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ORIGINAL ARTICLE

Methotrexate versus Cyclosporine in Moderate-to-Severe Chronic Plaque Psoriasis

Vera M.R. Heydendaal, M.D., Phyllis I. Spuls, M.D., Ph.D., Brent C. Opmeer, Ph.D., Corianne A.J.M. de Borgie, Ph.D., Johannes B. Reitsma, M.D., Ph.D., Wouter F.M. Goldschmidt, M.D., Patrick M.M. Bossuyt, Ph.D., Jan D. Bos, M.D., Ph.D., and Menno A. de Rie, M.D., Ph.D.

ABSTRACT

From the Departments of Dermatology (V.M.R.H., P.I.S., W.F.M.G., J.D.B., M.A.R.) and Clinical Epidemiology and Biostatistics (B.C.O., C.A.J.M.B., J.B.R., P.M.M.B.), Academic Medical Center, University of Amsterdam, Amsterdam. Address reprint requests to Dr. de Rie at the Department of Dermatology, Rm. A0-222, Academic Medical Center, University of Amsterdam, P.O. Box 22700, 1100 DE Amsterdam, the Netherlands.

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BACKGROUND

Methotrexate and cyclosporine are well-known systemic therapies for moderate-to-severe chronic plaque psoriasis. We conducted a randomized, controlled trial comparing methotrexate and cyclosporine in terms of effectiveness, side effects, and the quality of life.

METHODS

A total of 88 patients with moderate-to-severe psoriasis were randomly assigned to treatment for 16 weeks with either methotrexate (44 patients; initial dose, 15 mg per week) or cyclosporine (44 patients; initial dose, 3 mg per kilogram of body weight per day) and were followed for another 36 weeks. The primary outcome was the difference between groups in the psoriasis area-and-severity index after 16 weeks of treatment, after adjustment for base-line values; scores were determined in a blinded fashion by trained observers.

RESULTS

Two patients were excluded from the analysis after randomization because they were found to be ineligible, and one patient withdrew his consent. Twelve patients in the methotrexate group had to discontinue treatment because of reversible elevations in liver-enzyme levels, and 1 patient in the cyclosporine group had to do so because of an elevation in the bilirubin level, but all 13 were included in the analysis. After 16 weeks of treatment, the mean ($\pm$ SE) score for the psoriasis area-and-severity index decreased from 13.4 ± 3.6 at base line to 5.0 ± 0.7 among 43 patients treated with methotrexate, whereas the score decreased from 14.0 ± 6.6 to 3.8 ± 0.5 among 42 patients treated with cyclosporine. After adjustment for base-line values, the mean absolute difference in values at 16 weeks was 1.3 (95 percent confidence interval, -0.2 to 2.8 ; $P=0.09$). The physician's global assessment of the extent of psoriasis, the time to and the rates of remission, and the quality of life were similar in the two groups.

CONCLUSIONS

No significant differences in efficacy were found between methotrexate and cyclosporine for the treatment of moderate-to-severe psoriasis.

CHRONIC PLAQUE PSORIASIS IS A SKIN disease characterized by sharply demarcated, erythematous, squamous lesions, with an estimated worldwide prevalence of 0.1 to 3 percent.¹ Various therapies are available for the treatment of psoriasis, including topical ointments, such as calcipotriene, corticosteroids, tar, and anthralin; phototherapy with ultraviolet B radiation (UVB) and methoxsalen (psoralen) with ultraviolet A radiation (PUVA); systemic drugs such as acitretin; and the systemic immunosuppressant drugs methotrexate and cyclosporine.^{2,3} Methotrexate and cyclosporine are often used in daily clinical practice, but which of the two is more effective has not been established.

The current management of severe psoriasis is based on the principles of rotational therapy, which stresses frequent alternations in treatment approaches in order to reduce the cumulative risk of side effects.⁴ The choice of treatment is influenced by short-term as well as long-term considerations, including the severity of the disease, the effectiveness of a given medication and its side effects, the patient's quality of life, and the ease of treatment. In 1997, a systematic review of the literature showed that studies of cyclosporine were limited to open, noncomparative, dose-finding, or placebo-controlled trials.⁵ To our knowledge, no comparison with methotrexate has been made. According to the guidelines for the treatment of psoriasis, which are based on the 1997 review, UVB should be tried first, and if it proves to be ineffective, it should be followed in order by PUVA, methotrexate, acitretin, and finally, cyclosporine.⁶ We conducted a randomized comparison of methotrexate with cyclosporine as monotherapy for chronic plaque psoriasis, evaluating side effects, clinical effectiveness, time to and duration of remission, and quality of life.

METHODS

PATIENTS

Patients were recruited from the Department of Dermatology, Academic Medical Center, Amsterdam, and from local dermatologic centers between October 1998 and June 2000. Eligible patients were 18 years of age or older; had moderate-to-severe chronic plaque psoriasis, defined by a score of at least 8 on the psoriasis area-and-severity index (a score of 0 indicates the absence of psoriasis, and a score of 72 the most severe disease possible) (Fig. 1),⁷ with an insufficient response to topical or UVB therapy (or both); and had not previously been

Figure 1. Patient with Moderate-to-Severe Psoriasis, as Indicated by a Score of 9.7 on the Psoriasis Area-and-Severity Index (Panel A), and a Patient with Severe Psoriasis, as Indicated by a Score of 17.1 (Panel B).

Scores for the psoriasis area-and-severity index range from 0 (no psoriasis) to 72 (the most severe disease possible).

treated with either methotrexate or cyclosporine. Patients who met any of the following criteria were excluded: liver or renal impairment; insulin-dependent diabetes mellitus; a high risk of liver-function abnormalities; a positive serologic test for hepatitis B virus; uncontrolled hypertension; a history of cancer, including skin cancer or severe cardiovascular, pulmonary, cerebral, neurologic, or hematologic disease; or acute infection requiring antimicrobial therapy or associated with human immunodeficiency virus infection. Patients were also excluded if they were pregnant, breast-feeding, or noncompliant with an effective regimen of contraception.

Laboratory tests and ultrasonography of the liver were performed in all eligible patients. Patients

who were treated with methotrexate underwent the following laboratory tests every two weeks during the first month and monthly thereafter until week 20: a complete blood count and assays of electrolytes, serum creatinine, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and bilirubin. Patients who were treated with cyclosporine underwent the same laboratory tests according to the same schedule as well as urinalysis and an assay of magnesium every two months. During the screening period, a test for hepatitis B virus was also performed in all patients. If a relevant abnormality in any of the laboratory values was noted during treatment, the test was repeated at each visit until the results returned to normal. Patients with moderate or severe steatohepatitis (as established by ultrasonography of the liver) were excluded. The study was approved by the medical ethics committee at each center.

DESIGN

Eligible patients who had given written informed consent were randomly assigned on a 1:1 basis to receive 16 weeks of treatment with either methotrexate or cyclosporine. Randomization was performed centrally with the use of computer-generated random numbers and block size of eight patients. The screening period, during which no active treatment for psoriasis was permitted, lasted two weeks for patients who had been receiving topical therapies and four weeks for those who had been receiving UVB, PUVA, or systemic drugs. After 16 weeks of treatment, the patients were monitored for another 36 weeks. They returned for evaluation every two weeks during the first month of treatment and monthly thereafter.

TREATMENT REGIMENS

The initial dose of methotrexate was 15 mg per week (given in three divided doses with a 12-hour interval between doses, according to the schedule of Weinstein and Frost⁸), and the initial dose of cyclosporine was 3 mg per kilogram of body weight per day (given in two divided doses). After four weeks of treatment, the doses were increased, up to 22.5 mg per week in the case of methotrexate and 5 mg per kilogram per day in the case of cyclosporine, in patients in whom the reduction from base line in the score for the psoriasis area-and-severity index was less than 25 percent. In the event of an adverse effect, the dose could be decreased at any time according to published guidelines.^{9,10} During systemic

treatment, no concomitant antipsoriatic therapy was permitted, with the exception of emollients. During the follow-up period, active therapy for psoriasis was allowed if necessary, reflecting normal clinical practice. Drugs known to interfere with psoriasis or with the systemic treatments (or with both) were not allowed.

OUTCOMES

Effectiveness

The score for the psoriasis area-and-severity index was the primary outcome measure and was determined at base line and monthly thereafter by trained assessors who were unaware of the treatment assignments.⁷ The psoriasis area-and-severity index combines assessments of psoriasis-induced erythema, scaling, and skin thickness, each weighted according to the size of the affected area. At each visit, the physician performed a global assessment, which is a general evaluation of a patient's psoriasis, using a scale of 0 to 10, with a score of 0 indicating the worst imaginable disease activity and a score of 10 the absence of disease activity.¹¹

Side Effects

We evaluated side effects known to be associated with methotrexate or cyclosporine and effects that the patient deemed to be relevant to the treatment. The latter group of side effects was very small. For this reason, we focused our analysis on the first group of reported side effects. Side effects that did not require additional medications, adjustments in the dose of the study medication, or discontinuation of the study medication were classified as mild.

Quality of Life

We assessed the patients' quality of life with use of the validated Dutch version of the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36).¹² The patients completed the SF-36 at base line and every eight weeks thereafter. Summary scores were calculated for the physical component and mental component and were standardized for the Dutch population; a score of 50 reflects an average quality of life in the general population. Scores on each subscale range from 0 (worst) to 100 (best).

STATISTICAL ANALYSIS

In the primary analysis, we calculated the difference between groups in the mean score for the psoriasis area-and-severity index after 16 weeks of treatment after adjustment for the base-line score using an

analysis of covariance. If a patient missed a visit, we used the score from the previous visit. The physician's global assessment score and the quality-of-life score were analyzed in the same way. In addition, we used Student's t-test to compare the percent reduction from base line in scores for the psoriasis area-and-severity index in both groups, and we used chi-square tests to compare differences between groups in the number of patients reporting side effects.

Differences in the time to reach an almost complete remission, defined as more than a 90 percent reduction from base line in the score for the psoriasis area-and-severity index, and a partial remission, defined as more than a 75 percent reduction from base line, were compared and tested with the use of the log-rank test statistic. We calculated the timing of the return of disease activity (the time to relapse) and the rate of relapse after oral treatment had been completed in patients with a partial remission. Relapse was defined as a score for the psoriasis area-and-severity index that was more than 50 percent of the base-line score or the need for UVB or systemic therapy.

When designing this trial, we calculated that 42 patients would be needed in each group for the study to have a 95 percent power to rule out a difference of two points or more in mean scores for the psoriasis area-and-severity index after a 16-week treatment period, assuming that the mean ($\pm$ SE) expected difference is 0 ± 2.5 . We used all available outcome data for patients. No interim analyses were performed. Two-sided P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

PATIENTS

Between October 1998 and June 2000, 111 patients were screened, 88 of whom underwent randomization (Fig. 2). Three patients were subsequently excluded: two patients had creatinine clearance values (measured according to the method of Cockcroft and Gault¹³) that were too low, and one patient withdrew informed consent. Thus, a total of 43 patients in the methotrexate group and 42 in the cyclosporine group were included in the analysis. The base-line characteristics of these patients are shown in Table 1.

LABORATORY VALUES

Treatment had to be discontinued in 12 patients in the methotrexate group because of elevated liver

enzyme levels (the highest level measured was an alanine aminotransferase level of 198 U per liter). Treatment was discontinued in one patient in the cyclosporine group because of an elevation in the bilirubin level (total bilirubin, 44 mg per deciliter [760 μ mol per liter]) and icterus suggestive of the presence of Gilbert's syndrome (idiopathic hyperbilirubinemia). These laboratory abnormalities were transient, and values returned to normal within four to eight weeks after treatment was discontinued. After cessation of systemic therapy, these 13 patients were treated with active therapy for psoriasis, reflecting normal clinical practice.

Neither adjustments of the dose nor discontinuation of the study medication was necessary because of hypertension. Two patients who were receiving cyclosporine (3 mg per kilogram per day) were given antihypertensive medication. After the cessation of cyclosporine therapy, their blood pressure gradually returned to normal and antihypertensive treatment was stopped. Three patients were already using antihypertensive medications before cyclosporine was started, and the regimen was not altered.

OUTCOMES

Effectiveness

The overall rate of response was high: 94 percent of all patients had reached the threshold for a minimal response — a 25 percent reduction from base line in scores for the psoriasis area-and-severity index — after 12 weeks of treatment, before the dose was tapered. Figure 3 shows the mean scores for the psoriasis area-and-severity index during the study period. Sixteen weeks after randomization, the mean ($\pm$ SE) score was 5.0 ± 0.7 in the methotrexate group and 3.8 ± 0.5 in the cyclosporine group. After adjustment for base-line values, the mean score was 1.3 points lower in the cyclosporine group than in the methotrexate group (95 percent confidence interval, -0.2 to 2.8 ; $P=0.09$). The relative reduction in the scores from base line to 16 weeks of treatment was 64 percent in the methotrexate group, as compared with 72 percent in the cyclosporine group, an absolute difference of 8 percent (95 percent confidence interval, -2 to 18 ; $P=0.14$).

Seventeen patients (40 percent) in the methotrexate group and 14 patients (33 percent) in the cyclosporine group had an almost complete remission (defined as a reduction in the base-line score for the psoriasis area-and-severity index of more than 90 percent) during the 16 weeks of treatment ($P=0.55$). Partial remission (defined as a reduction in the base-line score of more than 75 percent) was

achieved in 26 patients (60 percent) in the methotrexate group and 30 patients (71 percent) in the cyclosporine group ($P=0.29$). The time needed to reach an almost complete remission and a partial remission did not differ significantly between the groups ($P=0.70$ and $P=0.07$, respectively, by the log-rank test). In four patients in the methotrexate group and in six patients in the cyclosporine group, an increase in the dose was needed after four weeks of treatment.

We found no significant differences between groups in the duration of either partial remission

($P=0.43$ by the log-rank test) or almost complete remission ($P=0.34$ by the log-rank test) after oral treatment was stopped. The median time from the cessation of treatment to the initiation of active therapy for psoriasis was four weeks in both groups.

After 16 weeks of treatment, there was no significant difference between the two groups in the mean score for the physician's global assessment. It was 7.0 ± 0.38 in the methotrexate group and 7.8 ± 0.29 in the cyclosporine group (absolute difference, 0.9; 95 percent confidence interval, -0.03 to 1.9 ; $P=0.06$).

Side Effects

The total number of reported side effects was 113 in the methotrexate group and 166 in the cyclosporine group; side effects were reported by 29 and 35 patients in the two groups, respectively. Significantly more patients in the methotrexate group reported nausea (19 of 43, vs. 4 of 42 in the cyclosporine group, $P<0.001$), whereas more patients in the cyclosporine group reported headaches (18 of 42, vs. 7 of 43 in the methotrexate group; $P=0.009$), muscle ache (12 of 42 vs. 3 of 43, $P=0.007$), and paresthesias in the fingertips and toes (14 of 42 vs. 1 of 43, $P<0.001$). Additional medication to relieve side effects was rarely needed in either group. No serious or irreversible side effects were observed.

Quality of Life

No significant differences between the two groups were found after 16 weeks of treatment in any of the subscales of the SF-36. The mean scores for the physical component and the mental component were 52 ± 1.7 and 51 ± 1.4 in the methotrexate group, respectively, and 53 ± 1.4 and 51 ± 1.4 in the cyclosporine group, respectively. After adjustment for base-line values, the estimated absolute difference in scores between the methotrexate and cyclosporine groups for the physical and mental components was -0.8 (95 percent confidence interval, -4.6 to 3.0 ; $P=0.69$) and -0.5 (95 percent confidence interval, -3.9 to 2.9 ; $P=0.75$), respectively.

DISCUSSION

In this randomized trial of two frequently used systemic treatments in patients with moderate-to-severe chronic plaque psoriasis, we found that methotrexate and cyclosporine were similarly effective. In both groups, scores for the psoriasis area-and-severity index started to decrease once treatment was begun. After 16 weeks of treatment, the mean adjusted absolute difference between the groups was small: only 1.3 points.

We conducted this study according to international guidelines that have been developed for both treatments.^{9,10} Despite the existence of these guidelines, the regimens of both methotrexate and cyclosporine vary substantially among countries in terms of the route (oral vs. intramuscular) and the dose. We used a starting dose of 15 mg of methotrexate per week. We chose this dose in the absence of evidence from dose-finding and treatment-duration studies. The guidelines, however, recommend an

Table 1. Base-Line Characteristics of the Patients.*

Characteristic	Methotrexate Group (N=43)	Cyclosporine Group (N=42)
Sex (no. of patients)		
Male	28	29
Female	15	13
Age (yr)	41.6 $\pm$ 13.0	38.3 $\pm$ 12.4
Psoriasis area-and-severity index†	13.4 $\pm$ 3.6	14.0 $\pm$ 6.6
Previous therapies (no. of patients)		
Ultraviolet B	28	25
Methoxsalen with ultraviolet A	10	8
Acitretin	5	5
Fumaric acid	3	0
Topical only	8	14
Age at onset of disease (yr)	25.1 $\pm$ 14.5	24.3 $\pm$ 13.3
Psoriatic arthritis (no. of patients)	3	1

* Plus-minus values are means $\pm$ SE.

† Scores for the psoriasis area-and-severity index range from 0 (no psoriasis) to 72 (the most severe disease possible).

initial dose of 2.5 to 5 mg because of the risk of myelosuppression during the first 10 days of treatment.⁹ In accordance with the guidelines,¹⁰ the dose of cyclosporine could be increased after four weeks in the event of an insufficient response (less than

a 25 percent decrease in the score on the psoriasis area-and-severity index from base line). The 16-week treatment period we used was proved to be effective in a previous study of cyclosporine, in which more than 80 percent of the study population had clinical improvement.¹⁴ Ho et al.¹⁵ demonstrated that tapering the dose of cyclosporine, rather than abruptly stopping treatment, does not increase the time to relapse. Since these results were not available when we initiated our study, we tapered the dose during the last four weeks of treatment.

Both treatments for moderate-to-severe psoriasis are readily available, and there is ample evidence of their effectiveness from placebo-controlled studies and uncontrolled studies. Our results of the effectiveness of cyclosporine are in agreement with those of earlier studies.^{16,17}

Overall, the tolerability of both drugs was good. Only one patient in the cyclosporine group had to discontinue treatment because of an adverse effect — an elevation in bilirubin. Twelve patients had to discontinue methotrexate treatment, all because of elevations in liver enzymes. These elevations were mild, and all values returned to normal within four to eight weeks after treatment had been discontinued. Liver enzyme elevations during methotrexate treatment have been well documented.¹⁸ Most of the side effects observed immediately after the receipt of methotrexate (abdominal discomfort, oral ulcerations, and cytenias) resemble the effects of folate

deficiency. Whether methotrexate-induced elevations in liver enzymes can be reduced by folate supplementation is heavily debated, and was not answered in a recently completed Cochrane review, owing to a lack of uniformity in outcome measures.¹⁹ A randomized, controlled trial involving patients with rheumatoid arthritis showed that the incidence of hepatotoxicity during methotrexate treatment was significantly lower in the group treated with folate than in the placebo group.²⁰ Since folate supplementation does not cause severe side effects and is not expensive, we now prescribe it for our patients who are taking methotrexate.

We demonstrated that the effectiveness and tolerability of methotrexate are similar to those of cyclosporine in patients with moderate-to-severe psoriasis. Differences between the treatments in terms of side effects, long-term adverse effects, ease of administration (once-daily vs. twice-daily treatment), and costs can be used to guide treatment decisions in individual cases.

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REFERENCES

1. Koo J. Population-based epidemiologic study of psoriasis with emphasis on quality of life assessment. *Dermatol Clin* 1996;14:485-96.
2. Lebwohl M, Ali S. Treatment of psoriasis. 1. Topical therapy and phototherapy. *J Am Acad Dermatol* 2001;45:487-98.
3. *Idem*. Treatment of psoriasis. 2. Systemic therapies. *J Am Acad Dermatol* 2001;45:649-61.
4. Weinstein GD, White GM. An approach to the treatment of moderate to severe psoriasis with rotational therapy. *J Am Acad Dermatol* 1993;28:454-9.
5. Spuls PI, Witkamp L, Bossuyt PMM, Bos JD. A systematic review of five systemic treatments for severe psoriasis. *Br J Dermatol* 1997;137:943-9.
6. Spuls PI, Bossuyt PMM, van Everdingen JJE, Witkamp L, Bos JD. The development of practice guidelines for the treatment of severe plaque form psoriasis. *Arch Dermatol* 1998;134:1591-6.
7. Fredriksson T, Pettersson U. Severe psoriasis — oral therapy with a new retinoid. *Dermatologica* 1978;157:238-44.
8. Weinstein G, Frost P. Methotrexate in psoriasis: a new therapeutic schedule. *Arch Dermatol* 1971;103:33-8.
9. Roenigk HH Jr, Auerbach R, Maibach HI, Weinstein GD. Methotrexate in psoriasis: revised guidelines. *J Am Acad Dermatol* 1988;19:145-56.
10. Lebwohl M, Ellis C, Gottlieb A, et al. Cyclosporine consensus conference: with emphasis on the treatment of psoriasis. *J Am Acad Dermatol* 1998;39:464-75.
11. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. *Lancet* 2001;357:1842-7.
12. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51:1055-68.
13. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.
14. Ho VC, Griffiths CEM, Albrecht G, et al. Intermittent short courses of cyclosporin (Neoral) for psoriasis unresponsive to topical therapy: a 1-year multicentre, randomised study. *Br J Dermatol* 1999;141:283-91.
15. Ho VC, Griffiths CEM, Berth-Jones J, et al. Intermittent short courses of cyclosporine microemulsion for the long-term management of psoriasis: a 2-year cohort study. *J Am Acad Dermatol* 2001;44:643-51.
16. Berth-Jones J, Henderson CA, Munro CS, et al. Treatment of psoriasis with intermittent short course cyclosporin (Neoral): a multicenter study. *Br J Dermatol* 1997;136:527-30.
17. Griffiths CEM, Powles AV, McFadden J, Baker BS, Valdimarsson H, Fry L. Long-term cyclosporin for psoriasis. *Br J Dermatol* 1989;120:253-60.

18. Wollina U, Ständer K, Barta U. Toxicity of methotrexate treatment in psoriasis and psoriatic arthritis — short- and long-term toxicity in 104 patients. *Clin Rheumatol* 2001; 20:406-10.
19. Ortiz Z, Shea B, Saurez Almazor M, Moher D, Wells G, Tugwell P. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. *Cochrane Database Syst Rev* 2001;2:CD000951.
20. van Ede AE, Laan RFJM, Rood MJ, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight week, multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2001; 44:1515-24.

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