ONCE-WEEKLY ADMINISTRATION OF HIGH-DOSAGE ETANERCEPT IN PATIENTS WITH PLAQUE PSORIASIS: RESULTS OF A PILOT EXPERIENCE (POWER STUDY)

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Etanercept is a soluble tumour necrosis factor receptor fusion protein which is approved for the treatment of plaque psoriasis at the dose of either 25mg twice weekly (BIW) or, for the initial 12 weeks, 50mg BIW. Alternative dosing regimens have not been evaluated in psoriasis. In this study, we compare the efficacy and tolerability of two etanercept dosing regimens - 50mg BIW and 100mg once weekly (OW) - for 12 weeks in 108 patients with moderate-to-severe recalcitrant psoriasis. Efficacy measures included Psoriasis Area and Severity Index (PASI), severity of pruritus recorded on a visual analogue scale (VAS) and the influence on quality of life assessed by means of Dermatology Life Quality Index (DLQI). Both etanercept regimens caused a significant change in all the efficacy parameters after 4 weeks and 12 weeks, at a comparable rate. At week 12, a PASI improvement of at least 50% from baseline (PASI 50) was achieved by 74% of patients treated with 50mg BIW and 78% of patients treated with 100mg OW. A PASI 75 response was obtained in 54% and 50% of patients treated with 50mg BIW and 100mg OW, respectively. Treatment was well tolerated with similar type and frequency of adverse events between the two groups.

Etanercept (Enbrel®, Wyeth Europe Ltd) is a soluble tumour necrosis factor (TNF) receptor fusion protein which is approved for the treatment of rheumatoid arthritis (RA), polyarticular-course juvenile RA, psoriatic arthritis (PA), ankylosing spondylitis (AS) and plaque psoriasis. In adult patients with RA, PA and AS, the dosage is 50mg per week given as 25 mg subcutaneous injections twice weekly (BIW). In RA, once weekly (OW) administration (single 50mg injection) is an alternative recommended dose. In plaque psoriasis, the drug can be administered at the dose of either 25mg BIW or, in the initial 12-week phase, 50mg BIW (1). Other dosing regimens have not been studied in psoriasis. We wanted to assess the efficacy and safety of 100mg OW administration of etanercept for 12 weeks in plaque psoriasis.

MATERIALS AND METHODS

This pilot study (study acronym, POWER: Psoriasis and Once Weekly Etanercept Response) was designed as an investigator-blinded study to compare the efficacy and

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tolerability of two different 12-week dosing regimens with etanercept. After obtaining informed consent, psoriatic patients regarded as candidates to receive etanercept were sequentially allocated to one of these two treatment groups according to a 1:1 ratio:

group A: etanercept 50mg BIW for 12 weeks;

group B: etanercept 100mg OW for 12 weeks.

Eligible patients were adult male or female subjects with chronic plaque psoriasis involving at least 10% of the body surface area and with a minimum psoriasis area and severity index (PASI) (2) of 10, in whom standard systemic therapies and phototherapy were contraindicated and/or had caused inadequate response in terms of efficacy or tolerability. Eligibility also required the absence of the following exclusion criteria: guttate, erythrodermic and pustular psoriasis; concomitant skin disorders that could interfere with study evaluations; known hypersensitivity to etanercept or to any of its excipients; active or chronic infections, including HIV, HBV and HCV infection, latent tuberculosis, history of recurrent infections and risk for sepsis; previous or active malignancies; relevant haematological, renal and hepatic disorders; congestive heart failure; demyelinating diseases; autoimmune rheumatic diseases; recent or concurrent vaccinations with live viruses or bacteria; pregnancy and lactation; previous treatment with biologicals, including etanercept; concomitant treatment with interleukin-1 antagonists and with any treatment or procedure capable of influencing psoriasis course and evaluation, including topical antipsoriatic drugs, keratolytics, artificial UV light and sun exposure. Non-medicated emollients were only permitted throughout the study period. Prior to the baseline evaluation, patients were to have stopped standard topical psoriasis therapies for at least 2 weeks and systemic psoriasis therapy or phototherapy for a minimum of 4 weeks.

A total of 108 patients, 63 males and 55 females with a mean age of 44.5 (range: 19-67), met the eligibility criteria (53 in group A and 55 in group B). Patients in group A (etanercept 50mg BIW) received Enbrel® 50mg as two subcutaneous injections of 25mg on the same day (with each injection given at different sites), repeated 3-4 days apart. In group B (etanercept 100mg OW), treatment was performed in a single administration per week with four subcutaneous injections of 25mg given on the same day at distinct sites.

Clinical assessment was performed at baseline, after 4 weeks and after 12 weeks (end of the study) and PASI was calculated by an independent observer who was unaware of the dosing regimen used. At each visit, the severity of psoriasis-associated pruritus was recorded by patients on a visual analogue scale (VAS), whereas the Dermatology Life Quality Index (DLQI) (3) was used to evaluate the impact on quality of life. Routine laboratory examinations (haematology, serum chemistry and urinalysis) were done at baseline and weeks 12.

Statistical analysis was performed on an intent-to-treat basis. Missing data due to any reason were imputed carrying forward the last assessment available (LOCF approach). In each group the average change of PASI, VAS for pruritus and DLQI scores from baseline was reported and was statistically analyzed using the Wilcoxon matched-pairs signed-ranks test (significance for p values less than 0.05). Additional efficacy endopoint was the response rate in each group defined as the proportion of patients who achieved both a $\geq$ 50% and a $\geq$ 75% improvement of PASI from baseline (PASI 50 and PASI 75, respectively). Treatment group comparisons of PASI, VAS and DLQI change were made using the Mann-Whitney U test; again, p values <0.05 were considered significant. The safety analysis was descriptive and based on the frequency of adverse events (AEs) and abnormal laboratory results in patients treated with etanercept for at least one day.

RESULTS

All the 108 eligible patients received treatment with etanercept. Of these, four patients were not included in the efficacy analysis because of premature discontinuation for administrative reasons (no. 2) or because of the use of prohibited treatments (intense exposure to sunlight or artificial UVA radiations: no. 2) before week 4. After 4 weeks of treatment, two patients were lost to follow-up and another withdrew his consent. Therefore, 101 patients completed the 12-week treatment period (50 in group A and 51 in group B).

At baseline, in the entire population, mean PASI was 18.1 and DLQI score had an average mean value of 10.7; 64% of patients complained of pruritus with a mean severity reported on VAS of 48 mm. The two treatment groups were homogeneous as no significant differences of baseline parameters were detected between the two arms ($p>0.05$).

Treatment with each regimen caused a significant improvement of PASI from baseline after week 4 ($p<0.05$) and week 12 ($p<0.01$) without any significant differences between the two regimens (Fig. 1, Table I). The response rate (shown in Table I) gave similar results in the two arms: at the end of treatment, about two thirds of the patients obtained a PASI 50 response whereas half of the patients achieved a PASI 75. The results of PASI were

Table I. *Efficacy results in the study population.*

	Group A (etanercept 50mg BIW)	**Group B** (etanercept 100mg OW)
Baseline parameters (mean± SD)		
PASI	17.8 ± 7.8	18.35 ± 8.5
DLQI	10.3 ± 7.2	10.9 ± 6.4
VAS for pruritus (mm)	49 ± 38	46.5 ± 35
Mean improvement at week 4 *		
PASI	36%	40%
DLQI	41%	39%
VAS for pruritus	43%	46%
Mean improvement at week 12 **		
PASI	74%	76%
DLQI	68%	66%
VAS for pruritus	69%	72%
PASI response rate (%)		
PASI 50 at week 4	29	37
PASI 75 at week 4	8	8
PASI 50 at week 12	74	78
PASI 75 at week 12	54	50

* *change of all parameters from baseline, in each group: $p<0.05$*
** *change of all parameters from baseline, in each group: $p<0.01$*
Comparison of each parameter between the two groups, at baseline, week 4 and week 12: $p>0.05$

confirmed by patient-reported efficacy measures (DLQI and VAS), which showed significant improvement of scores throughout the study period with both regimens at a comparable rate (Table I).

Treatment was well tolerated. Type and frequency of adverse events did not differ between the treatment groups (Table II). AEs, including the sporadic laboratory abnormalities, were of mild to moderate intensity and were not responsible for permanent discontinuation in any case. Five patients (two in group A and three in group B) required temporary withdrawal of treatment due to concurrent infection until its complete recovery. The most frequent AEs were injection site reactions which had a mild intensity in most cases.

DISCUSSION

Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human p75 TNF-receptor linked to the Fc portion of human IgG1. The efficacy and safety of monotherapy with etanercept in plaque psoriasis have been documented by various randomized placebo-controlled trials (4-7). Some of these studies (4, 6) showed the superiority over placebo of etanercept 25mg BIW in psoriatic patients with or without concomitant psoriatic arthritis. Other studies evidenced that a starting dose of 50mg BIW for 12 weeks provided a significantly greater benefit as compared with 25mg BIW, in a dose-dependent manner (5, 7). After the initial 12-week

Table II. *Adverse events in the study population.*

Type	Frequency (%)	
	Group A (etanercept 50mg BIW)	Group B (etanercept 100mg OW)
Injection site reaction	17	21
Upper respiratory infections	14	12
Flu-like syndrome	11	10
Headache	10	11
Injection site ecchymosis	8	9
Paresthesias	8	7
Fatigue	5	6
Gastrointestinal symptoms	4	5
Dizziness	3	2
Ecchymosis (at sites other than injection sites)	1	0
Increase of aminotransferases	1	1
Increase of triglycerides	1	1
Trombocytopenia	1	0

treatment phase with 50mg BIW, a sustained response can be obtained by a sequential maintenance treatment with 25mg BIW (5, 7). On the basis of these evidence-based observations, etanercept has been approved for the treatment of plaque psoriasis at a starting dose of either 25mg BIW or 50mg BIW for up to 12 weeks. Pharmacokinetic and clinical studies have not yet been evaluated alternative etanercept dosing regimens.

In the other approved indications (RA, PA and AS), the recommended dose is 25mg BIW, with the only exception of RA in which 50mg OW administration is also recommended (1). Pharmacokinetic modeling revealed that systemic exposure following 50mg OW dosage regimen was similar to that generated by 25mg BIW (8-9). Clinical data from RA patients indicated an overlap in pharmacokinetics and clinical outcomes between these dosing regimens (10).

The study herein reported has confirmed the efficacy and tolerability of etanercept 50mg BIW in plaque psoriasis and our results are highly consistent with other studies (5, 7, 11). Etanercept provided relevant benefit to psoriatic patients, as demonstrated not only by objective clinical evaluation (PASI) but also from the patient's perspective. In fact, a notable improvement of pruritus and quality of life issues was noted, in accordance with previous results (11).

Our pilot experience assessed, for the first time, the clinical outcome observed after the use of 100mg OW etanercept regimen in patients with plaque psoriasis. Interestingly, the efficacy and tolerability profile of this regimen was comparable to that observed with 50mg BIW. The bioequivalence of these regimens, if further confirmed by controlled studies, can have important practical advantages, as the 100mg OW regimen may favour patient's compliance and adherence to treatment, preserving the effectiveness and tolerability of the standard 50mg BIW regimen. In both regimens of our study 25mg injections were given because, during the study, Enbrel® was supplied only as 25mg vials. The compliance of patients to OW high-dose administration of etanercept can be further improved thanks to the recent availability of 50mg vials.

The study was performed in accordance with Good Clinical Practice and the ethical principles of the Declaration of Helsinki and subsequent amendments.

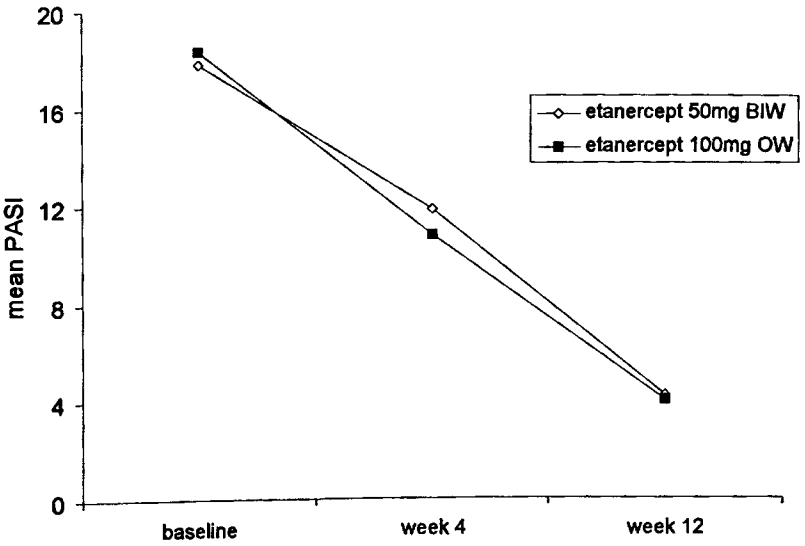

Fig. 1 *PASI variation over the 12-week treatment period with two etanercept dosing regimens. PASI improvement from baseline was statistically significant in each group at both week 4 ($p<0.05$) and week 12 ($p<0.01$). The comparison of PASI values between the two groups gave no significant differences ($p>0.05$) at baseline, week 4 and week 12.*

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REFERENCES

1. **No Authors listed.** 2005. Enbrel®. Package insert.
2. **Fredriksson T. and U. Pettersson.** 1978. Severe psoriasis: Oral therapy with a new retinoid. *Dermatologica 157:238.*
3. **Finlay A.Y. and G.K. Khan.** 1994. Dermatology Life Quality Index (DLQI)- a simple practical measure for routine clinical use. *Clin. Exp. Dermatol. 19:210.*
4. **Mease P.J., B.S. Goffe, J. Metz, A. VanderStoep, B. Finck and D.J. Burge.** 2000. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet 356:385.*
5. **Leonardi C.L., J.L. Powers, R.T. Matheson, B.S. Goffe, R. Zitnik, A.Wang et al; Etanercept Psoriasis Study Group.** 2003. Etanercept as monotherapy in patients with psoriasis. *N. Engl. J. Med. 349:2014.*
6. **Gottlieb A.B., R.T. Matheson, N. Lowe, G.G. Krueger, S. Kang, B.S. Goffe et al.** 2003. A randomized trial of etanercept as monotherapy for psoriasis. *Arch. Dermatol. 139:1627.*
7. **Papp K.A., S. Tyring, M. Lahfa, J. Prinz, C.E. Griffiths, A.M. Nakanishi, et al; Etanercept Psoriasis Study Group.** 2005. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br. J. Dermatol. 152:1304.*
8. **Nestorov I., R. Zitnik and T. Ludden.** 2004. Population pharmacokinetic modeling of subcutaneously administered etanercept in patients with psoriasis. *J. Pharmacokinet. Pharmacodyn. 31:463.*
9. **Zhou H.** 2005. Clinical pharmacokinetics of etanercept: a fully humanized soluble recombinant tumor necrosis factor receptor fusion protein. *J. Clin. Pharmacol. 45:490.*
10. **Keystone E.C., M.H. Schiff, J.M. Kremer, S. Kafka, M. Lovy, T. DeVries et al.** 2004. Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum. 50:353.*
11. **Krueger G.G., R.G. Langley, A.Y. Finlay, C.E. Griffiths, J.M. Woolley, D. Lalla et al.** 2005. Patient-reported outcomes of psoriasis improvement with etanercept therapy: results of a randomized phase III trial. *Br. J. Dermatol. 153:1192.*