**Methods**

*Study Design*

This was an investigator-initiated, single-centre, randomized, assessor-blinded study conducted in the Department of Dermatology in the Erasmus Medical Centre, Rotterdam, the Netherlands, between July 2013 and June 2015. This study was approved by the Institutional Review Board of the Erasmus University Medical Centre Rotterdam (MEC-2011-500). All patients provided written informed consent. The study was conducted according to the guidelines of Good Clinical Practice. The trial is registered in the European Clinical Trials Database (EudraCT) under EudraCT No. 2011-005685-38. This investigator-initiated study was supported by a grant of Pfizer Pharmaceuticals. Pfizer was not involved in any study procedure, but Pfizer was granted the right to read, but not to edit, the manuscript prior to submission for publication. Provision and reimbursement of etanercept medication was executed via the Dutch health insurance.

*Patients*

All included patients were 18 years or older, had had stable, moderate-to-severe plaque psoriasis for more than 6 months, affecting more than 10% of the body surface area, had a PASI >10 at screening and at baseline, and were candidates for biologic treatment according to the approved product labelling and to Dutch guidelines.

Patients were recruited from the dermatology outpatient clinic from our hospital. Patients were excluded if they had any other subtype of psoriasis or previous treatment failure on etanercept or fumarates or had a clinically significant adverse event with prior use of both drugs. Pregnant or lactating women were not eligible.

Patients with severe recalcitrant psoriasis who had experienced a lack of efficacy during prior use of other biologics were also eligible, in order to represent real-life daily practice. The wash-out period for a TNF-blocking agent or any other biologic was 3 months, and for other systemic treatments (including fumarates) or UV therapy it was 4 weeks. All patients were screened for hepatitis B and C, HIV and (latent) tuberculosis according to the Dutch psoriasis treatment guidelines.

*Study Objectives*

The primary objective of this study was to compare the clinical efficacy of the combination therapy of etanercept and fumarates with etanercept monotherapy per label after 24 weeks. The clinical efficacy was expressed as the proportion of patients achieving at least 75% reduction in their PASI after treatment. Additionally a longitudinal analysis was performed to assess the PASI reduction per week for each group.

Secondary objectives were to evaluate the efficacy at weeks 12 and 48, the proportion of patients with a PGA clear or almost clear, the change in DLQI score, and treatment satisfaction (visual analogue scale) scores after 12, 24 and 48 weeks. Drug survival after 1 year was assessed by a post hoc analysis and was defined as the proportion of patients who were still under the treatment they had originally been randomized to and who also achieved at least a 75% reduction in their PASI. Adverse events were collected through the entire study period.

*Study Procedures*

Using a computer-generated randomization list, patients were randomized at baseline to a 1:1 ratio to receive either etanercept combined with oral fumarates (combination group) or etanercept only (monotherapy group). Patients and the study physicians were not blinded for the allocated treatment group. The independent PASI assessor (E.P.P.) was blinded to treatment throughout the course of the study.

All patients received etanercept 50 mg subcutaneously twice weekly for 12 weeks followed by 50 mg once weekly for an additional 12 weeks. Subjects randomized to the combination group were treated with additional fumarates, of which the daily dose was gradually increased within 4 weeks from 215 mg once daily up to a maximum of 215 mg 4 times a day. A large batch of enteric-coated tablets containing a total of 215 mg fumaric acid esters (120 mg dimethylfumarate and 95 mg calcium mono-ethylfumarate) was specifically manufactured for this trial by Fagron (Capelle aan den IJssel, the Netherlands).

Patients in the monotherapy group who did not achieve a PASI-75 response after 24 weeks were switched to the combination therapy (suppl. fig. 1, 2). Patient visits were scheduled at weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40 and 48. At each study visit, data were collected on PASI and PGA scores, tolerability, adverse events and laboratory testing (full blood count, aspartate aminotransferase, alanine aminotransferase, bilirubin, γ-glutamyltransferase, serum creatinine, sedimentation rate, C-reactive protein and urine analysis). Patients were asked to fill in the DLQI questionnaire and a visual analogue scale for treatment satisfaction on a monthly basis. Patient data were collected using the computer programme Open Clinica.

*Statistical Analysis*

The proportion of patients achieving at least a 75% PASI reduction after 12, 24 (primary objective) and 48 weeks of treatment was analysed using a χ2 or Fisher exact test, used for the outcomes of the PGA and for the proportion of patients achieving drug survival. Patients who switched to combination therapy after 24 weeks were considered as failures in the monotherapy group. Patients lost to follow-up were not included in the PASI-75 response and PGA score analyses. For the longitudinal analysis, a linear mixed model analysis was used to calculate the reduction in PASI score per week up to 48 weeks. We used the lme4 package in R (<https://cran.r-project.org/web/packages/lme4/lme4.pdf>). Time and group, and the interaction, were predictors. We used log-transformed PASI in the regression model to achieve changes to be relative.

We used the unpaired t test for comparing changes in DLQI and visual analogue scale score between the monotherapy and combination therapy at 12, 24 and 48 weeks. If the residuals were not normally distributed, we used the bootstrap option in SPSS. We used descriptive statistics by presenting the PASI score per patient in a graph.