

CLINICAL REPORT

The Combination of Etanercept and Methotrexate Increases the Effectiveness of Treatment in Active Psoriasis Despite Inadequate Effect of Methotrexate Therapy

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Many patients with moderate-to-severe plaque psoriasis do not respond adequately to methotrexate monotherapy. This pilot study, with a small patient population, was performed to evaluate the effectiveness and safety of etanercept and methotrexate combination in patients with plaque psoriasis and inadequate response to methotrexate. Outpatients with plaque psoriasis (Psoriasis Area and Severity Index ≥ 8 and/or body surface area $> 10\%$), despite methotrexate treatment (≥ 3 months; ≥ 7.5 mg/week) were randomized to either etanercept with methotrexate tapered and discontinued ($n=28$) or etanercept with continuous methotrexate ($n=31$). Significantly more patients had a Physicians' Global Assessment of "clear"/"almost clear" in the combination group compared with etanercept/methotrexate taper (66.7 vs. 37.0%, respectively; $p=0.025$). Adverse events were similar for both groups, with no cases of tuberculosis, malignancies or opportunistic infections reported. Addition of etanercept to methotrexate achieved significant improvement in psoriasis after 24 weeks. *Key words: etanercept; methotrexate; psoriasis.*

(Accepted April 21, 2008.)

Acta Derm Venereol 2008; 88: 495–501.

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Psoriasis is a chronic, inflammatory skin disorder, estimated to affect about 2.5% of the global population and approximately 1.5% of people in central Europe (1, 2). Plaque psoriasis is the most common form, diagnosed in 80% of patients with psoriasis (3). About a quarter of those with psoriasis have moderate-to-severe disease, but psoriasis of almost any severity has a profound effect on patients' health-related quality of life (4, 5). This is commonly because of psychosocial effects (e.g. contemplating suicide, and difficulties interacting with work colleagues, family and friends or finding a job), or difficulties in performing normal daily activities (e.g. using hands, walking, sleeping, standing or sitting for

long periods, or sexual activities) (4). The definition of psoriasis severity includes the effect of the disease on patients' quality of life, disease history, signs and symptoms. For example, the "rule of tens" for current severe psoriasis is defined as at least 10% of body surface area (BSA) involved, or a Psoriasis Area and Severity Index (PASI) score of at least 10 or a Dermatology Life Quality Index (DLQI) score of at least 10 (6, 7).

Although topical treatments may suffice to control mild psoriasis, moderate-to-severe psoriasis often requires the use of phototherapy, systemic drugs, or both (1, 8). However, current systemic therapies for moderate-to-severe psoriasis are associated with short- and long-term toxicity, and a concomitant high level of patient dissatisfaction (8, 9). There is a need for well-tolerated and more effective therapies for this patient group.

Methotrexate is the most commonly used systemic treatment for moderate-to-severe plaque psoriasis in Europe (9, 10), and is effective in reducing disease severity by at least 50% in the majority of patients (11, 12). However, methotrexate is associated with potentially serious toxic effects, including haematological toxicity, hepatotoxicity and lung disease, limiting the dose and duration of treatment and requiring careful monitoring of hepatic, renal and haematological parameters (8). Methotrexate also lacks effectiveness in a substantial proportion of patients.

Etanercept is a fully soluble, human tumour necrosis factor (TNF) receptor and reduces the inflammatory response by inhibiting interactions between TNF and cell-surface receptors (13, 14). Etanercept monotherapy has been shown to be effective in treating plaque psoriasis in several randomized, double-blind trials, and is also associated with a good safety and tolerability profile (15–17). Recent trials in patients with rheumatoid arthritis who had an inadequate response to methotrexate monotherapy have shown that the addition of etanercept produces substantial clinical improvements without an increase in adverse events (18–20). Moreover, a study conducted in a small number of patients ($n=6$) with moderate-to-severe psoriasis showed that etanercept can allow the tapering of methotrexate dose

without increasing liver toxicity, infections or myelo-suppression (21).

The objective of this study was to evaluate the effectiveness of combining etanercept with continued methotrexate treatment and of etanercept with methotrexate taper in outpatients with active plaque psoriasis (PASI >8, BSA ≥10%), despite treatment with methotrexate for at least 3 months. The design of the study was chosen to be similar to routine practice with systemic therapies when treating psoriasis patients. This is a 24-week, randomized, open-label, parallel-group, multicentre pilot study.

METHODS

Study protocol

The study protocol was approved by local ethics committees and was conducted in accordance with the Declaration of Helsinki and its amendments. Patients giving written informed consent were recruited from two centres in each of the following countries: Denmark, Finland, Norway and Sweden. The randomization schedule was computer generated and performed in randomly permuted blocks of four, with one randomization list per centre. As this was an open-label study, patients were not blinded to the treatment they were assigned.

Patients were invited to participate in this study if they were at least 18 years of age and had active plaque psoriasis involving at least 10% of their BSA and/or a minimum screening PASI score of 8. In addition, patients had to have been treated with methotrexate at a dose of at least 7.5 mg/week for 3 months before the study and had an inadequate response. The 3-month period was chosen to obtain a stable methotrexate dose, although the majority of the patients had been on methotrexate treatment for many years. The minimum level of 7.5 mg methotrexate was chosen in order not to exclude the few patients who had been treated with higher doses of methotrexate, but where it had been necessary to reduce dose due to gastrointestinal-symptoms, liver toxicity or other side-effects such as tiredness.

Sexually active women of child-bearing age were required to use a medically accepted form of contraception. Exclusion criteria included: presence of predominantly guttate, erythrodermic or pustular psoriasis; previous use of a TNF-inhibitor; skin conditions other than psoriasis that could interfere with effectiveness evaluations of trial medications; use of systemic corticosteroids, psoralen plus ultraviolet A radiation, cyclosporine, acitretin, alefacept, efalizumab, tar compounds, vaccination with live attenuated vaccine or the presence of active severe infections in the 4 weeks before starting the trial; ultraviolet light B (UVB), topical group III or IV steroids, topical vitamin A or D or anthralin in the 2 weeks before starting the trial; a history of alcohol or drug abuse; lactation; clinically relevant diseases.

Randomization was performed at the baseline visit, and additional clinic visits were performed at 2, 4, 8, 12, 18 and 24 weeks to assess the effectiveness and safety of the trial medications.

Treatments

Patients were randomized to receive 24 weeks of treatment as follows: (i) etanercept with methotrexate tapered and discontinued during the first 4 weeks of the trial or (ii) etanercept combined with continued methotrexate treatment. For patients in both groups, etanercept was given subcutaneously, 50 mg twice weekly for 12 weeks, and then 25 mg twice weekly for the remaining 12 weeks of the study.

Outcome measures

The primary effectiveness variable was the proportion of patients who were classified as "clear" (score of zero) or "almost clear" (score of one) on the Physician's Global Assessment (PGA) scale at week 24. Secondary variables included the following: PGA "clear" or "almost clear" at 12 weeks; PGA of head, scalp and neck "clear" or "almost clear" at weeks 12 and 24; time to PGA "clear" or "almost clear"; PASI improvement at weeks 2, 4, 8, 12, 18 and 24; PASI 50, PASI 75 and PASI 90 responses (proportion of patients with an improvement of PASI of at least 50, 75 and 90% from baseline, respectively) at weeks 12 and 24; patients' global assessment of psoriasis, itching, joint pain and tiredness (each criterion was assessed using a scale from 0 (good, no itching, no pain, no tiredness, respectively), to 5 (severe, severe itching, severe pain and very tired, respectively) at weeks 12 and 24; and DLQI and EuroQoL 5D (EQ-5D) scores at weeks 12 and 24. Safety was evaluated by recording adverse events, vital signs, physical examinations, blood laboratory tests and the proportion of patients who discontinued due to adverse events.

Statistical analysis

The statistical analyses were performed by PCG. SAS® version 8.02 software was used in all analyses. Results were summarized by visit for the full analysis set (FAS; i.e. randomized patients who had taken at least one dose of study medication and had a least one post-randomization observation). The primary effectiveness variable was analysed using a two-sided 95% confidence interval (CI) for the difference between treatments for the proportion of patients who were "clear" or "almost clear" at week 24. A χ^2 -test of difference between treatments was performed. Secondary outcome measures were analysed in the same manner with the following exceptions. For percentage improvements in PASI scores, a two-sided 95% CI for the difference between treatments was calculated at each respective time-point. Differences between treatments were tested with ANCOVA with baseline values as the covariate. Time to PGA "clear" or "almost clear" used Kaplan–Meier estimates of time to "clear" or "almost clear" displayed in a graphical format and a corresponding log-rank test to look for any difference between treatments. Differences between treatments for patients' global assessment of psoriasis were analysed with the extended Mantel-Haenszel mean score statistic using modified ridit score and adjusting for value at baseline. DLQI and EQ-5D scores were analysed by calculating a two-sided 95% CI for the difference between treatments, with difference between treatments tested using ANCOVA with baseline value as the covariate. Safety variables were analysed using descriptive statistics, but no formal statistical comparisons were made.

A patient number of 60 for this pilot study was estimated for practical reasons rather than for statistical comparison between treatment groups, as data concerning the treatment of patients with psoriasis who fail methotrexate therapy are sparse. Thus, this study was designed to gather information about etanercept, with or without concurrent methotrexate, for this difficult-to-treat group of patients with plaque psoriasis. Sixty patients allows for a precision of ±0.13 percentage points for the 95% CIs with respect to the primary effectiveness variable.

RESULTS

Participant flow and baseline results

Fig. 1 shows the flow of patients through the study. Sixty patients were enrolled, of whom 59 were ran-

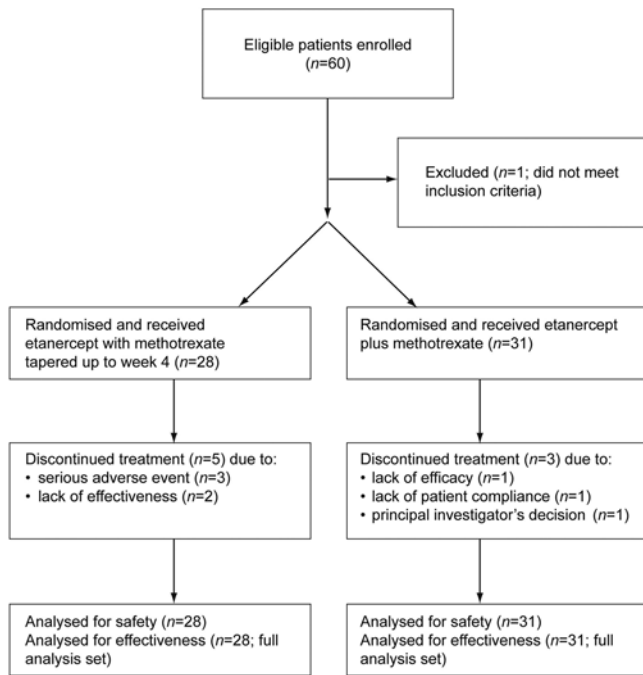


Fig. 1. Patient flowchart.

domized to one of two treatments: etanercept with methotrexate taper ($n=28$) or etanercept combined with continued methotrexate treatment ($n=31$), with one patient withdrawn due to a positive tuberculosis test during screening. All 59 patients were included in the safety analysis and effectiveness analysis (FAS). All results presented here are for the FAS data-set.

Five patients (17.9%) withdrew from the etanercept/methotrexate taper group and 3 (9.7%) from the combination therapy group during the course of the trial. For the etanercept/methotrexate taper group, 3 of these

withdrawals were because of serious adverse events and 2 were because of lack of effectiveness. For the combination therapy group, one patient each withdrew because of lack of effectiveness, lack of compliance and the decision of the principal investigator.

Baseline demographics and baseline effectiveness variables are presented in Table I. The methotrexate dose received prior to initiation of the study was similar in both the etanercept/methotrexate taper and combination groups (14.0 (range 7.5–25.0) and 13.4 (range 7.5–25.0) mg/week, respectively). The only significant difference between treatment groups regarding baseline characteristics was that a larger proportion of women were in the etanercept/methotrexate taper group compared with the combination treatment group ($p=0.046$).

Effectiveness

Improvements in psoriasis symptoms, as measured by the primary and secondary effectiveness variables, were observed in both treatment groups over the course of the study. The primary effectiveness variable (proportion of patients judged as “clear” or “almost clear” according to the PGA at week 24) was superior for etanercept combined with continued methotrexate treatment compared with etanercept/methotrexate taper (66.7 vs. 37.0%, respectively; $p=0.025$; adjusted for gender $p=0.027$; Fig. 2). There were marked improvements in PGA scores in the combination treatment group, with 86.6% of patients achieving scores of 0–2 at week 24 compared with 74.0% for the etanercept/methotrexate taper group.

Both treatment groups demonstrated an improvement in PASI score from baseline. Results showing the proportion of patients with a PASI improvement of at

Table I. Characteristics at baseline of patients randomized to receive etanercept with methotrexate tapered over the first 4 weeks or etanercept combined with continued methotrexate treatment

Characteristic or effectiveness measure	Treatment		Total ($n=59$)
	Etanercept/methotrexate taper ($n=28$)	Etanercept with continued methotrexate ($n=31$)	
Mean age, years	47.3	48.7	48.1
Mean body weight, kg	89.9	83.7	86.6
Mean body mass index, kg/m ²	30.1	27.6	28.8
Mean body surface area involvement, %	24.9	26.2	25.6
Mean psoriasis duration, years	21.0	23.0	22.0
Race, n (%) of patients			
Caucasian	27 (96.4)	30 (96.8)	57 (96.6)
Asian/South American	1 (3.6)	1 (3.2)	2 (3.4)
Gender, n (%) of patients			
Males	17 (60.7)	26 (83.9)	43 (72.9)
Females ^a	11 (39.3)	5 (16.1)	16 (27.1)
PGA	2.9	3.2	3.0
PGA, assessment of head, scalp and neck	2.3	2.3	2.3
PASI	16.8	17.4	17.1
DLQI, total score	11.2	9.0	10.1
Methotrexate dose, mg/week	14.0	13.4	13.7

^a $p=0.046$ for percentage of females given etanercept/methotrexate taper vs. those given etanercept combined with continued methotrexate treatment.

DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index; PGA: Physicians' Global Assessment of psoriasis.

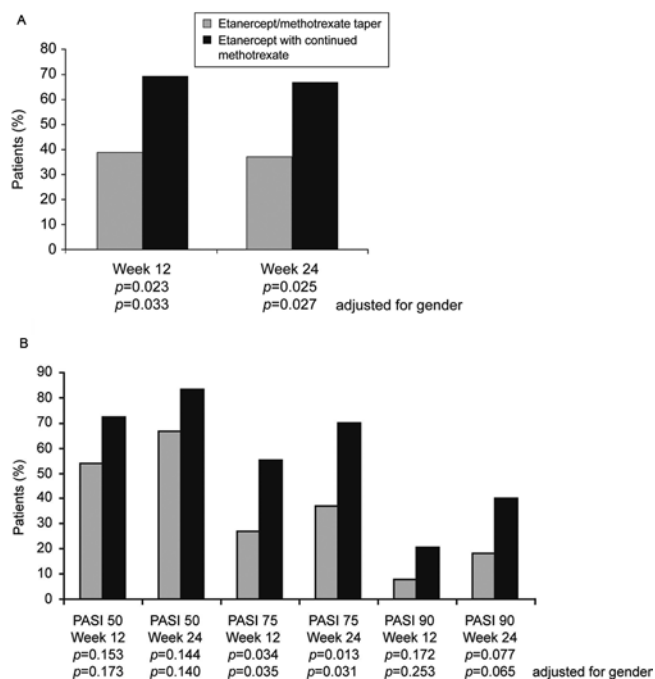


Fig. 2. The proportion of patients (A) classified as “clear” or “almost clear” on the Physician’s Global Assessment (PGA) of psoriasis scale and (B) with an improvement of Psoriasis Area and Severity Index (PASI) of at least 50%, 75% and 90% from baseline, respectively, at weeks 12 and 24 (data for all non-missing observations are shown).

least 50, 75 and 90% from baseline are shown in Fig. 2. Achievement of PASI 75 over time is shown in Fig. 3. Results for PASI 75 at both 12 weeks and 24 weeks were significantly better for combination treatment than etanercept/methotrexate taper even when adjusted for gender differences. Results for mean percentage improvements in PASI scores from baseline show that by 18 weeks of treatment, combination therapy was significantly superior to etanercept/methotrexate taper (79.9 vs. 62.8, respectively; $p=0.023$; adjusted for gender $p=0.019$), an effect that was maintained until the end of the study (76.4 vs. 51.3%, respectively; $p=0.019$; adjusted for gender $p=0.021$).

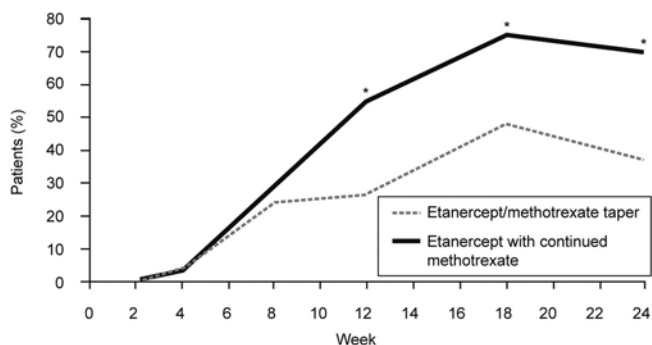


Fig. 3. Improvements in Psoriasis Area and Severity Index (PASI) scores of at least 75% from baseline at all time-points assessed (data for all non-missing observations are shown) $p < 0.05$ for the difference between study groups (with and without adjustment for gender).

Patients’ global assessment of psoriasis showed significant improvement at week 12 ($p=0.011$) and week 24 ($p=0.012$) for etanercept combined with continued methotrexate treatment vs. etanercept/methotrexate taper. PGA of head, scalp and neck “clear” or “almost clear” after 12 weeks was also significantly better for combination than etanercept/methotrexate taper treatments (93.1 vs. 65.4%, respectively; $p=0.010$; adjusted for gender $p=0.023$), but by week 24 this difference was no longer significant (86.7 vs. 66.7%, respectively; $p=0.072$, adjusted for gender, $p=0.155$).

DLQI scores indicated an improvement in quality of life over the study period for both groups. At week 24, there were greater reductions in DLQI from baseline for patients in the combination treatment group than those in the etanercept/methotrexate taper group (improvements of 74 and 48%, respectively; $p=0.076$; adjusted for gender $p=0.12$). Likewise, EQ-5D scores were improved in both groups at 24 weeks although the difference between the treatment groups did not reach significance ($p=0.217$). The actual increases in EQ-5D scores of 0.19 and 0.12 for the combination and etanercept/methotrexate taper groups, respectively, are considered a clinically meaningful change in quality of life (utility), where a minimally important difference is 0.07 (22).

Safety and tolerability

There was very little difference between treatment groups for the number of patients experiencing adverse events or the total number of adverse events reported (Table II). A total of 101 adverse events were reported: 51 in the etanercept/methotrexate taper group and 50 in the combination treatment group. The most common organ system class affected by adverse events was infections, where 7 (25.0%) and 12 (38.7%) adverse events were reported for the etanercept/methotrexate taper and combination groups, respectively. This was followed by general disorders and administration site conditions with 8 (28.6%) and 5 (16.1%), respectively, and skin and subcutaneous tissue disorders with 7 (25.0%) and 5 (16.1%) events, respectively. A total of 7 adverse events were considered serious, 5 events reported in 4 patients in the etanercept/methotrexate taper group and 2 events reported in one patient in the combination group, all of which were considered to be related to the study medication. Three of these serious adverse events were infections (2 in the etanercept/methotrexate taper group and one in the combination group). Pustular psoriasis, heart insufficiency and atrial fibrillation also occurred in the etanercept/methotrexate taper group and vomiting occurred in the combination group. Three patients discontinued due to adverse events in the etanercept/methotrexate taper group, but none in the combination treatment group. No cases of

Table II. Summary of adverse events

	Etanercept/methotrexate taper (n=28)	Etanercept with continued methotrexate (n=31)
<i>Number (%) of patients</i>		
Any adverse event	21 (75.0)	19 (61.3)
Any serious adverse events	4 (14.3)	1 (3.2)
Infection, hospitalized	1 (3.6)	0 (0.0)
Pustular psoriasis in hands ^a	1 (3.6)	0 (0.0)
Pneumonia	1 (3.6)	0 (0.0)
Heart insufficiency/atrial fibrillation	1 (3.6)	0 (0.0)
Vomited (blood in vomit)/respiratory infection	0 (0.0)	1 (3.2)
Discontinuation of study treatment due to adverse event	3 (13.0)	0 (0.0)
<i>Number (%) of events</i>		
Total adverse events	51	50
Related to study medication	28	26
Most common adverse event by organ system class		
Infections	7 (25.0)	12 (38.7)
General disorders and administration site conditions	8 (28.6)	5 (16.1)
Skin and subcutaneous tissue disorders	7 (25.0)	5 (16.1)
Total serious adverse events	5	2
Related to study medication	5	2

^aThis was not a transformation of disease.

malignancies, opportunistic infections or tuberculosis were observed.

DISCUSSION

This study reports on the effectiveness of the addition of etanercept to methotrexate treatment in patients with active plaque psoriasis despite methotrexate therapy. Treatment benefit with etanercept plus methotrexate was demonstrated across a wide range of measures and no concerns were raised relating to the tolerability of combination therapy.

Improvements in psoriasis symptoms from baseline were observed in both treatment arms, with the combination group demonstrating statistically superior results compared with etanercept/methotrexate taper in PGA "clear" or "almost clear", mean percentage improvement in PASI score from baseline and PASI 75 scores. This pilot study was conducted in a small patient population which may have contributed to the failure to reach a statistically significant difference in PASI 50 and PASI 90 results despite the combination group demonstrating higher numerical rates of improvement compared with etanercept/methotrexate taper at all time-points from 4 weeks.

Quality of life also improved for both groups, with greater improvement observed in the combination treatment arm compared with etanercept/methotrexate taper. However, the difference between treatments did not achieve statistical significance. Quality of life measurements are generally considered more variable than clinical endpoints, which could explain the failure to reach a statistically significant difference.

The effectiveness findings are important because the patient population studied is notoriously difficult to

treat. Patients in this study have suffered from psoriasis symptoms for an average of 22 years in total and PASI scores upon entry into this study were well above the minimum entry criteria (average 17.1; range 8–42). Therefore these patients represent a group with severe psoriasis symptoms, who have responded inadequately to methotrexate treatment. Patients were receiving an average methotrexate dose of 13.7 mg per week. In a large number of patients the initial methotrexate dose had been reduced due to intolerance for different reasons, such as gastrointestinal complaints, tiredness and liver toxicity. The patient population in this study represent the daily situation for the clinicians in dermatological departments, where a large number of the psoriasis patients with prolonged disease symptoms are treated with methotrexate and other systemic therapies. It is therefore important to consider new therapeutic options in patients with severe disease despite methotrexate treatment.

Data on PASI scores prior to methotrexate therapy could not be obtained for patients in this study. It is common for psoriasis studies to have a washout period of systemic therapy prior to baseline, which enables a "true" PASI response to the study treatment to be recorded. However, this was not possible with this particular study design. Taking this into consideration, a "true" PASI response to etanercept and methotrexate combination in treatment-naïve patients would be expected to be higher than the PASI 75 of 70% at week 24 reported for this study. However, the effectiveness results for PGA and PASI were very favourable for patients in the etanercept and methotrexate combination group, suggesting an additive effect for these two agents.

The additive effect observed in the present trial between etanercept and methotrexate is not surprising,

given that it is established practice to use rational combinations of treatments with different modes of action to treat psoriasis (1, 23). Thus, although the mechanism of action of methotrexate is not fully understood, it is thought to act as an immunosuppressant and targets lymphoid cell functions, whereas etanercept specifically targets TNF α (1, 8, 24).

The effectiveness of etanercept alone for moderate-to-severe psoriasis is well documented, both over 12–24 weeks (15–17), and over much longer periods of up to 3 years (25, 26). Such studies reveal high response rates: PASI 75 was achieved in 54–59% of patients at week 24 in three previous trials (15–17). The lower PASI 75 response observed here in the etanercept/methotrexate taper group (37% of patients achieved PASI 75 at week 24) is a consequence of multiple factors. First, as explained for the combination group, the “true” PASI responses that could be achieved with etanercept alone in treatment-naïve or “washed-out” patients would be higher than those obtained in this study with etanercept after withdrawal of methotrexate. Secondly, a reduced rate of improvement following the withdrawal of methotrexate in these patients with severe disease and an inadequate response to prior methotrexate monotherapy. A similar situation was observed when one agent was withdrawn from combined methotrexate and cyclosporine therapy administered to patients with severe psoriasis (27).

Etanercept was well tolerated in both treatment groups, with no new safety signals. Moreover, there were no cases of malignancies, opportunistic infections or tuberculosis in the study reported here. However, malignancies due to treatment would not be expected to appear in the time course of this study. These events have been observed with methotrexate, and, rarely, with etanercept monotherapy (8, 13). The results of this study are consistent with safety data from larger, long-term studies of combination therapy with etanercept and methotrexate. In a 3-year study of patients with rheumatoid arthritis treated with the combination of etanercept and methotrexate, clinical improvements were sustained through 3 years with no latent tolerability issues (28).

In conclusion, this study showed that patients with active plaque psoriasis despite methotrexate treatment benefited significantly from the addition of etanercept to their methotrexate treatment regimen with no adverse effect on safety. This study warrants repetition in a larger patient cohort and over a longer study period to confirm these initial observations. Nonetheless, these results are promising as they provide clinicians with a further option to address this difficult-to-treat patient population. Patients with psoriasis are a heterogeneous group and respond differently to the available therapies. Thus, the treatment regimen needs to be adapted to suit the individual's needs taking into account disease severity, impact on quality of life, practicality of treatment and treatment history.

Given the results presented here, clinicians should consider the addition of etanercept for patients responding inadequately to methotrexate.

Conflicts of interest: Dr C. Zachariae has served as a speaker and consultant for Wyeth. Drs N.-J. Mørk, A. Johannesson and S.-L. Karvonen have served as speakers for Wyeth. Dr H. Lorentzen has served as a speaker and consultant for Wyeth, and has received funding for his research work. Dr S. Walker is an employee of Wyeth Europa and Dr S. Qvitzau is an employee of Wyeth Denmark. Drs T. Reunala, E. Falk, B. Claréus, L. Skov and G. Mørk have no conflicts of interest.

This study was sponsored by Wyeth Europa, Maidenhead, Berkshire, UK.

Editorial support was provided by Fishawack Communications Ltd, UK.

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