

## ORIGINAL ARTICLE

# Clinical, Quality of Life, Patient Adherence, and Safety Outcomes of Short-Course (12 Weeks) Treatment with Cyclosporine in Patients with Severe Psoriasis (the Practice Study)

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**Background:** Apart from clinical outcomes, the “real-world” outcomes of intermittent short-course cyclosporine treatment remain poorly documented. **Objective:** To evaluate various outcomes of short-course cyclosporine treatment for severe psoriasis; and to describe dermatologists’ use of the Rule of Tens. **Methods:** A 12-week pharmacoepidemiological study; 112 evaluable patients recruited by 43 dermatologists. **Results:** The mean initial cyclosporine dose was  $2.88 \pm 0.74$  mg/kg/day. At 12 weeks, 64.3% of patients were continued beyond the study period at mean dose of  $2.51 \pm 0.91$  mg/kg/day. Percent body surface affected, Psoriasis Area Severity Index score, and patient and physician rating of psoriasis severity decreased significantly, while quality of life (QoL) improved significantly. Median patient satisfaction at 12 weeks was 85 (0~100 scale). Patient-reported non-adherence was 43.9% and 56.1%, respectively at both the time points ( $p=0.18$ ). In modeling on logarithmized outcomes variables, living along was consistently the single most important (negative) determinant of therapeutic and pa-

tient outcomes. Safety and tolerance parameters were similar to the ones reported in the literature. Only 7.3% of physicians correctly identified the measures included in the Rule of Tens and the Rule’s criterion for inferring severe psoriasis. **Conclusion:** With adequate monitoring and patient adherence, cyclosporine treatment reduces the severity of severe psoriasis, improves QoL, and is appropriately tolerated; leading to high patient satisfaction. Social support is a key determinant of therapeutic and patient outcomes and patients living along may require clinical attention. The relevance of the Rule of Tens was not evident. (*Ann Dermatol* 25(1) 28~35, 2013)

**-Keywords-**

Cyclosporine, Pharmacoepidemiology, Psoriasis, Treatment outcome

## INTRODUCTION

Psoriasis is a systemic immune-mediated chronic skin disease characterized by raised, well-demarcated, erythematous oval plaques with adherent silvery scales frequently associated with arthritis<sup>1,2</sup>. The prevalence is consistently quoted to be around 2.0%<sup>2</sup>. Psoriasis is considered severe if more than 10% of a patient’s body surface is affected<sup>3,4</sup> or if a patient scores more than 10 on the Psoriasis Area Severity Index<sup>4</sup>. However, there is evidence that this may not adequately reflect the clinical extent of disease<sup>5</sup>. Psoriasis has profound emotional, social, and

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physical impact on patients' quality of life<sup>5-11</sup>. Furthermore, stigmatization may be significant<sup>7,11-13</sup>. Clinicians' assessment of severity of disease often does not match with their patients' evaluation. Overall, these various factors have an impact on patients' adherence to treatment, while also affecting the treatment outcomes in general<sup>14-17</sup>. Finlay proposed the Rule of Tens in which a score exceeding 10 on the Body Surface Area (BSA), Psoriasis Area Severity Index (PASI), and/or the Dermatology Life Quality Index constitutes severe psoriasis<sup>18</sup>.

Intermittent short courses of about 12 weeks of treatment with cyclosporine, in combination with careful monitoring of renal function and blood pressure, is one of the standards of care in the treatment of severe psoriasis<sup>3,6,7,19-22</sup>. Cyclosporine has been shown to rapidly achieve control of psoriasis, induce remission, and improve quality of life<sup>22-29</sup>. However, "real-world" outcomes are affected by a number of factors, many of which remain to be poorly understood. The PRACTICE study was a pharmacoepidemiological study examining, under "real world" conditions, cyclosporine treatment patterns and clinical, quality of life (including patient satisfaction), adherence, and safety outcomes of 12-weeks of cyclosporine treatment, initiated as per the prescribing physician's best clinical judgment, in an evaluable sample of 112 patients with severe psoriasis recruited by 43 dermatologists in Belgium. The study also aimed to describe physicians' use of the Rule of Tens and their assessment of the Rule's usefulness and consistency with clinical impressions.

## MATERIALS AND METHODS

### Design

PRACTICE was designed as a prospective, observational, open-label, multi-site pharmacoepidemiological study with two fixed data points: baseline (initiation of cyclosporine treatment) and follow-up at 12 weeks. Interim visits were optional at the treating physician's discretion. The study was approved by the Ethical Committee of University Hospital of Antwerp (Antwerp, Belgium).

### Patient population

Subjects eligible for participation in the study were adult males and females with severe psoriasis being treated with commercially available cyclosporine microemulsion (Neoral<sup>®</sup>, Novartis, Basel, Switzerland) in accordance with the approved indication approved in Belgium. All subjects provided written informed consent to participate in the study. Excluded were patients previously treated with cyclosporine, patients with renal insufficiency and/or uncontrolled hypertension, patients receiving concomitant

ultraviolet B or PUVA phototherapy, or patients with a medical condition which in the investigator's opinion precluded participation in the study.

A total of 167 patients were enrolled by 57 dermatologists. Of these, 112 subjects treated by 43 physicians completed the study and constituted the evaluable sample. Reasons for attrition included loss to follow-up (n=40), adverse events (n=9), patient withdrawal (n=2), patient relocation (n=2), treatment termination because of satisfactory effect (n=1), and unknown reason (n=1). There were no statistically significant differences on key baseline characteristics between the enrollment and evaluable samples, except that there were proportionately more patients with psoriatic arthritis in the evaluable sample (see also Statistical Analysis section).

### Variables and measurements

This being an observational study, only patient data as available from routine clinical practice were recorded and there were no mandatory assessments or tests. Baseline data included: sociodemographics, history of psoriasis, prior treatments for (severe) psoriasis, current psoriasis status (% of Body Surface Area affected [%BSA], PASI), patient-reported quality of life (Dermatology Life Quality Index [DLQI]), physician and patient rating of psoriasis (0~5), serum creatinine, blood pressure, cyclosporine treatment (reason and dose), comorbidities, concomitant medications, and adherence (Basel Assessment of Adherence Scale [BAAS]; patient and physician perceptions Visual Analog Scale [VAS]). At the 12-week follow-up point, data collected included: current psoriasis status (BSA, PASI), quality of life (DLQI), physician and patient rating of psoriasis (0~5), serum creatinine, blood pressure, cyclosporine treatment, concomitant medications, adherence (BAAS and patient and physician VAS), patient satisfaction (VAS), and safety and tolerance. Data collected at optional interim visits included concomitant treatments, cyclosporine treatment, serum creatinine, blood pressure, and safety and tolerance. Because of high intercorrelations among these variables, a composite nonadherence index was calculated from items 1 through 3 of the BAAS and the inverse of the patient VAS self-rating of adherence; yielding an index from 0 (perfect adherence) to 5 (high nonadherence). The study's complete data model is available from the corresponding author.

### Statistical analysis

Data were analyzed using the SPSS ver. 15 (SPSS Inc., Chicago, IL, USA) and SAS (SAS Institute, Cary, NC, USA) statistical programs. In addition to routine descriptive statistics, changes from baseline to follow-up in clinical, DLQI, and adherence outcomes were assessed using the

Sign test for dependent samples and proportional odds modeling using Generalized Estimating Equations controlling for psoriatic arthritis. Changes in the proportions of nonadherent patients were evaluated by means of the test for dependent proportions. Random-Intercepts Modeling using Restricted Likelihood Estimation controlling for psoriatic arthritis status was used to model outcomes and assess changes in serum creatinine and blood pressure. Blood

pressure control status was examined using McNemar testing. The study was sufficiently powered to detect differences in the primary outcome variables.

## RESULTS

### Patient population

The sample ranged in age from 20 to 85 years (mean:

**Table 1.** Psoriasis history and status at enrollment (\*)

History			
Age (years) at diagnosis of severe psoriasis (range; mean $\pm$ SD; Mdn) (n=106)		1 ~ 82; 34.0 $\pm$ 18.1; 31.0	
Flares in 6 months prior to enrollment (range; mean $\pm$ SD; Mdn) (n=93)		0 ~ 10; 2.25 $\pm$ 1.91; 2.00	
Family history of severe psoriasis (n=XXX) (n=100)	Parent	31.2%	
	Sibling	8.0%	
	Child	3.6%	
	None	46.4%	
Selected prior treatments	Ever received (n=112)	Receiving at enrollment (n=112)	
	Vitamin D analogs	72.3%	48.2%
	Methotrexate	28.6%	17.9%
	Tar	25.0%	0.9%
	Retinoids	30.4%	5.4%
	PUVA	62.5%	9.8%
	UVB	28.6%	8.9%
Number of changes in treatment (range; mean $\pm$ SD; Mdn) (n=98)		0 ~ 10; 2.01 $\pm$ 1.77; 2.00	
Status at enrollment			
Principal type of psoriasis (n=97)	Plaque	70.5%	
	Palmo-plantar	9.8%	
	Guttate	2.7%	
	Erythrodermic	2.7%	
	Inverse	0.9%	
Number of lesions (range; mean $\pm$ SD; Mdn) (n=107)		0 ~ 18; 8.7 $\pm$ 4.2; 9.0	
Location of lesions (multiple locations possible) (n=107)	Elbow	71.4%	
	Lower arm	69.7%	
	Lower leg	67.9%	
	Knee	67.0%	
	Upper leg	66.1%	
	Buttock	63.4%	
	Upper arm	62.5%	
	Back	60.7%	
	Head	55.4%	
	Chest/abdomen	55.4%	
	Back of hand	29.5%	
	Nails	29.5%	
	Face	23.2%	
	Top of foot	22.3%	
	Genitals	22.3%	
	Palm of hand	22.3%	
Sole of foot	21.4%		
Neck	19.6%		
Other	0.9%		
Number of patients with concurrent psoriatic arthritis (n=110)		13	
... of these, number treated with anti-inflammatory agents		5	

SD: standard deviation, Mdn: median. (\*)Missing data not reported, thus totals may not equal 100%.

**Table 2.** Changes in treatment outcomes

	Baseline (0 week)			Follow-up (12 weeks)			Mean (%)	Mdn (%)	P <sub>sign</sub> *	P <sub>GEE</sub> †		
	n	Range	Mean ± SD	Mdn	n	Range					Mean ± SD	Mdn
%BSA affected (0~100)	101	0~90	23.49±21.06	15.50	99	0~55	7.00±9.43	4.00	70.0	74.2	<0.0001	<0.0001
PASI score (0~72)	66	2.4~55.8	15.88±9.15	13.90	61	0~21.3	5.11±5.42	3.00	67.8	78.4	<0.0001	<0.0001
Patient rating of severity of psoriasis (0~5)	108	1~5	4.02±0.88	4.00	103	0~5	1.37±1.23	1.00	65.9	75.0	<0.0001	<0.0001
Physician rating of severity of psoriasis lesions (0~5)	102	2~5	3.60±0.86	4.00	104	0~5	1.39±1.07	1.00	61.4	75.0	<0.0001	<0.0001
DLQI score (0~30)	112	0~27	12.13±5.95	12.00	104	0~29	3.61±5.12	2.00	70.2	83.4	<0.0001	<0.0001
Patient adherence: patient VAS self-rating (0~100)	94	0~100	79.2±22.9	90.00	106	0~100	86.6±18.6	90.00	9.3	0.0	0.0003	<0.0001
Patient adherence: physician VAS rating (0~100)	105	0~100	73.9±25.1	80.00	103	0~100	87.4±20.0	95.00	18.3	18.8	0.0395	0.0021
Patient nonadherence: composite index (0~5)	94	0~5	0.81±1.20	0.19	94	0~4.94	0.58±1.02	0.19	28.4	0.0	0.44	0.18
Patient satisfaction (0~100)		%				%				Δ	P <sub>prop</sub> †	
Patient nonadherence: % of patients per BAAS (n=97)		43.9				56.1				12.2%	0.36	0.32

SD: standard deviation, Mdn: median, %BSA: % of Body Surface Area affected, PASI: Psoriasis Area Severity Index, DLQI: Dermatology Life Quality Index, VAS: Visual Analog Scale, BAAS: Basal Assessment of Adherence Scale. \*Significance level for the Sign test. † Significance level for Generalized Estimating Equations analysis, controlling for psoriatic arthritis status. ‡ Significance level for the test for dependent proportions.

45.0 ± 13.8 years), mostly male (62.1%), with 12th grade or higher education (85.7%), employed (74.3%), and predominantly Caucasian (97.0%). At the start of the study, the majority of patients lived at home with spouse/ partner (73.3%) or relatives (7.6%), but 19.1% lived alone.

Table 1 summarizes patients' psoriasis history and psoriasis status at enrollment. Mean age at which psoriasis was diagnosed was 34.0 ± 18.1 years (range 1 ~ 82); 42.8% had a family member with severe psoriasis. In terms of current disease, 70.7% of patients had the plaque type of psoriasis, on average 8.7 ± 4.2 lesions, mainly on the extremities. Thirteen patients (11.6%) had been diagnosed with psoriatic arthritis. The 93 (83.0%) patients with flares in the six months prior to enrollment had experienced 2.25 ± 1.91 such episodes. The most common prior treatments were vitamin D analogs (72.3%) and PUVA phototherapy (62.5%), though treatment rates were lower at enrollment. On average, patients' treatment regimens had been changed 2.01 ± 1.77 times prior to initiation of cyclosporine treatment.

### Cyclosporine management and outcomes

The reasons for starting patients on cyclosporine included lack of disease control (67.9%), intolerance (9.8%), non-compliance (2.7%), and contra-indication (1.8%), in addition to 3.6% for other nonspecified reasons (14.3% not reported). Initial dosing ranged from 0.50 to 4.38 mg/kg/day (mean 2.88 ± 0.74). At 12-week follow-up, 64.3% of patients were continued on cyclosporine beyond the study period at a mean dose of 2.51 ± 0.91 mg/kg/day, a statistically significant reduction in dose ( $p=0.005$ ).

Only 7.3% of physicians correctly identified the measures included in the Rule of Tens and the Rule's criterion for inferring severe psoriasis. Mean ratings of the usefulness of the Rule of Tens was 31.1 ± 29.5 and mean ratings of the consistency of the Rule with clinical impressions was 49.6 ± 33.7 (0 ~ 100 scale).

As shown in Table 2, all clinical outcomes (%BSA, PASI, patient and physician ratings of severity of psoriasis) decreased significantly from baseline to follow-up both without and with adjustment for psoriatic arthritis status (all  $p < 0.0001$ ). The quality of life (QOL) scores (DLQI) improved significantly ( $p < 0.0001$ ) and the median patient satisfaction at follow-up was 85 on a 100-point scale (mean 76.0 ± 24.4). Patients and physicians perceptions of patients' adherence were higher at follow-up than at baseline ( $p$  ranging from 0.0395 to  $< 0.0001$ ). The percentage of patients reporting nonadherence behavior as per the BAAS increased nominally from 43.9% to 56.1%, but this rise was not statistically significant; and neither was the change observed in the composite nonadherence

index.

Modeling on logarithmized outcome variables revealed that the 19.1% of patients living alone tended to have a higher %BSA and PASI score at follow-up, yet %BSA declined in line with how recently the diagnosis of severe psoriasis was made. Physician ratings of severity of lesions tended to be higher for patients living alone, but were attenuated by how recently the diagnosis of severe psoriasis had been made. Patients' QOL (DLQI) tended to be lower if patients lived alone. It also decreased with each flare experienced in the six months prior to the start of cyclosporine therapy. It was mitigated by how recently the severe psoriasis diagnosis had been made. Patient satisfaction was found to be affected negatively among patients living alone, but was influenced positively by a more recent diagnosis of psoriasis and less flares having been experienced in the six months prior to the start of cyclosporine treatment (Table 3).

**Table 3.** Modelling of treatment outcomes

	Coefficient	SE*	P <sub>coeff</sub> <sup>†</sup>
%Body Surface Area (BSA) affected at 12 weeks (log)			
Intercept	2.087	0.218	<0.0001
Living alone	1.036	0.238	<0.0001
Age at diagnosis of severe psoriasis	-0.020	0.005	0.0002
PASI (log)			
Intercept	1.292	0.146	<0.0001
Living alone	0.942	0.375	0.0168
Physician rating of severity of psoriasis lesions (log)			
Intercept	1.025	0.094	<0.0001
Living alone	0.334	0.110	<0.0037
Age at diagnosis of severe psoriasis	-0.010	0.002	0.0002
DLQI (log)			
Intercept	0.943	0.249	<0.0001
Living alone	1.016	0.226	<0.0001
Age at diagnosis of severe psoriasis	-0.011	0.005	0.0405
Number of flares in six months prior to study	0.142	0.050	0.0064
Patient dissatisfaction with cyclosporine treatment (log of invert of satisfaction)			
Intercept	2.861	0.255	<0.0001
Living alone	0.759	0.233	0.0002
Age at diagnosis of severe psoriasis	-0.022	0.005	0.0003
Number of flares in six months prior to study	0.148	0.051	0.0055

PASI: Psoriasis Area Severity Index, DLQI: Dermatology Life Quality Index. \*Standard error of the coefficient. †Significance of coefficient for Restricted Likelihood Estimation modelling controlling for psoriatic arthritis status.

**Table 4.** Serum creatinine and blood pressure

	Baseline (0 week)			Follow-up (12 weeks)			P <sub>PRIM</sub> *
	n	Range	Mean ± SD	n	Range	Mean ± SD	Mean%
Serum creatinine (mg/dl)	89	0.51 ~ 1.30	0.89 ± 0.16	85	0.48 ~ 1.51	0.94 ± 0.18	0.00001
SBP (mmHg)	66	2.40 ~ 55.80	15.88 ± 9.15	61	0.40 ~ 21.30	5.11 ± 5.42	67.8%
DBP (mmHg)	108	1.00 ~ 5.00	4.02 ± 0.88	103	0.40 ~ 5.00	1.37 ± 1.23	65.9%
% of 112 patients		Normotensive			Normotensive		P <sub>McN</sub> †
Per SBP (<140 mmHg)	112	82.1%		112	70.5%		0.0158
Per DBP (<90 mmHg)	112	84.8%		112	74.1%		0.0285

SD: standard deviation, SBP: systolic blood pressure, DBP: diastolic blood pressure. \*Significance level for Random Intercepts Model controlling for psoriatic arthritis status, †Significance level for McNemar test.

### Safety

Adverse events were reported in 36.0% of patients. Most frequently reported were neurological symptoms (headache, paresthesia, and tremor) and gastrointestinal disorders. Fourteen percent of patients discontinued the treatment due to adverse events. Mean serum creatinine levels significantly increased by 0.05 mg/dl over the 12-week treatment period ( $p=0.0001$ ; Table 4). Only two patients experienced an increase in serum creatinine >30.0% of baseline in two subsequent measurements (threshold of maximal increase as outlined in the scientific leaflet). There was a mean 4 mmHg increase in systolic ( $p=0.003$ ) and 3 mmHg increase in diastolic ( $p=0.003$ ) blood pressure from baseline to the end of the study; about 20% of the patients became hypertensive during the course of the study ( $p<0.02$ ).

### DISCUSSION

The principal findings of this study on “real-world” short-course (12 weeks) treatment of severe psoriasis with cyclosporine is that this agent reduces objective dermatological parameters (%BSA and PASI), provides effective control of the disease, improves quality of life, and is associated with high patient satisfaction. Safety outcomes were in line with those reported in the literature.

The %BSA affected declined by 70.0% in mean (from 23.4% to 7.0%) and by 74.2% in median (from 15.5% to 4.0%). The PASI scores decreased by 67.8% in mean (from 15.88 to 5.11) and by 78.4% in median (from 13.9 to 3.0). Thus, both the psoriasis parameters were reduced from the severe to the non-severe range after 12 weeks of cyclosporine treatment. These results are consistent with the efficacy of cyclosporine shown in randomized controlled trials on psoriasis<sup>1,4,20-22</sup>. Physicians and patients

concurrent in their evaluation of clinical improvement. Patient severity ratings lessened by 65.9% in mean (from 4.02 to 1.37) and by 75.0% in median (from 4.0 to 1.0), and physicians reduced their ratings of lesion severity by 61.4% in mean (from 3.60 to 1.39) and by 75.0% in median (from 4.0 to 1.0).

It is not surprising to note that patients tended to be very satisfied with their cyclosporine treatment and rated their quality of life as having improved by 70.2% in mean (from 12.13 to 3.61) and by 83.4% in median. Patient satisfaction with cyclosporine treatment was quite high (median of 85 on 0~100 scale), which is known to be associated with better clinical outcomes<sup>16,30</sup>.

These strong results are despite the fact that nonadherence was a clinical issue in this sample, as it is known to be in dermatology in general<sup>15,16</sup>. Whether cyclosporine therapy increases patients' adherence is not clear from our study. Subjective patients' and physicians' adherence ratings suggest that there may have been an improvement. However, actual nonadherence behavior was highly prevalent (43.9% at baseline and 56.1% at follow-up).

The single most important determinant of therapeutic and patient outcomes, as revealed in the multilevel models, was the negative impact of living alone (which 19.1% of patients did). Generally, patients who live with a spouse/partner or relatives have the benefit of an additional caregiver to complement their own self-care, something that those living alone do not have. In addition, living alone may create a sense of social isolation (or lack of social support) that colors perceptions of quality of life and satisfaction with treatment<sup>10</sup>. A more recent diagnosis of severe psoriasis was associated with better %BSA, QOL, and patient satisfaction outcomes. In addition, patients who had suffered more flares prior to the initiation of cyclosporine treatment reported lower QOL and treatment satisfaction. This observation points at the potential role of

chronicity of illness and suffering among patients with severe psoriasis.

Safety and tolerance parameters were similar to those reported in the literature. Patients on cyclosporine need to be carefully monitored for nephrotoxicity, hypertension and other side effects<sup>22</sup>. Current treatment guidelines stipulate reduction of cyclosporine dose if serum creatinine increases by 30.0% above the baseline value. However, any changes in renal function are usually functional and are normally reversed by cessation of cyclosporine therapy<sup>4</sup>. If blood pressure increases beyond the upper limit of normal, cyclosporine dose should be reduced by 25.0~50.0% and/or an appropriate antihypertensive agent should be started<sup>4</sup>.

Physicians' use and perceived value of the Rule of Tens, which aims to integrate dermatological parameters with patient perspectives to define severe psoriasis, was limited. The relevance and validity of the Rule of Tens requires further investigation.

Despite this study being limited to one country, only one treatment cycle, and not being population-based but sampled by convenience, it confirms that short-course (12 weeks) cyclosporine treatment, with appropriate safety monitoring of renal and blood pressure parameters, is highly effective in adherent patients and is associated with high patient satisfaction.

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