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Research

# Post Marketing Surveillance Study to Assess Safety and Efficacy of Cyclosporine Micro-Emulsion (Neoral®) Treatment in Psoriasis Patients

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**Key Words:** Psoriasis; cyclosporine micro-emulsion; safety; efficacy; PASI, DLQI

## Abstract

**Background:** To assess efficacy and safety of Cyclosporine micro-emulsion (Neoral®) in psoriasis treatment

**Material and Methods:** A total of 102 patients (mean age: 42.1 ± 11.2; 51.0% were males) who were considered appropriate for Cyclosporine micro-emulsion (Neoral®) treatment by study investigators were enrolled in this multicentre post marketing surveillance study (COLO400CTR05) at 2 different centers in Turkey between September 2005 – June 2009. Data were collected at a total of 17 visits in 12 months for each patient. Efficacy was evaluated in terms of PASI and DLQI scores, while alteration in blood pressure and serum creatinine levels together with adverse events were recorded to evaluate safety during follow up.

**Results:** Of 102 patients 87.3% completed the 3rd month visit. Psoriasis vulgaris was the leading diagnosis (90.2%) and the average duration of psoriasis was 15.2±8.6 years. When compared to values obtained in the last visit, a significant but steady decline was observed in PASI as well as DLQI scores at each consecutive visit performed during the course of the study ($p<0.05$ for PASI scores and $p<0.001$ for DLQI scores). Relapse was identified in 8.8% of patients. Adverse events were reported to be mild in 60.0% of patients while the relation of adverse events to the study medication was considered to be suspicious in 86.0% of cases.

**Conclusion:** In conclusion, offering steady state and graduated resolution of extent and severity of disease and positive impact on quality of life, cyclosporine therapy in micro-emulsion form seems to be associated with low relapse rate as well as high patient compliance in severe psoriasis treatment for up to 12 months of follow up performed in accordance with therapeutic guidelines.

## Introduction

Since the approval of micro-emulsion formulation (Neoral) which is more bioavailable than original formulation, cyclosporine remains an invaluable therapeutic options for psoriasis both inducing remission and in maintenance therapy [**1, 2, 3**].

Safe and effective use of cyclosporine requires judicial patient selection and careful monitoring, but can lead to considerable and significant improvement in poor quality of life [**4**] resulting from loss of self-confidence and concerns over physical appearance associated with the course of the disease as well as feeling highly stigmatized [**5**].

However, psoriasis is a chronic skin condition that often requires long-term therapy to control disease symptoms [**6**] and the severity of psoriasis and lack of response to other modalities often necessitates longer periods of therapy than recommended in published guidelines [**4**]. Whilst approved to be effective and safe alternative for psoriasis treatment when administered for 12 weeks in a short term [**7**], long-term continuous cyclosporine monotherapy has been reported to be associated with increased risk of renal dysfunction and hypertension in psoriasis patients [**8**]. In this regard, long-term management of psoriasis unresponsive to topical therapy is a challenge for the dermatologist in relation to such side effects that must be considered prior to the commencement of therapy and the lack of guidance regarding the appropriate and effective use of cyclosporine in the treatment of severe psoriasis [**3**].

While most studies evaluating treatment modalities in psoriasis focus on short-term alleviation of symptoms, limited data are available on the efficacy and tolerability of systemic psoriasis treatment in the long term [**6**].

In this regard, owing to lack of essential data concerning efficacy and tolerability of cyclosporine micro-emulsion (Neoral®) in the treatment of severe psoriasis patients in Turkey, the present study was designed to assess the efficacy and safety of Cyclosporine micro-emulsion (Neoral®) in the management of severe psoriasis during 12-month follow up.

## Materials and Methods

### *Subject Population*

A total of 102 patients (mean age: 42.1 ± 11.2) including 52 males (51.0%) and 50 females (49.0%) who were considered appropriate for Cyclosporine micro-emulsion (Neoral®) treatment by study investigators were enrolled in this multicentre post marketing surveillance study (COLO400CTR05) conducted at 2 different centers in Turkey between September 2005 – June 2009. Data were collected at a total of 17 visits in 12 months for each patient.

Since this is a post marketing surveillance study, a treatment has not been specified as well as no invasive procedure has been established. Cyclosporine micro-emulsion (Neoral®) and other drugs were administered in accordance with the licensed prospectus as prescribed by their doctors. Data on efficacy and safety parameters were collected in regular time intervals spread over 12 months in the routine clinical practice.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was approved by the institutional ethics committee and conducted in accordance with ethical principles stated in the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (ICH/GCP), with applicable local regulations, and the Declaration of Helsinki.

### *Cyclosporine Micro-emulsion (Neoral®) Treatment*

Cyclosporine micro-emulsion (Neoral®) formulation was initially given at a dose of 2.5 mg/kg per day in two divided doses. This dosage could be increased by increments of 0.5 to 1.0 mg/kg per day up to a maximum of 5 mg/kg per day to achieve satisfactory clinical response. This was defined as 75% improvement in surface area. Dosage reductions were allowed, in accordance with established guidelines, if creatinine concentrations rose more than 30% above baseline, or in the event of hypertension. New-onset hypertension was defined as a systolic blood pressure of at least 160 mm Hg or a diastolic blood pressure of at least 95 mm Hg on two or more occasions; severe hypertension was defined as systolic blood pressure of at least 200 mm Hg or diastolic blood pressure of at least 110 mm Hg on two or more occasions. Treatment was continued until clearance of psoriasis, defined as 90% or more reduction in the area affected, or for a maximum of 12 weeks [**6**].

### *Assessments Performed During Study Visit*

Data on efficacy associated with Psoriasis area Severity Index (PASI) and Dermatology Life Quality Index (DLQI) scores in accordance with the flow chart of the study are given in **Table 1**. Medical background, PASI and DLQI scores, basal serum creatinine levels (the average of 3 consecutive measurements in 3 different days) were recorded in the first visit at the beginning of the treatment. In the consecutive visits, side effect/ adverse events were also recorded besides PASI and DLQI scores. Blood pressure and serum creatinine levels were recorded if differed with respect to previous visit. Relapse rate and related PASI score were also recorded for the visits following the treatment discontinuation.

Psoriasis Area and Severity Index (PASI), a global rating that incorporates both the surface area and the severity index, 14 was computed for each patient in a scale of 0 to 4 with composite score ranged from 0 to 72 [**6**].

A specific copyrighted index, the Dermatology Life Quality Index (DLQI) [**9**] was used to assess the impact of psoriasis and treatment on the patients' quality of life. This questionnaire evaluates the im-

**Table 1.** Study Flow Chart

| | Baseline visit | Visits performed during treament | Visits performed after treatment discontinuation |
|---|---|---|---|
| Study week | 0 | 2-52th weeks (Visits 1-17) | |
| Patient's history | ✔ | ✔ | ✔ |
| Patient's general appearence | ✔ | ✔ | |
| PASI score | ✔ | ✔ | |
| Quality of life index | ✔ | ✔ | |
| Record of adverse events | | ✔ | |
| Blood pressure measurement | ✔ | ✔ | |
| Serum creatinine values | ✔ | ✔ | |
| Relapse evaluation | | | ✔ |

pact of psoriasis on 6 main subjects: symptoms and feelings, daily activities, leisure, work or school, personal relationship, and treatment. The self administered questionnaire was completed at the beginning and end of each treatment period [**6**].

Efficacy was evaluated in terms of PASI and DLQI scores as well as relapse rate, while the alteration in blood pressure and serum creatinine levels as well as adverse events occurred during the study whether or not related to the study medication were the main safety parameters.

### *Statistical Analyses*

Statistical analysis was made using software (version 13.0, SPSS Inc. Chicago, IL, USA). The efficacy of treatment during the course of study was analyzed via Single track variance analyses (ANOVA) of DLQI or PASI scores. Efficacy and safety parameters were summarized using descriptive statistics. Data were expressed as "mean ± standard deviation (SD)" and percent (%) where appropriate. $p<0.05$ was considered statistically significant.

**Table 2 .** Patient Flow and Basic Clinical Characteristics Related to Psoriasis Diagnosis

| | |
|---|---|
| **Enrolled n (%)** | 102 (100.0) |
| Completed | 69 (67,6) |
| Dropped out | 33 (32,4) |
| Side effect | 10 (9,8) |
| Abnormal laboratory findings | 2 (2,0) |
| Treatment fialure | 0 (0,0) |
| In case of medical condition of the patient not requiring treatment anymore | 9 (8,8) |
| Patient not to come for the visits | 10 (9,8) |
| Other | 2 (2,0) |
| **Psoriasis profile n (%)** | |
| Vulgaris | 92 (90,2) |
| Erythrodermic | 3 (2,9) |
| Hairy skin | 3 (2,9) |
| Guttat | 2 (2,0) |
| Palmoplantar | 1 (1,0) |
| Unknown | 1 (1,0) |
| **Psoriatic arthritis n (%)** | |
| Yes | 6 (5,9) |
| No | 96 (94,1) |
| **Duration of psoriasis (years; mean±SD)** | 15,2±8,6 |
| **Consanguinity n(%)** | |
| Present | 14 (13,7) |
| Absent | 88 86,3) |

## Results

### *Demographics and Baseline Clinical Characteristics*

A total of 102 patients (51.0% were male) were enrolled in this study; and 67.6% of them completed the study, while 33 patients discontinued because of lost to follow-up (n=10), adverse events (n=10), patient's need for medication no longer existed (n=9), and other reasons (n=4).

According to psoriasis profile of the enrolled patients (n=102) given in **Table 2**, psoriasis vulgaris was the leading diagnosis (90.2%) followed by erythrodermic psoriasis (2.0%). Psoriatic arthritis was evident in 5.9% of patients and the average duration of psoriasis was 15.2±8.6 years. Lack of consanguinity was evident in 86.3% of study population (**Table 2**).

### *Efficacy evaluations*

**Table 3** shows the alteration in average PASI and DLQI scores of the patients who completed first 3 months (7 visits) of the follow up. When compared to values obtained in the last visit, a significant but steady decline was observed in PASI and DLQI scores in each consecutive visit performed during the course of the study ($p<0.05$ for PASI scores and $p<0.001$ for DLQI scores; **Figure 1**).

**Table 3 .** Average PASI and DLQI Scores of Patients who Completed First 7 Visits of Follow up

| Visit | n | PASI Score | DLQI Score |
|---|---|---|---|
| Baseline (visit 0) | 102 | 14.5±7.8 | 15.6±5.6 |
| 15th day (visit 2) | 99 | 10.8±5.1* | - |
| 1st month (visit 3) | 96 | 8.0±5.2*,q | 10.0±4.9**,qq |
| 2nd month (visit 5) | 91 | 4.6±4.1*,+,q | 5.8±5.1**,qq |
| 3rd month (visit 7) | 88 | 3.1±2.9*,+,q,w | 3.6±3.7**,qq,w |

p<0.05 and **p<0.001; compared to baseline scores
q p<0.05 and qq p<0.001; compared to 15th day scores
+ p<0.05 and ++p<0.001; compared to first month scores
w p<0.05; compared to second month scores

Relapse was identified in 11 patients (8.8%) and the total number of visits with relapse was determined to be 21. Average PASI score obtained at the time of relapse was 6.14±5.3.

### *Safety Evaluations*

There was no significant difference in blood pressure and serum creatinine levels during cyclosporine treatment. Data on adverse event profile, relation to study medication and precautions taken are given in Table 4. Accordingly, a total of 50 adverse events were reported in 31 patients. In total, 6.0% of adverse events were reported to be severe while 34.0% were moderate and 60.0% were mild. The relation of adverse events to the study medication was considered to be suspicious in 86.0% of cases. Dose adjustment (46.0%), add-on treatment (22.0%) and non-drug treatment (10.0%) were the main precautions taken for adverse events while, no precautions were taken in 12.0% of cases (**Table 4**).

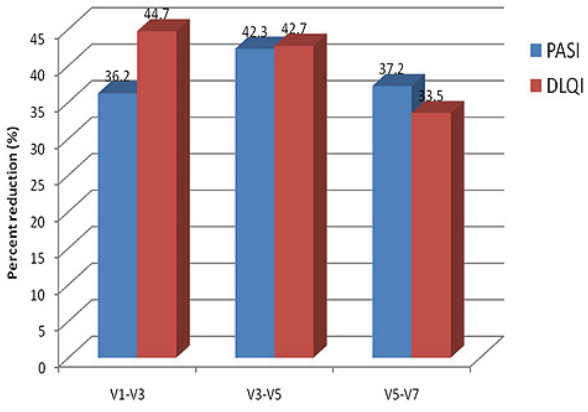


**Figure 1.** Percent reduction in PSAI and DLQI scores during study visits

**Table 4 .** Intensity, Causality and Management of Adverse Events (50 Adverse Events in 31 Patients)

| **Intensity** | **n(%)** |
|---|---|
| Mild | 30 (60,0) |
| Moderate | 17 (34,0) |
| Severe | 3 (6,0) |
| **Causality (relation to study medication)** | **n(%)** |
| Suspicious | 43 (86,0) |
| Non-suspicious | 7 (14,0) |
| **Precautions taken** | **n(%)** |
| Dose adjustment | 23 (46,0) |
| Add on treatment | 11 (22,0) |
| Non-drug treatment | 5 (10,0) |
| No precautions | 6 (12,0) |
| Unknown | 5 (10,0) |

Most frequently reported adverse events were "hypertension" (30.0%) and hypertrichosis (16.0%). No serious adverse event was observed.

## Discussion

Indicated for the treatment of severe, recalcitrant, plaque psoriasis in immune-competent adults [**10**], adequate doses of systemic cyclosporine have been consistently reported to yield an impressive response in psoriasis [**11, 12, 13**] even in such cases that cannot be controlled by any other therapy [**10**]. Since psoriasis has been considered to act by limiting the extent and severity of clinical lesions as well as leading significant morbidity disturbing life quality, concomitant evaluation of clinical outcome and DLQI in psoriasis patients enables integrated view of the extent and severity of the disease [**6, 14, 15**].

Indeed, amongst the current options in psoriasis treatment, cyclosporine in micro-emulsion form has been considered as such a therapeutic agent effective in achieving disease control and remission, enhancing life quality with relatively safe and well tolerated profile [**16**].

Accordingly, our findings indicating efficacy of Cyclosporine micro-emulsion (Neoral®) therapy in patients with severe psoriasis with respect to significant improvement obtained in PASI and DLQI scores starting from the first month and leading remission by the 3rd month of follow up are in agreement with the results of the previous randomized controlled trials that have established cyclosporine as an agent rapidly effective in achieving control of psoriasis, inducing remission and impro-

ving quality of life [**3, 16**]. Indeed, this success has been reported to be specific to microemulsion formulation both in its magnitude and consistency when compared to original cyclosporin formulation [**15**].

In contrast to sharp improvements in life quality (76-91%) and PASI (91%) scores reported by intermittent short-course cyclosporine therapy in the past studies [**15, 16**], a 36.2% improvement in PASI scores together with 44.7% improvement obtained in DLQI scores in the first month of follow up in our population seem to be a milder and "*tarde sed tute*" in nature. In fact, early but steady state improvement in PASI and DLQI associated with sustained remission in our population correlates with the sustained remission reported in some patients after only one course of cyclosporine therapy in PISCES (The Psoriasis Intermittent Short Course of Efficacy of Sandimmun Neoral) study [**17**].

As a matter of fact, since cyclosporine cannot be used indefinitely, the relapse time of which was documented to be short after discontinuation is inevitable [**17**]. Fortunately, on discontinuation, patients relapse in a time-dependent manner but worsening beyond the baseline is uncommon [**10**].

In this regard, when compared to past reports indicating relapse in 55% of subjects in 4 months and 69% of them in 6 months after stopping treatment [**16**], much lower relapse rate obtained in our population enclosing less than 10% of patients may be associated with this "tarde sed tute" nature of improvement obtained in the clinical status and life quality.

Accordingly, low relapse rate associated with steady state and gradual decline in PASI and DLQI scores in our population may indicate the lesser likelihood of overlapping treatments during cyclosporine therapy is being tapered off to avoid relapse to pretreatment levels of disease activity. Nevertheless, based on the likelihood of altered relapse rates for longer duration of follow up, essentiality of a new treatment that has been suggested in the literature to be added on or shortly before discontinuing cyclosporine therapy cannot be disregarded [**4**].

In correlation to well documented and dose-dependent long-term side effects of cyclosporine treatment including decreased renal function and hypertension both of which are somewhat reversible with a decrease in dose or discontinuation of cyclosporine, [**10**] hypertension was the most commonly encountered adverse event in our population where 86.0% of adverse events were identified to be causally related to study medication and dose adjustment was applied in 46% of the events.

Indeed, tailoring of therapy to the needs of the individual patient has been considered as the fundamental point of cyclosporine use in the treatment of psoriasis according to patient management protocols established for the use of cyclosporine in psoriasis [**16**]. Besides, the side-effect profile of cyclosporine therapy has been well known and considered to be predictable and manageable with adherence to treatment guidelines that have been indicated to reduce the risk of adverse events in a significant manner [**11, 18**]. Hence, lack of significant impairment in renal functions as well as blood pressure regulation among our subjects may indicate the achievement of risk control and correction per individual via proper screening, appropriate dosage and regular monitoring in the clinical practice [**16**].

In conclusion, offering steady state and graduated resolution of extent and severity of disease and positive impact on quality of life, cyclosporine therapy in micro-emulsion form seems to be associated with low relapse rate as well as high patient compliance in severe psoriasis treatment for up to 12 months of follow up performed in accordance with therapeutic guidelines.

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