines advise a step-by-step therapeutic approach, involving topical treatment as a first-line therapy followed by non-biological systemic agents such as methotrexate, apremilast and fumaric acid esters as second-line therapy and biologicals, such as the tumour necrosis factor antagonists and anti-interleukin12–23 monoclonal antibody, as third-line therapy.[1 2] In this observational study, the systemic second-line therapy with methotrexate, apremilast and fumaric acid esters is evaluated. Methotrexate has been used in the treatment of psoriasis since 1958 and has been licensed in Germany since 1991. The analogue of folic acid competitively inhibits the enzyme dihydrofolate reductase and several other folate-dependent enzymes.[3] Systemic therapy with fumaric acid esters gained approval in Germany in 1994. So far, only a mixture of dimethylfumarate and three salts of ethyl hydrogenfumarate are available as a standardised drug.[4] Apremilast is a relatively new systemic agent on the market which was approved in January 2015 by the European Commission. The small-molecule inhibitor of phosphodiesterase-4 regulates levels of cyclic AMP which is thought to indirectly modulate the production of inflammatory mediators.[5] Plaque psoriasis with its chronic relapsing nature often inflicts significant

morbidity and leads to a substantially impaired quality of life. Another factor which must be considered is a widespread dissatisfaction with existing treatments.[6] The three non-biological systemic agents apremilast, methotrexate and fumaric acid esters not only have a different side-effect profile but also distinct methods and frequencies of administration, time to treatment response and response rates which might present important contributing factors influencing the quality of life and treatment satisfaction. However, this is of particular significance as all of these factors could have negative implications on therapy adherence and patient compliance. Data collection and a detailed breakdown of these subjects, for instance, effectiveness, side effects or convenience, are essential to acquire an accurate understanding of the underlying problems and could therefore conceivably affect and improve patient outcome. Nevertheless, to date, only few subjective studies, based on patient-reported outcome, have been reported.[7] This study has been designed to provide these essential measures in a prospective, observational real-life setting.

DESIGN/METHODS

Study design

This is a prospective, single-centre, observational study evaluating 60 patients suffering from plaque psoriasis.

Study objectives

The objectives of this study are to investigate the outcome measures to assess quality of life, treatment satisfaction and the clinical response to therapy in a real-life setting during the initial 6 months of treatment with a non-biological systemic agent.

Study population and criteria for inclusion/exclusion

Sixty patients suffering from plaque psoriasis initiating therapy with the non-biological systemic agents apremilast, methotrexate or fumaric acid esters at the Department of Dermatology, University of Heidelberg of 18 or more years of age who had given written informed consent will be eligible. The decision for initiating systemic therapy is given according to the S3 guidelines of the German Society of Dermatology and standard operating procedures (SOP) of the hospital. Patients with impaired mental state and those deemed to have insufficient understanding of the German language will not be included in this study.

Methods

Patients receiving systemic therapy with apremilast, methotrexate or fumaric acid esters are being evaluated in this observational study, since these three are the most common non-biological agents prescribed in our department. Recruitment of patients is performed until 20 patients per group are included. In all three groups, quality of life, treatment satisfaction and clinical response to therapy will be noted in a case report form. Furthermore, age, gender, prior treatments, medical history, joint involvement (psoriasis arthritis), concomitant therapies and long-term medication will be documented and considered in the final analysis. Treatment satisfaction will be evaluated using the German version of the Treatment Satisfaction Questionnaire for Medication (German TSQM, V.1.4) which focuses on four patient-reported therapeutic outcomes: effectiveness, side effects, convenience and global satisfaction; metrics are linearised to a subscale score ranging from 0 (extremely dissatisfied) to 100 (extremely satisfied).[8] Quality of life will be measured using the Dermatology Life Quality Index (DLQI).[9] Additionally, effectiveness of the therapy will be scored using the objective outcome measure Psoriasis Area Severity Index (PASI).[10] Patients complete the TSQM and DLQI questionnaires at baseline (week 0) and after 4, 12 and finally 24 weeks of systemic treatment, since 6 months after treatment initiation a clear treatment response and possible side effects should be notable. Data collection with the standardised DLQI and TSQM questionnaires is the only study-related procedure. All the other interventions and procedures during the study relate to routine medical care of the patients according to the SOP of the hospital and current therapy guidelines. The study protocol was written in accordance with the strengthening the reporting of observational studies in epidemiology statement.[11]

Statistical considerations

Sample size calculation

This is an observational pilot study. As this is the first study investigating the effect of apremilast, methotrexate or fumaric acid esters on quality of life and treatment satisfaction, a formal sample size calculation is not realisable. For reasons of feasibility, we use a sample size of 20 patients per group, resulting in an overall sample size of 60 patients. Using this sample size, a standardised effect (Cohen's effect size) of 0.74 can be shown with a power of 80% and a two-sided significance level of 5% in a pairwise comparison of the groups. The effect refers to differences on the TSQM, DLQI questionnaire or PASI score (without any correction for multiple testing) at a specific time point (in a cross-sectional analysis).

Statistical analysis

In the first step, all variables will be analysed descriptively. Continuous variables will be described by use of the mean, the SD, the median, minimum and maximum and the first and the third quartile. Absolute and relative frequencies will be reported to describe categorical data. These analyses will be done for the whole sample as well as for each group separately. Furthermore, as psoriatic arthritis and prior treatment are considered to be important influencing factors, we will do an exploratory analysis to examine possibly existing differences between the groups. The aim of this study is to obtain a first insight about possibly existing differences on the TSQM, the DLQI questionnaire and the PASI score between patients treated with apremilast, methotrexate or fumaric acid

esters. Therefore, we apply a mixed linear regression model to analyse differences between these treatment groups for each endpoint (dependent variables), separately. The group, the time and the interaction of both as well as the baseline value will be included as fixed effects (independent variables). A random intercept (patient ID) will be additionally included to account for the correlation structure of the data. It is planned to assume an autoregressive correlation structure. However, this assumption will be critically reviewed when analysing the data. We will provide effect estimates (for differences between the time points, between the groups and between the variations over time in the different groups) as well as results on the correlation estimation between the time points obtained in the linear mixed regression model. Furthermore, each time point will be analysed separately using analysis of covariance and linear regression models (adjusted for baseline). Pairwise comparisons between the groups will be applied to further clarify any existing differences using t-tests. In addition, exploratory analyses will be performed to describe differences between the groups regarding age, gender, prior treatments, medical history, joint involvement (psoriasis arthritis), concomitant therapies and long-term medication. This will be done to identify possibly existing confounding effects. Since this is an exploratory analysis of observational data, the p-values will be interpreted only in a descriptive way. However, to simplify the reporting of the results the significance level will be set to 5%. No adjustment for multiple testing will be performed. In the linear mixed model (the main model), no missing values will be imputed because all the data available can still be included without any further loss of information in case of missing values at a certain time point. However, a last observation carried forward (LOCF) approach as well as a multiple imputation approach will be applied as sensitivity analyses. All analyses will be carried out using R (R Core Team, 2015, V.3.2.2).[12]

Ethical considerations and regulatory obligations

Declarations, ethic aspects and dissemination

The information contained in this protocol and the implementation of the study is consistent with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (2013), the principles of ICH-GCP guidelines (E6) and the current laws. In the context of the approved SOPs which are based on ICH-GCP guidelines (E6) and the German implementation of good clinical practice (GCP) for clinical work, the patients will be informed orally and in written form about aim, character and consequences of the data collection. Before initiation of the study protocol, the patient information sheet and the consent form were presented to the independent ethics committee of the medical faculty of the University of Heidelberg. Ethics approval was provided by the ethics committee of the medical faculty of the University of Heidelberg. Ethics approval number is S-298/2015. The names of patients and all confidential data are subject to professional discretion and the 'Bundesdatenschutzgesetz (BDSG)'. Processing of medical data will only take place in pseudonymous form. Third person will not be allowed to access patient data. Each participant will be informed that the participation in this study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. There is no personal benefit and no additional risks for study participants, since the data collection using the TSQM and DLQI questionnaires is the only study-related procedure. The design and the final results of the study will be published and made available to the public.

Recruitment and status of the study

Approval of ethics committee was granted in October 2015. Date of first enrollment was September 2015. The recruitment of patients is in progress. The estimated total time frame for recruitment of 60 patients is 18 months. The total duration of the study is expected to be 24 months, including analysis.

Contributors CF, LU and KS participated in the development and the implementation of the study (sample size, protocol, submission to ethics committee, data management). LU performed the data handling and statistical analysis. CF, TES, NT, LU and KS helped to draft and to review the paper. All authors read and approved the final manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Ethics approval Ethics approval was provided by the ethic committee of the medical faculty of the University of Heidelberg. Ethics approval number S-298/2015.

Provenance and peer review Not commissioned; externally peer reviewed.

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