# Ciclosporin Microemulsion for Severe Atopic Dermatitis: Experience on Adolescents and Adults in Hong Kong

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**ABSTRACT**

*Ciclosporin microemulsion (Sandimmun Neoral®) is an oral formulation of ciclosporin with more consistent intestinal absorption. In this prospective, open study, ciclosporin microemulsion was used to manage adolescent and adult patients with severe refractory atopic dermatitis. Twenty-five patients participated (age range 12-34). Ciclosporin microemulsion was started at 3 mg/kg/day, slowly stepping up to a maximum of 5 mg/kg/day according to the response of the individual patient. The duration of treatment was 12 weeks with a further eight weeks of follow up. Ciclosporin microemulsion was found to be fast acting and effective in our patients: disease severity score decreased by 63%; extent of disease score decreased by 46%; pruritus score decreased by 77%. We concluded that ciclosporin microemulsion used as short course treatment was an effective therapy for severe refractory atopic dermatitis in adolescents and adults with acceptable side effects.*

**Keywords:** Atopic dermatitis, ciclosporin

## INTRODUCTION

Ciclosporin is a potent immuno-modulatory drug which, in the recent years, has been introduced as a treatment for various dermatoses.

Van Joost et al in 1987 first reported their successful use of ciclosporin in severe atopic dermatitis.[1] Thereafter, many studies reported success in using low dose (2.5-5 mg/kg/day) ciclosporin in treating severe atopic dermatitis.[2] These studies used traditional formulation of ciclosporin (Sandimmun® soft gelatin capsules). This preparation has highly variable bioavailability, ranging from 10% to 60%, leading to problems like discordance of dose-effects relation and difficulties in dose adjustment.

Ciclosporin microemulsion (Sandimmun Neoral®)[3] is an oral formulation characterized by better and more consistent absorption from the gastro-intestinal tract and hence more predictable pharmacokinetic properties. It has been shown that ciclosporin microemulsion absorption is largely independent of food, diurnal rhythm and bile flow. This enables greater ease in individualizing dosage and maintaining ciclosporin concentration in the therapeutic window.

In the present study, we used ciclosporin microemulsion (Sandimmun Neoral®) in adolescents and adults with severe refractory atopic dermatitis. This study was designed to determine (a) whether short course ciclosporin microemulsion is effective in such patients, (b) the safety and tolerability of ciclosporin microemulsion (c) the maintenance of effects after discontinuation of this medication.

## METHODS

This was a prospective open multi-centers study done in three government dermatological clinics in Hong Kong, namely Yaumatei, Chaiwan, and Yung Fung Shee Dermatology Clinics. The study was developed to ensure adherence to Good Clinical Practice (GCP). Consents were obtained from all patients. The same investigator throughout the study made all clinical assessments for each individual patient.

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## Patient selection

Adolescents or adults of either sex with severe atopic dermatitis who fulfilled the diagnostic criteria of Hanifin and Rajka, and were refractory to conventional therapy, will be treated with ciclosporin microemulsion for 12 weeks. Inclusion and exclusion criterions were listed in Table 1.

## Study protocol

Following a two-week washout period (or four weeks if receiving systemic therapy, for example PUVA, cytotoxic drugs, or systemic corticosteroids), patients started receiving ciclosporin microemulsion. The maximum duration was 12 weeks followed by eight weeks follow-up period to assess the maintenance of effects.

The commencing dose of ciclosporin microemulsion was 3.0 mg/kg/day, given in two equally divided doses to be taken at 12-hour-intervals. Doses were increased by 1 mg/kg/day at each visit according to the clinical response and side effects in the first eight weeks. On achieving total clearance of disease or after a maximum of eight weeks, ciclosporin microemulsion dose will decrease by half for a further four weeks and then stopped.

Patients were allowed to continue the same topical treatments and oral antihistamines that they had been using before throughout the washout and study period. They were instructed to adjust the use of topical treatments according to their subjective clinical improvement.

Ciclosporin microemulsion dose was reduced by 0.5-1 mg/kg/day in the following circumstances: significant rise of serum creatinine (>30% baseline); rise in serum potassium above upper limit of normal laboratory range; 100% or above increase of serum bilirubin or liver enzymes above baseline or twice the upper limit of normal laboratory range; confirmed hypertension (diastolic pressure >95 mmHg, systolic pressure >160 mmHg) despite hypertensive therapy.[4]

Ciclosporin microemulsion would be discontinued in case of: sustained raise of serum creatinine >30% baseline or other laboratory parameter or hypertension despite of dose reduction; any serious adverse events believed to be drug related; pregnant during treatment; poor compliance; or patient wished to leave the study.

A total of seven visits were arranged for each patient: in week -2, 0, 2, 4, 8, 12, 20. Frequency of visits would be increased in case of adverse events.

## Efficacy evaluation

An Extent of Disease Score (EDS) was used to assess the area of involvement. Body surface was divided into eight areas according to the rule-of-nine used in burn patient assessment: head & neck (1), upper limbs (2, 3), lower limbs (4, 5), front & back of trunk (6, 7), genital (8). Each area was assessed for whether 0, 1/3, 2/3 or the whole area was involved. Hence EDS= (Fractions of involvement of area 1, 2, 3) × 9 + (Fractions of involvement of area 4, 5, 6, 7) × 18 + Fraction of involvement of area 8. A Disease Severity Score (DSS) employing the six signs: erythema, edema, oozing, excoriation, lichenification and dryness were used to give scores to each of the eight areas as in EDS on a scale of 0-3 (0=none, 1=mild, 2=moderate, 3=severe) EDS= summation of score of the eight areas.

**Table 1. Inclusion and exclusion criteria**

| Inclusion criteria | Exclusion criteria |
|---|---|
| Both sex age 12-65 | Systemic therapy with corticosteroid, cytoxic drug, PUVA within |
| Written consent | four weeks of entry to study |
| Refractory atopic dermatitis | Impaired renal function |
| Satisfy diagnostic criteria for atopic dermatitis | Impaired liver function |
| | Hypertension |
| | History or presence of malignancy |
| | Hyperkalaemia, hyperuricaemia |
| | Clinical major coexisting diseases |
| | Concomitant treatment with nephrotoxic drug |
| | Pregnancy |
| | Uncooperative patient |

The symptoms like pruritus and sleep-loss were recorded using a 10-point linear scale. Quality of life evaluation was assessed with a simple 10-question questionnaire, each question with 4-point scale. It was done at week-0 and week-8. All the topical medication was brought back at each visit to the investigators to be weighed and recorded. Global evaluations of efficacy were done by the investigators in week-8 and week-20.

### Safety evaluation

Vital signs including blood pressure, serum creatinine, urinalysis and blood biochemistry was evaluated regularly during the study. Patients were questioned and examined for adverse effects. All adverse events were recorded at each visit.

### Statistical analysis

Comparisons of baseline (week-0) with end of treatment (week-12) and end of follow-up (week-20) for extent (EDS), severity (DSS), symptoms, and blood pressure were performed using Wilcoxon tests or paired t-tests.

**Table 2. Baseline characteristics**

| | |
|---|---|
| Total number recruited | 26 |
| Withdrawn | 1 |
| Male:Female | 20:6 |
| Age range | 12-34 |
| 12-19 | 12 |
| 20-29 | 11 |
| 30 or above | 3 |
| mean | 5.3 |

## RESULTS

### Baseline characteristics

A total of 26 patients were recruited. All except one finished the study. Half of the patients were adolescents and the other half were young adults. Most of them were male. The baseline characteristics are shown in Table 2.

### Efficacy

The mean disease severity score is shown in Figure 1. The mean disease severity decreased rapidly from 61 at baseline (SEM 3.0, n=25) to 23 (SEM 2.07, n=25) at the end of treatment period (63% decrease, $P< 0.001$). At the end of the follow-up period, the disease severity score was 35 (SEM 3.9, n=25), still significantly lower than that of baseline (56% baseline, $P<0.001$).

One patient reached remission during the treatment period, which is defined as improvement of disease severity score for more than 90%. On the other hand two patient out of 25 failed to response satisfactorily to ciclosporin microemulsion during the 12 weeks treatment. Failure of response is defined as improvement of DSS less than 30%.

The mean extent of disease score is shown in Figure 2. The mean extent of disease decreased rapidly from 61% at baseline (SEM 4.2, n=25) to 32%(SEM 2.27, n=25) at the end of treatment period (46% improvement, $P<0.001$). At the end of the follow-up period, the mean extent of disease was 41% (SEM 4.6, n=25) still significantly lower than that of baseline (67% baseline, $P<0.001$).

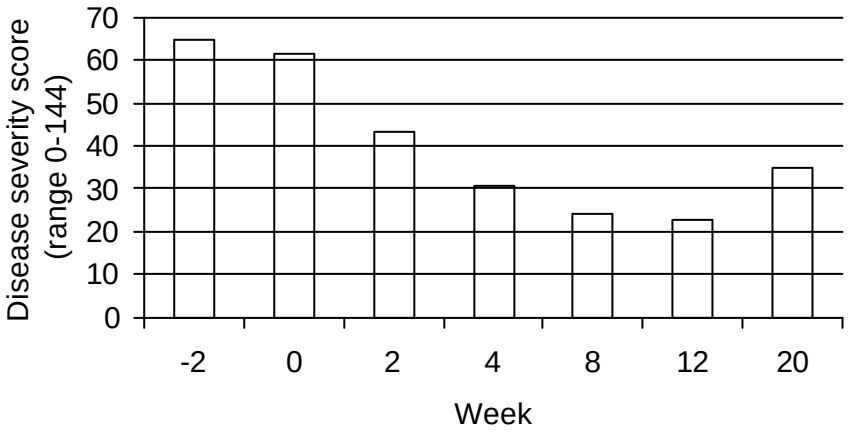


**Figure 1: Disease severity score**

The mean pruritus score decreased rapidly from 6.3 at baseline (SEM 0.29, n=25) to 3.5 (SEM 0.38, n=25) at the end of treatment period (decreased 77%, P<0.001). At the end of the follow-up period, the mean pruritus score was 5. Pruritus was observed to be the earliest and most prominent feature to relapse after stopping ciclosporin microemulsion.

The mean sleep loss score decreased rapidly from 4.9 at baseline (SEM 0.59, n=25) to 2.2 (SEM 0.41, n=25) at the end of treatment period (decreased 77%, P<0.001). At the end of the follow-up period, the mean sleep loss score was 3.4. The mean symptoms score are shown in Figure 3.

The quality of life improvement was shown in Table 3. There was a significant improvement of quality of life after eight weeks of treatment with ciclosporin microemulsion. The mean disability index dropped significantly from 13.4 at baseline (SEM 1.23, n=25) to 7.6 at week 8 (SEM 0.93, n=25) (P<0.001).

Global evaluations were done in week-8 and 20 (Figure 4). At week-8, 21 out of 25 patients were evaluated to have their disease mild or almost cleared. After discontinuation of ciclosporin microemulsion for eight weeks, seven remained mild or almost cleared of disease.

**Table 3. Disability index**

| | Week 0 | Week 8 |
|---|---|---|
| Mean | 13.4 | 7.6 |
| SEM | 1.23 | 0.93 |

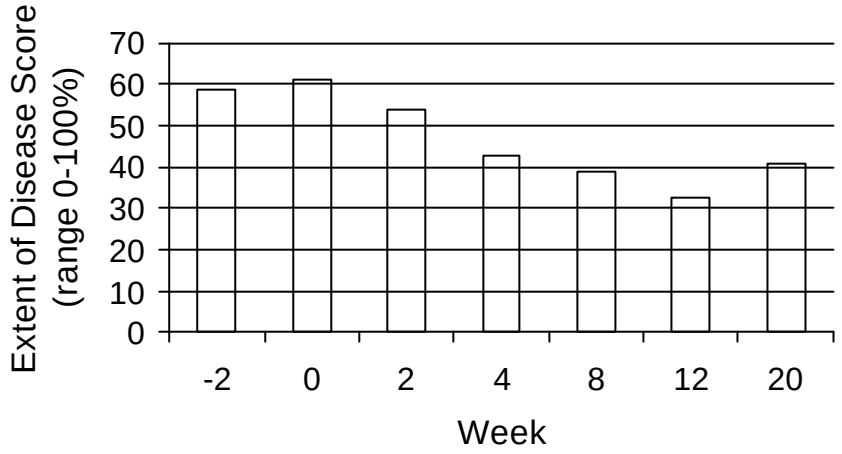


**Figure 2: Extent of disease score**

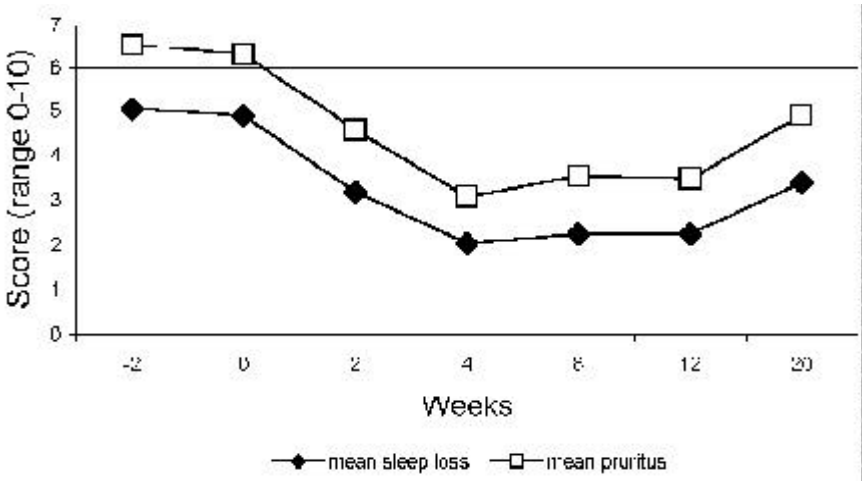


**Figure 3: Symptoms score**

Decrease in topical steroid went parallel with the improvement of clinical condition. Despite of this observation we found topical steroid measurement not a useful parameter for the assessment of severity. The compliance is poor: only 16 out of 25 patients brought back their topical steroids on every visit. The variation of topical steroid use is great between patients with similar scores of severity.

### Follow-up

Six out of 25 patients (24%) relapsed during 2-week post-treatment period, which was defined as an increase of DSS to 70% of baseline or above. Five of these six patients their DSS rose to above 90% baseline. In five out of six of these patients, the EDS also increased to 75% or more of baseline.

### Safety

There was no significant change of blood pressure reported. No patient had their diastolic blood raised above 95 mmHg. One patient out of 25 had his serum creatinine raised above 30% baseline when measured at 8th week, which returned to normal in the dose reduction period. There were no significant changes of other laboratory parameters reported.

The withdrawn patient reported a 125% rise of serum creatinine at week-2; ciclosporin microemulsion was stopped and the creatinine checked on same day was normal, so the previous result was considered as spurious. He did not re-enter the study.

Side effects were reported in four patients and all were considered as mild and acceptable (Table 4). The only major adverse event was skin infection reported in one patient. This was a first episode herpes simplex infection on the face complicated with staphylococcal aureus superinfection. It was quickly controlled with valiciclovir and cloxacillin without reduction of ciclosporin microemulsion dose.

## DISCUSSION

Our study had demonstrated that ciclosporin microemulsion given as short course (12 weeks) low dose (maximum dose 5 mg/kg/day) was a fast acting, effective treatment for severe and refractory atopic dermatitis in adolescents and young adults.

We observed a significant improvement in clinical signs and symptoms during treatment. There was also a significant improvement of quality of life with treatment. This result was in accordance with previous reports using traditional preparation of ciclosporin.[5]

Adverse events were few and mild. One patient had HSV infection, which was easily treated. One patient has raised creatinine that was reversible. None of them had significant raise in blood pressure. The young age of our patients may account for the small side effects reported.

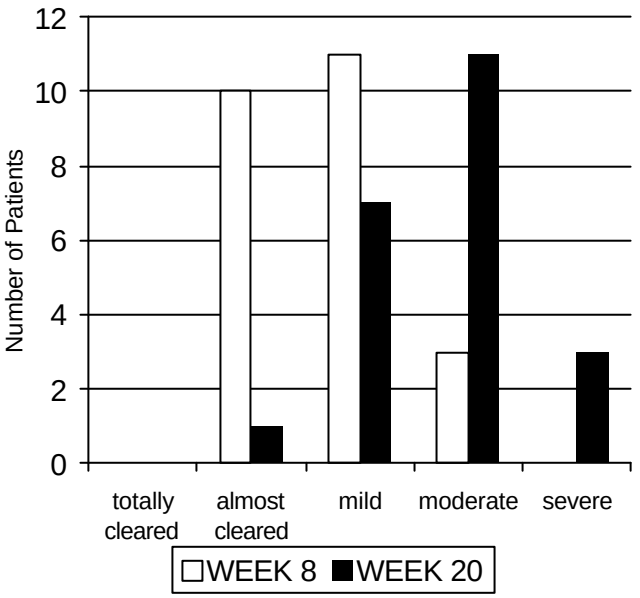


**Figure 4: Global evaluation at week-0 and week-8 (n=25)**

**Table 4. Adverse events reported**

| Nature of adverse events | Outcome | Number |
|---|---|---|
| GI upset while taking ciclosporin | Resolved after ciclosporin finished | 1 |
| Raised of creatinine >130% baseline | One case withdrawn; one case recovered | 2 |
| Gum hypertrophy | Resolved after ciclosporin finished | 1 |
| Hand tremor | Resolved after ciclosporin finished | 1 |
| Skin infection: herpes simplex with impetiginization | Recovered with valiciclovir, ampicillin, cloxacillin | 1 |

Despite of the better gastrointestinal absorption of the micro-emulsion preparation, the safety and adverse effects were comparable with previous study using traditional preparation of ciclosporin. This feature enables mg to mg dose conversion from the traditional preparation to the new micro-emulsion formulation.

Six out 25 patients relapsed during the eight weeks observation. No rebound was observed. In the remaining patients, all clinical parameters increased with cessation of the 12-week's ciclosporin microemulsion treatment. This was similar to the previous reports using short course ciclosporin treatment. Short course ciclosporin cannot give sustained effect for patients with severe atopic dermatitis. In practice, many of the patients will need long term ciclosporin, either intermittently or continuously.

Studies had been published reporting the safety of using ciclosporin on a long-term base.[6,7] Although they found ciclosporin used on a long-term base to be safe and side effects mild and reversible, only a few included renal biopsy as part of their studies. Evidences from ciclosporin used on dermatoses and non-dermatological patients recently had demonstrated irreversible renal damage when ciclosporin were used for over two years.[8,9] There were evidences that renal damage may happen even earlier. The time-course of renal damage is still not well understood and remains to be demonstrated in ongoing studies. For those patients who need long term treatment with ciclosporin, renal clearance should be monitored and renal biopsy should be considered in collaboration with a nephrologist.

There were a number of limitations of our study. This was not a double-blind control trial. The number of patients recruited was small and all of them were young and healthy. These might account for the few number of side effects encountered. Moreover, the course of treatment was short and the follow-time was brief. Nevertheless, our observation using ciclosporin microemulsion on refractory atopic dermatitis confirmed the findings in previous reports using traditional ciclosporin formulation. We concluded that ciclosporin microemulsion used as short course treatment was an effective therapy for severe refractory atopic dermatitis in adolescents and adults. Its side effects were acceptable when weighed against its benefits.

## Acknowledgments

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