



ORIGINAL ARTICLE

The Advantage of Cyclosporine A and Methotrexate Rotational Therapy in Long-Term Systemic Treatment for Chronic Plaque Psoriasis in a Real World Practice

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Background: Psoriasis is a chronic inflammatory disease. In the treatment of psoriasis, cyclosporine is commonly prescribed systemic agents. However, long-term use of cyclosporine is not recommended because of side effects such as nephrotoxicity or hypertension. **Objective:** To ascertain the improved safety of rotational therapy using cyclosporine and methotrexate, we investigated the frequency of abnormal results in laboratory test after long term rotational therapy using cyclosporine and methotrexate. **Methods:** From January 2009 to June 2014, patients who were treated with cyclosporine or methotrexate were enrolled. The clinical data and usage of medications were reviewed. Laboratory tests were conducted before starting the treatment and regularly follow-up. The occurrences of any laboratory abnormalities during the treatments were investigated. **Results:** A total of 21 psoriatic patients were enrolled. The mean of medication period and cumulative dose of cyclosporine and methotrexate were 497.81 ± 512.06 days and 115.68 ± 184.34 g in cyclosporine and 264.19 ± 264.71 days and 448.71 ± 448.63 mg in methotrexate. Laboratory abnormalities were found in total two patients after rotational therapy: two patients (9.5%) in aspartate aminotransferase/alanine aminotransferase and

one patient (4.8%) in uric acid. No laboratory abnormalities were found in renal function test. **Conclusion:** We found that the rotational approaches using cyclosporine and methotrexate reduced the possibility of the development of nephrotoxicity. In addition to other advantage such as quick switching from one agent to another, the rotational therapy using cyclosporine and methotrexate can minimize the adverse events during the systemic treatment of chronic plaque psoriasis. (Ann Dermatol 29(1) 55 ~ 60, 2017)

-Keywords-

Clinical chemistry tests, Combined modality therapy, Cyclosporine, Methotrexate, Psoriasis

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease that affects around 1% ~ 3% of the population¹. The psoriatic skin lesions and symptoms can become psychological burdens to patients². In the treatment of psoriasis, a wide range of treatment modalities have been introduced; the severity and activity of psoriasis can be determining factors in choosing treatment modalities³. Among the various systemic treatment modalities, cyclosporine is one of the most commonly prescribed agents⁴. The effectiveness of cyclosporine is supported by prolonged clinical experiences and the results of several clinical studies⁴. However, there are limitations in the use of cyclosporine in the treatment of psoriasis. Long-term continuous use of cyclosporine is not recommended because of possible side effects such as nephrotoxicity and hypertension⁵. Because psoriasis is a chronic and relapsing disease, it is difficult to achieve sustained remissions and to use a sin-

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gle systemic agent for a long time⁶. To overcome the shortcomings of single-agent therapy, combination and rotational approaches were introduced⁶. In contrast to combination therapy, which uses two or more treatment modalities concomitantly to achieve synergistic or additive effects, rotational therapy uses one treatment modality at a time and changes it into another.

Rotational therapy was first introduced as rotating among Goeckerman treatment, methotrexate, etrinate, and psoralen and ultraviolet A radiation^{6,7}. Recently, the treatment modalities that can be used in rotational therapy were extended⁸. Among the various combinations, rotational therapy using cyclosporine and methotrexate was suggested to be a good combination that can minimize the risk of nephrotoxicity and hypertension due to cyclosporine treatment⁹. However, no clinical studies focusing on the changes in the laboratory test findings in patients treated with rotational therapy using cyclosporine and methotrexate have been reported. In this study, we investigated the frequency of abnormal results in laboratory tests after long term rotational therapy using cyclosporine and methotrexate and assessed the possible risk factors that can predict adverse effects from rotational therapy using cyclosporine and methotrexate.

MATERIALS AND METHODS

Subjects and treatment schedules in the treatment with cyclosporine and methotrexate

From January 2009 to June 2014, patients with various forms of psoriasis, who were treated with cyclosporine or methotrexate, were enrolled. The clinical data about demographic features, including comorbidities, duration of disease, dose and duration of cyclosporine or methotrexate were reviewed. The psoriasis severity was evaluated by the psoriasis area and severity index (PASI) before starting cyclosporine or methotrexate. The duration of disease was defined as total days since the onset of psoriasis.

With the exception of topical treatments, only one agent was administered at a time after appropriate baseline laboratory tests. Initially, cyclosporine was administered at 3 ~ 4 mg/kg/day given in two divided doses. The dose of cyclosporine was changed on a two week interval based on the clinical efficacy. In cases of an aggravation or a relapse, the dose of cyclosporine was increased; if the patient showed a remission, the dosage was decreased to the lowest possible dose. The starting dose of methotrexate was 0.2 ~ 0.4 mg/kg/week orally with 1 mg folic acid daily. The dose of methotrexate was adjusted after 2 ~ 3 months of treatment based on the clinical efficacy. The preference of each patient, response to the treatment, and

development of side effects were considering factors in determining whether maintaining the treatment modality or changing to other modality. This study was approved by the institutional review board of Seoul National University Bundang Hospital (No. B-1412-278-120).

Laboratory tests

To check the patients' health condition, screening laboratory tests were performed before initiating the therapy. The screening laboratory tests included a complete blood count (CBC), serum creatinine (Cr), blood urea nitrogen (BUN), uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), tests for hepatitis B and C viruses, and a urinalysis. If any abnormalities were detected in the results of the laboratory tests, the patient was not enrolled. The follow-up laboratory tests were conducted 1 month after initiation of treatment and then every 2 months thereafter. The normal range of each laboratory test was consistent with that of laboratory reference values in Seoul National University Bundang Hospital and was as follows: white blood cell count, 4,000 ~ 10,000/mm³; red blood cell count, 4,000,000 ~ 5,400,000/mm³ for women and 4,200,000 ~ 6,300,000/mm³ for men; hemoglobin level, 12 ~ 16 g/dl for women and 13 ~ 17 g/dl for men; platelet count, 130,000 ~ 400,000/mm³; serum Cr level, 0.7 ~ 1.4 mg/dl; BUN level, 10 ~ 26 mg/dl; uric acid level, 3.0 ~ 7.0 mg/dl and AST and ALT levels, 0 ~ 40 IU/L. The normal range of urinalysis was consistent with that of laboratory reference values in Seoul National University Bundang Hospital.

Statistical analysis

SAS Software ver. 9.3 (SAS Institute Inc., Cary, NC, USA) was used in analyzing the data. The data were analyzed by using appropriate methods for time-to-event data. The time to a defined event was measured by calculating the day of detection of laboratory abnormalities. The patient without laboratory abnormalities was defined as the patient with normal laboratory findings. In analyzing whether there were significant differences between the patients with or without laboratory abnormalities in the epidemiologic data, baseline severity of psoriasis, or usage of treatment, we performed Cox proportional hazards regression models. An univariate Cox proportional hazards regression analysis was used to identify which factors are associated with the laboratory abnormalities. Data were expressed as the mean ± standard deviation and a *p*-value < 0.05 was considered to be statistically significant.

RESULTS

A total of 21 patients with psoriasis were enrolled. The mean age of the enrolled patients was 44.00 ± 11.50 years (Table 1). Among the psoriatic patients, seven (33.3%) were men and 14 (66.7%) were women. The mean disease duration of the enrolled patients was 107.38 ± 107.66 months. The PASI score evaluated before the initiation of rotational therapy using cyclosporine and methotrexate was 14.43 ± 8.44 . Among these, the PASI scores of 12 (57.1%) patients were greater than 10. Fifteen (71.4%) patients had no comorbidities while seven patients had one or more diseases other than psoriasis.

The mean total medication period was 762.00 ± 560.87 days. The mean period of use and cumulative dose of cyclo-

sporine was 497.81 ± 512.06 days and 115.68 ± 184.34 g, respectively, while that of methotrexate was 264.19 ± 264.71 days and 448.71 ± 448.63 mg, respectively.

Among 21 psoriatic patients, laboratory abnormalities were found in two patients after rotational therapy using cyclosporine and methotrexate. Abnormalities in AST/ALT were found in two patients (9.5%) and one patient (4.8%) had an abnormality in uric acid (Table 1). In one patient, laboratory abnormalities were found in AST/ALT and uric acid. The abnormalities in AST/ALT were found during the methotrexate treatment in two patients, while the abnormality in uric acid in one patient was observed during cyclosporine treatment. No laboratory abnormalities were found in any patients for CBC, BUN/Cr, or urinalysis.

The results of the Cox proportional hazards regression model are summarized in Table 2. A Cox proportional hazards regression model showed that there were no statistically significant differences in the epidemiologic data, duration of psoriasis, baseline severity of psoriasis, or usage of treatment between the patients with or without laboratory abnormalities. However, although statistically not significant, the patients with laboratory abnormalities were found in the group with high PASI scores (PASI > 10) (hazard ratio, 5.474; 95% confidence interval, 0.414 ~ 769.510; $p=0.381$). In addition, we also performed univariate Cox proportional hazards regression analysis to identify which factors are associated with the laboratory abnormalities in uric acid or liver transaminase (Table 3, 4). The results of univariate Cox proportional hazards regression analysis showed that there were no statistically significant differences in the epidemiologic data, duration of psoriasis, baseline PASI, or usage of cyclosporine and methotrexate between the patients with or without laboratory abnormalities. However, the laboratory abnormalities in uric acid and liver transaminase were found only in men with no underlying diseases.

Table 1. Clinical, demographic and laboratory characteristics of studied patients (n=21)

Characteristic	Value
Age (yr)	44.00 ± 11.50
Sex	
Female	14 (66.7)
Male	7 (33.3)
Duration of disease (mo)	107.38 ± 107.66
PASI score	14.43 ± 8.44
≤ 10	9 (42.9)
> 10	12 (57.1)
Total medication period (d)	762.00 ± 560.87
CsA medication period (d)	497.81 ± 512.06
MTX medication period (d)	264.19 ± 264.71
CsA cumulative dose (g)	115.68 ± 184.34
MTX cumulative dose (mg)	448.71 ± 448.63
Underlying diseases	
None	15 (71.4)
Diabetes	1 (4.8)
Hypertension	6 (28.6)
Dyslipidemia	1 (4.8)
Liver disease	0 (0)
Kidney disease	0 (0)
Others*	1 (4.8)
Laboratory abnormality	2 (9.5)
CBC	0 (0)
AST/ALP	2 (9.5)
Uric acid	1 (4.8)
BUN/Cr	0 (0)
U/A	0 (0)

Values are presented as mean \pm standard deviation or number (%).

PASI: psoriasis area and severity index, CsA: cyclosporine, MTX: methotrexate, CBC: complete blood count, AST: aspartate aminotransferase, ALP: alanine aminotransferase, BUN: blood urea nitrogen, Cr: creatinine, U/A: urinalysis.

*Angina.

DISCUSSION

In the treatment of psoriasis in both induction of remission and maintenance, the usefulness of cyclosporine is supported by the clinical experiences and the results of clinical studies⁴. The use of cyclosporine at doses of 2.5 to 5 mg/kg per day for 3 to 4 months showed significant improvement of psoriasis in up to 90% of patients^{5,10-12}. Based on the rapid and significant effects of cyclosporine, intermittent short courses of cyclosporine therapy are widely used. However, during cyclosporine treatment of patients with psoriasis, the occurrence of various adverse events was reported. Among them, nephrotoxicity has been regarded as one of the most important side effects.

Table 2. Univariate analyses results of all laboratory tests by group (n=21)

Characteristic	Normal group (n=19)	Abnormal group (n=2)	Univariate HR (95% CI)	Univariate p-value
Age (yr)	45.26±11.05	32.00±11.31	0.909 (0.750~1.051)	0.213
Sex*				
Male	5 (26.3)	2 (100)	7.501 (0.610~1034.421)	0.288
Female	14 (73.7)	0 (0)		
Duration of disease (mo)	107.21±107.73	109.00±151.32	0.997 (0.979~1.011)	0.715
PASI score*				
≤10	9 (47.4)	0 (0)	5.474 (0.414~769.510)	0.381
>10	10 (52.6)	2 (100)		
Total medication period (d)	766.53±582.44	719.00±425.68		
CsA medication period (d)	521.84±533.43	269.50±84.15	0.996 (0.980~1)	0.284
CsA cumulative dose (g)	123.11±192.68	45.13±19.62	1 (1~1)	0.254
MTX medication period (d)	244.69±243.31	449.50±509.82	1.001 (0.996~1.004)	0.730
MTX cumulative dose (mg)	415.95±416.16	760.00±832.97	1 (0.998~1.003)	0.723
Underlying diseases				
Diabetes*	1	0	4.593 (0.032~87.481)	0.511
Hypertension*	6	0	0.529 (0.004~6.863)	0.742
Dyslipidemia*	1	0	4.593 (0.032~87.481)	0.511
Others*,†	1	0	-	-

Values are presented as mean±standard deviation, number (%), or number only. HR: hazard ratio, CI: confidence interval, PASI: psoriasis area and severity index, CsA: cyclosporine, MTX: methotrexate. *Firth's correction was applied. †Angina.

Table 3. Univariate analysis results of uric acid levels by group (n=21)

Characteristic	Normal group (n=20)	Abnormal group (n=1)	Univariate HR (95% CI)	Univariate p-value
Age (yr)	45.00±10.82	24.00	0.857 (0.460~1.029)	0.263
Sex*				
Male	6 (30.0)	1 (100)	5.732 (0.297~813.231)	0.453
Female	14 (70.0)	0 (0)		
Duration of disease (mo)	101.95±107.46	216.00	1.008 (0.990~1.030)	0.366
PASI score*				
≤10	9 (45.0)	0 (0)	-	0.999
>10	11 (55.0)	1 (100)		
Total medication period (d)	779.20±569.73	418.00		
CsA medication period (d)	506.25±523.86	329.00	0.999 (0.989~1.003)	0.710
CsA cumulative dose (g)	118.52±188.66	59.00	1 (1~1)	0.753
MTX medication period (d)	272.95±268.44	89.00	0.983 (0.930~1.003)	0.336
MTX cumulative dose (mg)	462.60±455.63	171.00	0.992 (0.962~1.002)	0.413
Underlying diseases				
Diabetes*	1	0	6.603 (0.043~118.752)	0.409
Hypertension*	6	0	0.745 (0.005~14.584)	0.900
Dyslipidemia*	1	0	6.603 (0.043~118.752)	0.409
Others*,†	1	0	6.603 (0.043~118.752)	0.409

Values are presented as mean±standard deviation, number (%), or number only. HR: hazard ratio, CI: confidence interval, PASI: psoriasis area and severity index, CsA: cyclosporine, MTX: methotrexate. *Firth's correction was applied. †Angina.

Compared to cyclosporine, the main side effects of methotrexate are irreversible liver cirrhosis, bone marrow suppression, and mucosal damage¹³. In addition, acute side effects such as elevation of liver enzymes are frequently reported during treatment with methotrexate^{13,14}. In this

study, abnormalities in AST/ALT were found in two patients (9.5%) while only one patient (4.8%) had an abnormality in uric acid levels. The abnormalities in AST/ALT were found during methotrexate treatment and the abnormality in uric acid was observed during cyclosporine

Table 4. Univariate analysis results of liver transaminase levels by group (n=21)

Characteristic	Normal group (n=19)	Abnormal group (n=2)	Univariate HR (95% CI)	Univariate p-value
Age (yr)	45.26 ± 11.05	32.00 ± 11.31	0.903 (0.738 ~ 1.036)	0.194
Sex*				
Male	5 (26.3)	2 (100.0)	8.787 (0.715 ~ 1211.889)	0.252
Female	14 (73.7)	0 (0)		
Duration of disease (mo)	107.21 ± 107.73	109.00 ± 151.32	0.998 (0.979 ~ 1.011)	0.740
PASI score*				
≤ 10	9 (47.4)	0 (0)	3.337 (0.270 ~ 461.138)	0.526
> 10	10 (52.6)	2 (100.0)		
Total medication period (d)	766.53 ± 582.44	719.00 ± 425.68		
CsA medication period (d)	521.84 ± 533.43	269.50 ± 84.15	0.997 (0.986 ~ 1.001)	0.361
CsA cumulative dose (g)	123.11 ± 192.68	45.13 ± 19.62	1 (1 ~ 1)	0.472
MTX medication period (d)	244.68 ± 243.31	449.50 ± 509.32	1.002 (0.997 ~ 1.005)	0.378
MTX cumulative dose (mg)	415.95 ± 416.16	760.00 ± 832.98	1.001 (0.998 ~ 1.003)	0.383
Underlying diseases				
Diabetes*	1	0	3.014 (0.022 ~ 37.498)	0.562
Hypertension*	6	0	0.393 (0.003 ~ 4.850)	0.623
Dyslipidemia*	1	0	3.014 (0.022 ~ 37.498)	0.562
Others*,†	1	0	6.148 (0.041 ~ 112.482)	0.429

Values are presented as mean ± standard deviation, number (%), or number only.

HR: hazard ratio, CI: confidence interval, PASI: psoriasis area and severity index, CsA: cyclosporine, MTX: methotrexate.

*Firth's correction was applied. †Angina.

treatment. No laboratory abnormalities were found in CBC, BUN/Cr, or urinalysis.

In a previous study, hyperuricemia and increased liver enzymes were the most frequently observed laboratory abnormalities after cyclosporine treatment¹⁵. During cyclosporine treatment, hyperuricemia was observed in 20.7% and increased liver enzymes in 18.9% of patients¹⁵. In addition, we have also found that abnormally elevated liver enzymes are the most commonly found laboratory abnormalities followed by elevation in the uric acid level after intermittent short courses of cyclosporine therapy (unpublished data). It is noteworthy that laboratory tests other than renal function are important in the care of psoriasis patients and regular checkups are necessary during treatment for psoriasis.

The short term use of cyclosporine in the treatment of psoriasis is supported due to the reduced risks of side effects such as nephrotoxicity^{5,12,16}. The risk of nephrotoxicity is significantly reduced in patients given intermittent short courses of cyclosporine therapy (12-week use of cyclosporine) compared to that in the group with continuous cyclosporine therapy^{5,12,16}.

However, evidence about the safety of short courses of cyclosporine therapy is limited. In one study that investigated the recovery of nephrotoxicity after the use of cyclosporine, histological changes such as interstitial fibrosis were not fully recovered until 6 months after the withdrawal of cyclosporine¹⁷. The authors insist that recovery

from nephrotoxicity after the use of cyclosporine requires time¹⁷. We found no laboratory abnormalities in renal function after rotational approaches with cyclosporine and methotrexate in contrast to previous studies using intermittent short courses of cyclosporine therapy. In this regard, rotational approaches with cyclosporine and methotrexate can give enough time to restore the changes after cyclosporine therapy and prevent permanent renal damage.

Although intermittent short courses of cyclosporine therapy can induce rapid improvement of psoriasis, sustained remission and disease control after discontinuation of cyclosporine are limited^{12,16}. In one study, the average interval between the withdrawal of cyclosporine and the initiation of another systemic therapy was reported to be 182 days¹⁸. Because psoriasis is a chronic and relapsing disease, long-term treatment using a single systemic agent can be harmful for the patients. To overcome the limitation of treatment using a single agent, combination and rotational approaches were introduced⁶. In this study, the enrolled patients were treated with cyclosporine or methotrexate. We found no laboratory abnormalities in renal function after rotational approaches with cyclosporine and methotrexate. This is an important result and the reduction in nephrotoxicity and hepatotoxicity can be associated with the use of cyclosporine in a rotational approach with methotrexate. Our results support the usefulness of rotational therapy.

In addition to other advantages such as quick switching from one agent to another, we found decreased occurrences of laboratory adverse events during a rotational approach with cyclosporine and methotrexate in the treatment of psoriasis. However, this study was a retrospective study and there is possible risk of bias. A healthy patient can tolerate one agent and then also tolerate another agent. To confirm the effectiveness and safety of rotational treatment with cyclosporine and methotrexate, a prospective randomized controlled study is needed.

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