A MULTICENTER OPEN-LABEL EXPERIENCE ON THE RESPONSE OF PSORIASIS TO ADALIMUMAB AND EFFECT OF DOSE ESCALATION IN NON-RESPONDERS: THE APHRODITE PROJECT

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There is much evidence to show the efficacy of adalimumab, a human monoclonal antibody targeting tumour necrosis factor-alpha, in the treatment of plaque psoriasis. In this open-label experience, 147 high-need patients suffering from plaque psoriasis, with a mean Psoriasis Area and Severity Index (PASI) of 18.8, and concomitant psoriatic arthritis (PsA) received subcutaneous injections of 40 mg of adalimumab every other week (EOW). This was actually the dosage regimen recommended for PsA, as the drug had not then been approved for psoriasis at the time of the patients' enrolment. At week 12, an improvement of at least 50% of the PASI (PASI-50) was observed in 111 (77%) patients. Continuation of treatment in responders with adalimumab 40 mg EOW led to a sustained response, with the PASI-50 achieved by 97% of patients in the as-treated analysis at week 24 (PASI-75 in 82% and PASI-90 in 45% out of 109 patients who received EOW injections up to week 24). Thirty subjects who failed to attain the PASI-50 response at week 12 were treated with adalimumab 40 mg every week for a further 12 weeks. At week 24, 80% of these patients obtained a PASI-50 response after dose escalation. Tolerability was good in the majority of patients. Only two patients discontinued treatment because of an adverse event (repeated flu-like episodes and a pleuropericarditis of unknown origin, respectively).

Adalimumab is a fully human IgG1 monoclonal antibody that binds with high specificity and affinity to tumor necrosis factor (TNF)-alpha. The drug is currently approved for the treatment of adults with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis (PsA), Crohn's disease, and

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moderate to severe chronic plaque psoriasis. Several randomized controlled trials evaluated the safety and efficacy of adalimumab in both PsA and psoriasis (1-4). These trials documented that adalimumab is effective in improving the articular and cutaneous manifestations of psoriatic disease, as well as the quality of life of affected patients, with a rapid onset of response and sustained effects over ≥ 1-year treatment period. One of these trials, the so called CHAMPION study, which was a multicenter, 16-week, randomized, double-blind double-dummy, placebo-controlled study, compared for the first time a biologic agent (adalimumab) with a traditional systemic drug (methotrexate) in patients with moderate- to-severe chronic plaque psoriasis (4). In this study, adalimumab demonstrated significantly superior efficacy *versus* both placebo and methotrexate.

The aim of this open-label multicenter study is to evaluate the efficacy of adalimumab on plaque psoriasis and the effect of dose escalation in non-responders at week 12. This study was carried out on high-need patients with psoriasis and concomitant PsA, who were resistant and/or intolerant to and/or had a contraindication to other systemic therapies, either conventional or biological.

MATERIALS AND METHODS

Eligible patients included men and women aged 18 to 75 years with active PsA and concomitant moderate-to-severe plaque psoriasis of at least 1-year duration, who failed to respond to, or had a contraindication to, or were intolerant to systemic, traditional or biologic, drugs. In accordance with the European Medicines Agency Efficacy Working Party criteria (5), moderate to severe psoriasis was defined by a Psoriasis Area and Severity Index (PASI) value (6) of 10 or more, and a body surface area (BSA) involvement more than 10%, or alternatively by an affected BSA less than 10% but with lesions localized on visible difficult-to-treat sites (i.e., palmoplantar surfaces). An adequate wash-out period was requested between the start of study assessments and the end of previous psoriasis therapies, and this had to be of at least 2 weeks for topical medications, 4 weeks for non-biologic systemic therapies and phototherapy, and 12 weeks for biologic therapies. Concomitant therapies active on either PsA or psoriasis were not allowed, with the exception of emollients and episodic administration of non-steroidal anti-inflammatory drugs. Patients requiring concomitant strategies to manage skin and/or articular symptoms different from those scheduled in the protocol were considered non-responders and withdrawn from the study analysis.

Relevant exclusion criteria were represented by pregnancy and lactation, any active infection, as well as chronic, latent or recurrent infectious diseases, including latent tuberculosis (TB) or seropositivity against hepatitis B and C viruses. Patients with a history of demyelinating disease, heart failure, lupus erythematosus, immunodeficiencies, cancer or lymphoproliferative disease (other than successfully treated basal cell carcinomas) were also excluded.

Treatment regimen consisted in subcutaneous injections of 40 mg of adalimumab (Humira®, Abbott Laboratories Ltd, UK), provided as pre-filled syringes and administered every other week (EOW). The primary efficacy parameter was the response at week 12 defined as a ≥ 50% improvement in PASI score (PASI-50) relative to week 0. Responders were eligible for continuation of treatment at the same dosage and were followed up for a further 12 weeks. Patients who did not achieve the PASI-50 at week 12 underwent dose escalation to adalimumab 40 mg per week until week 24. Efficacy assessments were performed every 4 weeks through the calculation of both the PASI and BSA affected. At the same visits, patients were asked to assess the severity of their pruritus and pain by means of a visual analog scale (VAS) graded from 0 to 100 mm. Efficacy results were reported also as the proportion of patients attaining a ≥ 75% or ≥ 90% improvement in PASI score (PASI-75 and PASI-90, respectively) at week 12 and week 24 as compared with week 0.

Safety evaluations were conducted through physical examinations, assessment of laboratory investigations, report and monitoring of adverse events (AEs).

Statistical analysis was performed on an intent-to-treat basis. Missing data due to any reason were imputed carrying forward the last assessment available. The change of PASI, BSA involved, and VAS scores from baseline was statistically analyzed using the Wilcoxon signed-ranks test (significance for p values less than 0.05). Safety analyses included all patients who received at least one dose of study medication. Descriptive statistics were provided for demographic, efficacy, and safety parameters.

The study protocol followed the principles of the declaration of Helsinki, and a written informed consent was obtained from each individual.

RESULTS

A total of 147 patients were found to be eligible

Table I. *Demographic and general characteristics of 147 patients treated with adalimumab.*

Men / women - n (%)	76 (52%) / 71 (48%)
Age, mean - yrs	48.6
Age, range - yrs	20-75
Psoriasis duration, mean - yrs	15.2
PsA duration, mean - yrs	7.6
Onset of psoriasis relative to PsA - n (%)	
before	115 (78%)
together	19 (13%)
after	10 (7%)
not known	3 (2%)
PASI, mean (SD)	18.8 (7.6)
BSA affected, mean (SD)	22.1% (16.8)
Pruritus severity score (SD) - mm	45.3 (19.3)
Pain severity score (SD) - mm	39.5 (26.9)

The table reports details of demographic data, duration of psoriasis and psoriatic arthritis (PsA), patients' assessment of symptoms by means of a visual analog scale, as well as psoriasis severity expressed by the Psoriasis Area and Severity Index (PASI) and body surface area (BSA) involvement.

for study entry and received at least one dose of adalimumab. The study population flow-chart is summarized in Fig. 1, whereas Table I reports demographic and general characteristics of patients and their psoriatic disease. Out of the 144 patients who completed treatment regimen at week 12, there were 111 (77%) PASI-50 responders, who were therefore eligible for continuation of treatment at the standard dosage of 40 mg EOW, whereas 33 (23%) patients did not achieve the PASI-50, thus requiring dose escalation. The actual number of patients who entered the second phase of the trial after week 12 was 30 patients among those eligible for dose escalation and 109 in the standard regimen arm, being the remaining patients lost to follow-up or withdrawn for administrative reasons. Over the first 12 weeks of treatment, the majority of patients experienced a relevant and progressive improvement of the mean PASI score and BSA affected, as well as of the severity of symptoms ($p < 0.001$ - Fig. 2). More than half of the responders at week 12 reached the PASI-75 response; in particular, the percentages of patients achieving the PASI-75 and the PASI-90 among the 144 patients evaluated at week 12 were 45% and 12%, respectively (Table II). The response to adalimumab in patients who continued to receive 40 mg EOW (as-treated population) was sustained through week 24. In fact, the majority of patients (97%) treated with the standard dose maintained their PASI-50 response, and in some of them the response to adalimumab appeared to be further improved due to the achievement of the PASI-75 and/or PASI-90

Table II. *Response rates in patients with psoriasis treated with adalimumab.*

Dose of adalimumab and treatment period (total patients, n)	**PASI-50** n(%)	**PASI-75** n(%)	**PASI-90** n(%)
40 mg EOW			
Week 12 (n= 144)	111 (77%)	65 (45%)	17 (12%)
Week 24 (n= 144)	106 (74%)	89 (62%)	49 (34%)
Week 24 (n= 109, 'as-treated' analysis)	106 (97%)	89 (82%)	49 (45%)
40 mg/week			
Week 24 (n= 30, 'as-treated' analysis)	24 (80%)	13 (43%)	7 (23%)

The table reports the PASI-50, -75, and -90 responses observed after treatment with adalimumab 40 mg EOW (n= 144) at week 12 and week 24, as well as the response in non-responders at week 12 who received adalimumab 40 mg every week up to week 24. The results are reported also as the responders' rate in the 'as-treated' populations, e.g, patients who received the standard dose throughout the entire study period (n= 109) or those who underwent dose escalation (n= 30)

responses (Table II). In patients who achieved less than PASI 50 at week 12 and therefore received adalimumab 40 mg per week, dosage escalation was capable of inducing the PASI-50 response in 80% of them, with PASI-75 and PASI-90 response rates in 43% and 23%, respectively (Table II).

Adalimumab therapy was generally well tolerated. AEs were mostly mild or moderate and typically deemed unrelated or probably unrelated to treatment (Table III). The most frequently reported AEs were injection site reactions, which were mild and transient and did not result in premature cessation of treatment. A total of two patients discontinued treatment because of an AE, represented by repeated flu-like episodes in one case, and pleuropericarditis in the other. This last event was also the only serious AE which occurred in the entire case series, and its origin was likely to be viral but was not elucidated. The patient was hospitalized and the event completely resolved after a few weeks of symptomatic treatment. Both patients experienced these AEs during the second trimester of the study period and belonged to the standard treatment regimen, as well as one patient in whom the interruption of treatment was made because of an elective surgery.

DISCUSSION

Adalimumab is approved for the treatment of adults with rheumatoid arthritis, ankylosing spondylitis, PsA, Crohn's disease, and moderate to severe chronic plaque psoriasis, which is the latest recent indication. In rheumatic diseases, including PsA, the recommended dosage of adalimumab is 40 mg administered as a subcutaneous injection EOW, whereas the regimen recently approved for psoriasis treatment consists in the administration of 80 mg at week 0, followed by 40 mg EOW starting at week 1. At the time of conduction of this pilot multicenter experience, adalimumab was approved for the treatment of PsA but not psoriasis, so that the patient population comprised only psoriasis patients with concomitant active PsA, and treatment was performed using the dosage recommended in PsA. Despite the absence of the initial 80-mg induction injection in our experience, our results show that adalimumab is well tolerated and very effective

Table III. *Adverse events reported during the 24-week study period. The table reports the adverse events reported during the study period and the number of patients in whom they occurred (analysis in the safety population consisting of 147 patients).*

Event	Patients (n.)
Injection site reactions	9
Flu-like symptoms	3
Urinary tract infection	3
Upper respiratory tract infection	2
Increase of transaminases	2
Increase of blood triglycerides	2
Thrombocytosis	2
Arthralgias	2
Gingivitis	2
Urticarial rash	2
Muscle cramps	1
Asthenia	1
Back pain	1
Headache	1
Pleuropericarditis	1
Hyperglycemia	1

in improving psoriasis and related symptoms, in agreement with the results of previous controlled trials (2-4, 7-8). Treatment with adalimumab 40 mg EOW provided a PASI-50 response rate at week 12 of 77%, and displayed a sustained and/or incremental efficacy in the majority of responders under continuous treatment up to week 24. Interestingly, patients who did not attain response at week 12 did so after treatment with adalimumab 40 mg every week for a further 12 weeks. In fact, 80% of the patients who underwent dose escalation reached the PASI-50 at week 24.

Treatment with adalimumab at 40 mg every week is not recommended in psoriasis; instead such an increase of dosing frequency is indicated in patients with either rheumatoid arthritis, not taking concomitant methotrexate, or Crohn's disease who experienced a reduced response during maintenance treatment. The efficacy and safety of monotherapy with adalimumab 40 mg per week were previously evaluated in an open-label study in 30 psoriasis and PsA patients who were resistant or intolerant to other biologics (9), and in a phase II dose-ranging randomized controlled study (2). The phase II study also evaluated the effect of dose escalation in patients in the placebo/EOW and EOW groups (18 and 12 patients, respectively) who had less than PASI-50 in the open-label phase from week 25 to week 60. At week 60, 40% of these patients obtained the PASI-50 response (2), although there was no detailed information on the duration of dose escalation in this patient series. In clinical practice, patients treated with anti-TNF therapies, especially anti-TNF antibodies, may require dose escalation to obtain additional benefit and/or to counteract a reduced level of response during maintenance treatment (10-11). Despite the absence of systematic and prospective studies, the available evidence suggests that dose escalation can be successful in many of these patients. Reasons for the need of increased doses of anti-TNF drugs to maintain or sustain response in some patients are not known (12-13). Non-response to anti-TNF monoclonal antibodies has been related to lower serum drug concentrations, as well as to high concentrations of neutralizing antibodies directed against the drug. Of note, restoration of clinical response after the increase of dosing frequency in patients who were previously non-responders to adalimumab was associated with the disappearance of anti-adalimumab antibodies (14).

In conclusion, our results confirm the available data about efficacy and tolerability of adalimumab for psoriasis, highlighting the possibility of increasing efficacy through dose escalation, which can be successful even in patients who failed to

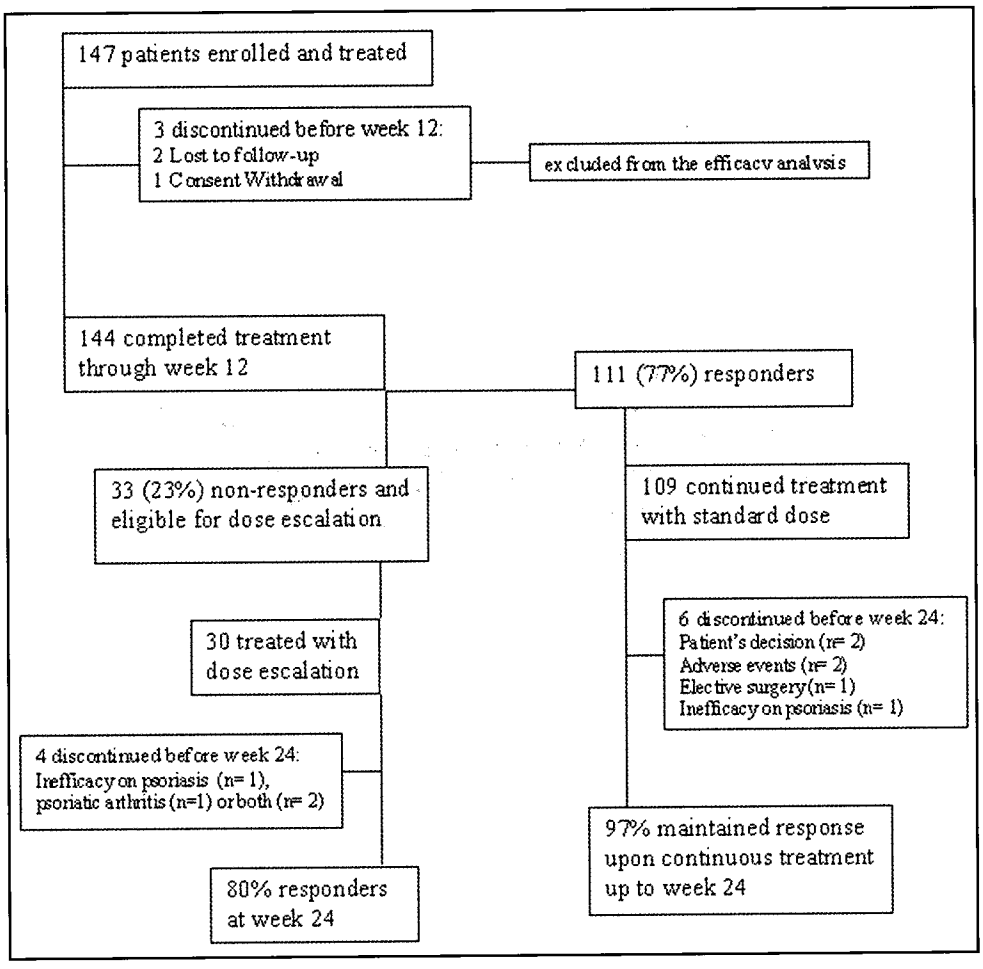

Fig. 1. *Study profile. Patients' disposition at the baseline and throughout the study period, as well as the rate of responders (defined as patients attaining the PASI-50) are shown. Out of 144 patients treated with adalimumab 40 mg EOW for 12 weeks, the PASI-50 response was observed in 111 (77%). Among patients who continued to be treated with the standard dose regimen, 97% maintained the PASI-50 response at week 24. Thirty subjects who were non-responders at week 12 received adalimumab 40 mg every week and 80% achieved response at week 24.*

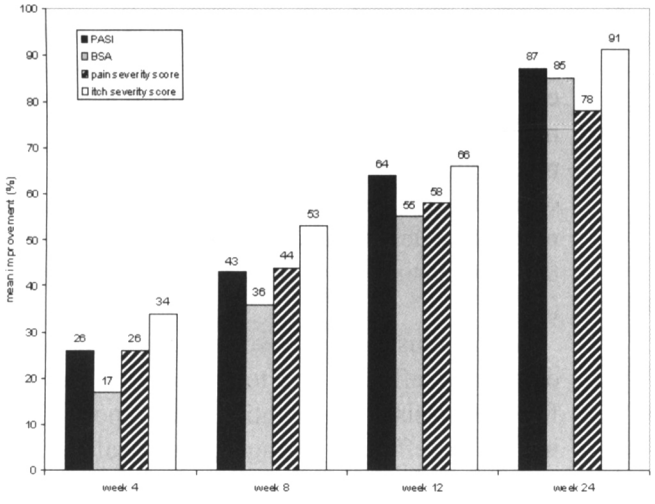

Fig. 2. *Mean percentage improvement of efficacy parameters with adalimumab 40 mg EOW over the study period. Adalimumab at a dosage of 40 mg EOW caused a statistically significant reduction of the mean PASI and BSA affected, as well as of the severity scores for pain and pruritus. All 147 patients received adalimumab 40 mg EOW up to week 12, whereas week 24 results refer only to the 109 PASI-50 responders who continued the standard dosage administration. $p < 0.001$ for each parameter during the entire treatment period as compared to week 0, as well as for the comparison of parameters at week 24 vs week12.*

respond to standard dosages.

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