ELSEVIER

Ciclosporin Microemulsion Preconcentrate Treatment of Patients With Behçet's Disease

Yujiro Fujino,* Satoru Joko,*
Kanjiro Masuda,*[1] Ikuko Yagi,† Mitsuko Kogure,†[2]
Junichi Sakai,‡[3] Masahiko Usui,‡ Satoshi Kotake,§ Hidehiko Matsuda,§
Eiko Ikeda,‖[4] Manabu Mochizuki,‖ Satoshi Nakamura¶ and Shigeaki Ohno¶

*Department of Ophthalmology, University of Tokyo School of Medicine, Tokyo, Japan; †Department of Ophthalmology, Tokyo Women's Medical College, Tokyo, Japan; ‡Department of Ophthalmology Tokyo Medical College Hospital, Tokyo, Japan; §Department of Ophthalmology, Hokkaido University School of Medicine, Hokkaido, Japan; ‖Department of Ophthalmology, Kurume University, School of Medicine, Fukuoka, Japan; ¶Department of Ophthalmology, Yokohama City University School of Medicine, Kanagawa, Japan

Purpose: The new microemulsion preconcentrate (MEPC) formulation of ciclosporin has been developed to reduce problems in intestinal absorption and to stabilize fluctuations in blood levels. A multicenter, open-label clinical trial of MEPC was conducted to assess its efficacy and safety in Behçet's disease patients with ocular involvement.

Methods: The patient population comprised 17 de novo patients (patients not previously treated with ciclosporin in the currently available formulation) and 30 patients whose ciclosporin formulation was switched from the conventional formulation to MEPC. The patients were treated with the test formulation for 16 weeks in the former (de novo) group and for 12 weeks in the latter (switched) group.

Results: In the de novo group, ocular attacks decreased significantly as compared to the pretreatment incidence in 11 of the 14 patients (78.6%) evaluated after MEPC therapy. Ocular attacks also decreased significantly in the switched group. In the de novo group, visual acuity improved with MEPC therapy in 20 of the 28 eyes (71.4%) examined, and the overall efficacy evaluation was "improved" or "markedly improved" in 13 of the 16 patients evaluated (81.3%). The one case each of onset of neuro-Behçet's disease and intestinal Behçet's disease observed in the de novo group were regarded as adverse reactions.

Conclusion: It was concluded that ciclosporin MEPC is useful for controlling the ocular symptoms of Behçet's disease, and that it can be used as effectively and safely as the conventional formulation. **Jpn J Ophthalmol 1999;43:318–326**

Key Words: Behçet's disease, ciclosporin, ciclosporin-MEPC.

Introduction

Behçet's disease is an intractable disease of unknown etiology. Eye symptoms, one of the four major classes of symptoms, are resistant to treatment and the prognosis for visual acuity is poor. In the late 1970s, medical interest focused on cyclosporin, an immunosuppressant that selectively inhibits T cells. In 1981, in the field of ophthalmology, Nussenblatt[1] reported the efficacy of this peptide antibiotic in suppressing the development of experimental autoimmune uveoretinitis, and Nussenblatt et al[2,3] later reported its usefulness in the treatment of intractable human uveitis. A controlled, double-blind clinical trial of ciclosporin was conducted in patients with Behçet's

[1]Currently at Kanto Rosai Hospital, Kanagawa.
[2]Currently at Kogure Eye Clinic, Tokyo.
[3]Currently at Sakai Eye Clinic, Saitama.
[4]Currently at Ikeda Eye Clinic, Fukuoka.

Received: October 2, 1998

Correspondence and reprint requests to: Yujiro FUJINO, MD, Department of Ophthalmology, Tokyo University Branch Hospital, 3-28-6 Mejirodai, Bunkyo-ku, Tokyo 112-8688, Japan

Published by Elsevier Science Inc.
0021-5155/99/$–see front matter
PII S0021-5155(99)00025-8

disease in Japan in 1985, and greater efficacy than colchicine was demonstrated.[4] The Ministry of Health and Welfare approved ciclosporin for Behçet's disease in 1988.[5] Since then, ciclosporin has become an indispensable drug for the treatment of Behçet's disease, but intestinal absorption of the drug remains a problem. An average intestinal absorption of 33% has been reported in renal transplant patients with interindividual variations from 20%–50%, and there is intraindividual variation resulting mainly from the influence of diet. Occasional cases of poor absorbers have also been reported.[6] Trough blood levels of ciclosporin have been documented to vary among Behçet's disease patients treated with the same dosages, and interassay variations have been observed even in the same individual.[7] It has been suggested that poor intestinal absorption of the drug is at least partially responsible for the poor control of ocular symptoms.[8] To solve this problem, a new microemulsion formulation of ciclosporin (ciclosporin MEPC, referred to below as MEPC) was developed.[9] It is pharmaceutically designed to become microemulsified when it comes into contact with body fluids, eg, gastric juices. MEPC has been demonstrated to reduce problems in intestinal absorption and to stabilize fluctuations in blood levels.[10] Malabsorption of the current formulation has been reported to be partially overcome by MEPC in psoriasis patients, with a consequent improvement in clinical symptoms.[11] Its clinical use in organ transplantation and autoimmune diseases, such as psoriasis, has been reported.[12–16] The use of MEPC at the same dosage and same route of administration as the current formulation has been approved in more than 30 countries worldwide. However, its use in Behçet's disease patients has never been reported. In the present study, we used MEPC to treat Behçet's disease patients with ocular symptoms and we report our clinical experience with MEPC in such patients below.

Materials and Methods

The study was a multicenter, open-label phase III clinical trial begun in April 1996 and completed in September 1997 (Table 1). It consisted of two parts: in one part, the efficacy, safety, and usefulness of MEPC were assessed in de novo patients (de novo group); and in the other part, the safety of MEPC was evaluated in patients in whom treatment with the conventional formulation of ciclosporin was switched to the same dose of MEPC (switched group). The study protocol was reviewed and approved by the institutional review board of each participating medical institution. After thorough explanation of the study, informed consent to participate was obtained in writing from each potential subject before the start of the study.

Subjects

The subjects were Behçet's disease patients who had complete or incomplete active ocular signs and symptoms according to the diagnostic criteria proposed by the Ministry of Health and Welfare Specific Diseases Study Group on Behçet's Disease (1987). The ages of the study subjects ranged from 20 to 64 years. The study comprised two patient groups. One group consisted of patients in need of ciclosporin therapy (de novo group) and the other consisted of patients who had been treated with the conventional formulation of ciclosporin for at least 4 months and who were presumably going to receive the drug in the new formulation for another 3 months (switched group). The following types of patients were excluded from the study:

- Patients who had failed to respond to the conventional formulation (this criterion applied only to the switched group);
- Patients with neuro-Behçet's disease;

Table 1. Medical Institutions and Investigators Participating in Clinical Trials

Medical Institution	Department	Representative Investigator	Investigator
Hokkaido University School of Medicine	Ophthalmology	Hidehiko Matsuda	Satoshi Kotake
University of Tokyo School of Medicine	Ophthalmology	Kanjiro Masuda	Yujiro Fujino Satoru Joko
Tokyo Medical College	Ophthalmology	Masahiko Usui	Junichi Sakai
Tokyo Women's Medical College	Ophthalmology	Mitsuko Kogure	Ikuko Yagi
Yokohama City University School of Medicine	Ophthalmology	Shigeaki Ono	Satoshi Nakamura
Kurume University School of Medicine	Ophthalmology	Manabu Mochizuki	Eiko Ikeda

[a]Chief investigator.

Jpn J Ophthalmol
Vol 43: 318–326, 1999

- Patients with irreversible ocular lesions, such as macular degeneration, macular hole, optic atrophy, or chorioretinal atrophy;
- Patients with renal dysfunction;
- Patients with ongoing malignancy or a history of malignancy;
- Patients with hypertension that could not be controlled with antihypertensive drugs;
- Patients with poorly controlled diabetes mellitus;
- Patients with hyperkalemia or hyperuricemia;
- Patients with serious disorders of the brain, heart, liver, or pancreas;
- Pregnant or nursing women;
- Patients with childbearing potential;
- Patients expecting to become pregnant during the study period;
- Patients with systemic infections;
- Patients with hypersensitivity to drugs;
- Patients who had received any other investigational drug within 6 months before the study;
- Other patients whose condition was inappropriate for participation in the study as judged by a physician.

Study Procedure

Dosage and administration. In the de novo group, MEPC was started at a dose level of 5.0 mg/kg per day, the approved therapeutic dosage of the current formulation,[5] and subsequently individualized according to symptoms. In the switched group, patients received MEPC at the same dose level and in the same manner as the current formulation. In addition, the following formulations were used in the de novo group to permit minor adjustments to the dosage: 10 mg capsules of the new formulation as well as conventional preparations, such as oral solution, and 50 mg and 25 mg soft gelatin capsules. No systemic use of any other immunosuppressants, any other investigational drugs, live vaccines, or systemic corticosteroids was allowed during treatment with MEPC.

Observation parameters. In the de novo group, the following items were examined before treatment and at 1 (as often as practicable), 2, 4, 8, 12, and 16 weeks of MEPC therapy, and in the switched group, they were examined on the day of switching from the conventional formulation and at 1 (as often as practicable), 2, 4, 8, and 12 weeks of MEPC therapy: (1) visual acuity and ophthalmometry, and (2) extraocular manifestations (major and minor symptoms of Behçet's disease). The occurrence of ocular attacks was recorded by noting the date(s) of the attack(s), the laterality of the affected eye(s), type of attack (anterior uveitis, posterior uveitis, vitritis, or panuveitis), and severity of attack (mild, moderate, or severe).

Laboratory test parameters. The following parameters were examined in the de novo group before treatment and at 1 (as often as practicable), 2, 4, 8, 12, and 16 weeks of MEPC therapy, and in the switched group, on the day of switching from the conventional formulation and at 1 (as often as practicable), 2, 4, 8, and 12 weeks of MEPC therapy: blood pressure, hematology, blood biochemistry (eg, renal function tests, liver function tests), urinalysis (qualitative protein, qualitative glucose, β_2-microglobulin), and plasma trough level of MEPC.

Evaluation procedure. In the de novo group, upon completion of the treatment period (ie, at week 16 of MEPC therapy) or whenever the drug was discontinued, ocular manifestations were compared with pretreatment status for final global improvement rating on a 5-point scale: markedly improved, improved, slightly improved, no change, or aggravated. The safety of treatment was also rated by assignment to one of four categories: safe, almost completely safe, minor safety problem exists, or safety problem exists, taking into account adverse events (eg, adverse reactions, adventitious disease) and clinical laboratory data. The usefulness of treatment was evaluated by integrating the global improvement and safety rating data, and it was rated on a 5-point scale: very useful, useful, slightly useful, not useful, or undesirable. In the switched group, only the safety was rated by using the same scale as above.

Results

Cases

A total of 47 patients, including 17 de novo patients, were enrolled in the study. Fourteen of the 17 de novo patients completed the study, and 3 discontinued taking the drug or dropped out. One of the 17 patients was excluded from the improvement and usefulness ratings because of the possible influence of cataract surgery performed during the study, and the patient's data were included only in the safety rating. Thirty patients were switched from the conventional formulation to MEPC; 29 of them completed the study and one patient discontinued taking the drug (Figure 1).

Patient Background Factors

Table 2 shows the background of the de novo patients. Fourteen of the 17 patients (82.4%) were men. The ages of the 17 de novo patients ranged

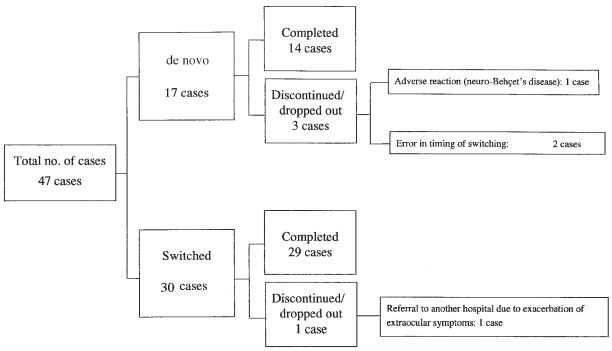

Figure 1. Enrollment and breakdown of patients.

from 19–68 years and averaged 36.5 ± 14.1 years. The disease was of the incomplete type in 13 patients (76.5%) and of the complete type in the remaining 4 (23.5%). The initial ocular manifestations occurred within 5 years of the onset of the illness in 12 patients (70.6%), whereas 3 other patients (17.6%) had at least a 10-year history of ocular inflammation. Fifteen patients (88.2%) had bilateral ocular involvement, and 5 had intercurrent ophthalmic disorders (cataract, glaucoma, or posterior synechia). Concomitant medication for Behçet's disease consisted of systemic drugs in 4 patients (23.5%) and topical medication in nearly all of the patients (16 cases, 94.1%). In the switched group, the majority of the patients were men (23 of 30 cases, 76.7%), and their ages ranged from 24 to 65 years (mean 42.1 ± 9.8 years). The disease was of the incomplete type in 21 of the 30 cases (70.0%). Initial ocular manifestations occurred within 5 years before the study in 10 of the 30 cases (33.3%), while the other 8 patients (26.7%) had experienced ocular inflammation for more than 10 years. Twenty-six patients (86.7%) had bilateral ocular involvement, and 13 patients (43.3%) had intercurrent ophthalmic disorders (cataract or glaucoma). Concomitant drugs for Behçet's disease were administered to 14 patients (46.7%) systemically and to 26 patients (86.7%) topically.

Efficacy

Changes in ocular attacks. Figure 2 shows the frequency of ocular attacks during a 4-week period before MEPC therapy and during the 16 weeks of MEPC therapy in 14 of the 17 de novo patients. Three patients were excluded, because one underwent cataract surgery during the study and 2 were treated upon referral from other clinics and thus their pretreatment frequency of attacks was unknown. Pretreatment mean frequency of ocular attacks was 0.60 ± 0.05 attacks/4 weeks and significantly decreased to 0.21 ± 0.07 attacks/4 weeks after treatment in this study ($P < .001$, Wilcoxon I). The mean frequency of attacks decreased in 11 of the 14 patients (78.6%), remained unchanged in 2 patients (14.3%), and increased in 1 patient (7.1%). In the switched group, the mean frequency of ocular attacks before switching to MEPC therapy was 0.39 ± 0.07 attacks/4 weeks and significantly decreased to 0.16 ± 0.05 attacks/4 weeks at week 12 of MEPC therapy ($P < .0004$, Wilcoxon I). The mean frequency of attacks diminished in 16 of the 30 patients (53.3%), remained unchanged in 11 patients (36.7%), and increased in 3 patients (10.0%) (Figure 2).

Changes in visual acuity. Changes in the visual acuity of 28 affected eyes in the de novo group are shown in Figure 3. Two eyes were operated on for cataracts during the study period, and 1 eye that

Table 2. Background Characteristics of Patients

	Category	De novo	Switched
Gender	Man/Woman	14/3	23/7
Age	Mean ± SD	36.5 ± 14.1	42.1 ± 9.8
Primary disease	Complete type	4	9
	Incomplete type	13	21
Ocular lesion	Unilateral, right	1	0
	Unilateral, left	1	4
	Bilateral	15	26
Duration of ocular symtoms	<1 year	4	0
	1–5 years	8	10
	5–10 years	2	12
	≥10 years	3	8
Previous therapy	No	4	13
(Systemic medication for primary disease)	Yes	13	17
Concomitant medication	No	13	16
(Systemic medication for primary disease)	Yes	4	14

Jpn J Ophthalmol
Vol 43: 318–326, 1999

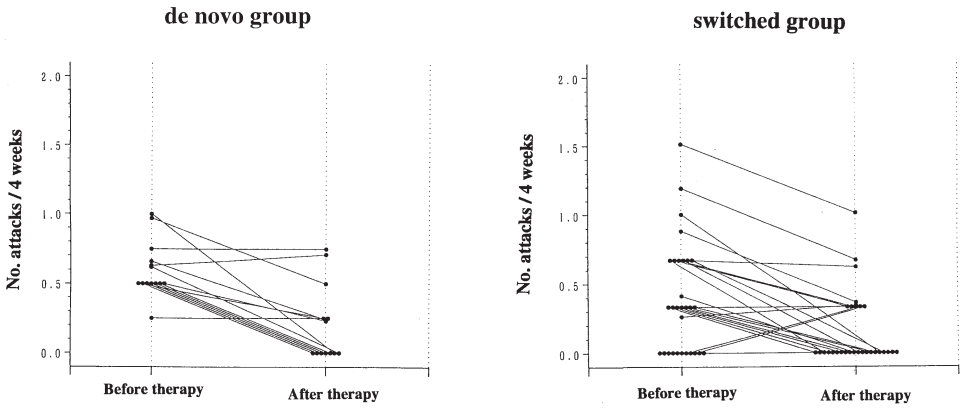

Figure 2. Changes in frequency of ocular attacks before and after therapy in de novo group and switched group. Duration of therapy was 4 months in de novo group and 3 months in switched group.

showed rapid worsening of the cataract and 3 eyes blinded by phthisis bulbi or other causes were excluded. Compared with the pretreatment vision, visual acuity improved in 20 of the 28 eyes (71.4%), remained unchanged in 5 eyes (17.9%), and deteriorated in 3 eyes (10.7%). The visual acuity of the patients in the switched group was examined in 52 affected eyes, after excluding 8 eyes blinded by phthisis bulbi or other causes. Visual acuity improved in 14 of the 52 eyes (26.9%) as compared with the results of the examination before switching, remained unchanged in 22 eyes (42.3%), and deteriorated in 16 eyes (30.8%) (Figure 3).

Final overall improvement. Table 3 shows the final global improvement rating in the de novo group based on the changes in ocular attacks, visual acuity, and ophthalmological findings as assessed by the attending physician. An "improved" or better therapeutic response was obtained in 13 of 16 patients (81.3%). With regard to the use of colchicine, five of the patients had never received colchicine either before or during the study, eight patients had received colchicine in single therapy and were switched to MEPC alone during the study, and three patients had received colchicine single therapy and were switched to MEPC-colchicine combination therapy during the study. In the global improvement rating, ocular symptoms were rated as "improved" or "markedly improved" in all five patients who had never received colchicine either before or during the study. Among the eight cases switched from colchicine to MEPC, five (62.5%) were rated as "improved" or "markedly improved," and the other

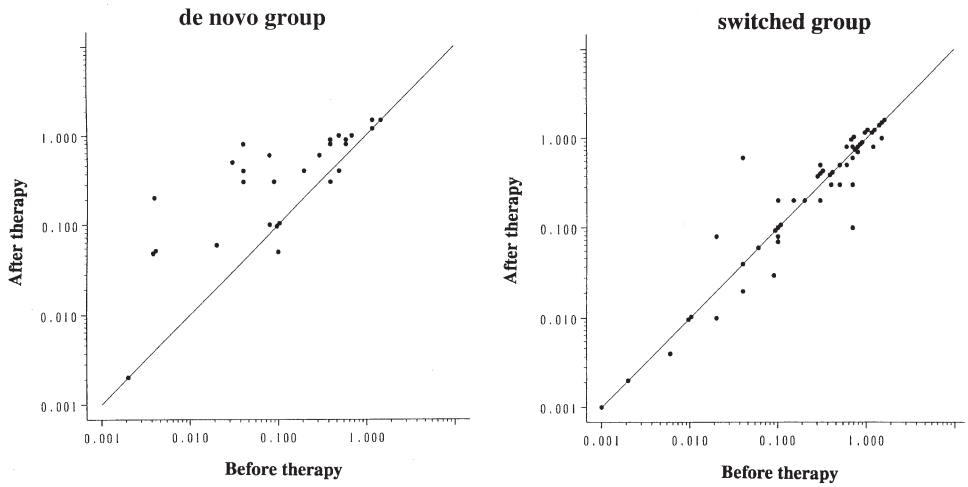

Figure 3. Changes in corrected visual acuity before and after therapy. Duration of therapy was 4 months in de novo group and 3 months in switched group.

Table 3. Final Overall Improvement Rating

						95% Two-Sided CI of Improvement Rate	
Markedly Improved	Improved	Slightly Improved	No Change	Aggravated	Total	Lower Limit	Upper Limit
4 (25.0%)	9 (56.3%)	2 (12.5%)	1 (6.3%)	0 (0.0)	16.0	54.4	96.0

Note. Percentage of cases with "improved" or better responses: 81.3% (13/16).
CI: confidence interval.

three (37.5%) as "slightly improved" or "no change." All three cases concomitantly treated with colchicine and MEPC were rated as "improved" or "markedly improved."

Adverse events and abnormal laboratory values. The subjective and objective symptoms that developed in the 17 de novo patients during the study period are shown in Table 4. Adverse events occurred in nine patients (52.9%), irrespective of their relation to MEPC. A causal relationship with MEPC could not be ruled out for 12 events in 5 patients (29.4%). They comprised one event of increased blood pressure; two events of CNS symptoms (neuro-Behçet's disease and numbness of the fingers); and nine events of gastrointestinal symptoms, such as intestinal Behçet's disease, diarrhea, and nausea. Thus, most of the adverse events encountered involved the gastrointestinal system. Medication with the test drug was discontinued in the case of neuro-Behçet's disease, but none of the other adverse events interfered with continuation of treatment or required dose reduction. Adverse events occurred in 9 of 30 patients (30.0%) in the switched group, irrespective of their relation to MEPC. A causal relationship with MEPC could not be ruled out for four adverse events in three patients (10.0%). They included two events of diarrhea, one event of hypertension, and one event of abdominal pain. All these symptoms remitted after dose reduction and did not interfere with continuation of the study.

Eighty-seven abnormal changes in laboratory values were observed in 16 (94.1%) of the 17 patients in the de novo group, irrespective of their relation to MEPC. Of these abnormal laboratory changes, 27 events in 10 patients appeared to be causally related to MEPC, and a causal relationship remained unclear for eight events in 6 patients. Ninety abnormal changes in laboratory data were reported in 28 (93.3%) of the 30 patients in the switched group, irrespective of their relation to MEPC. A causal relationship with MEPC medication was suggested for 25 events in 11 patients, and a causal relationship remained unclear for 8 events in 8 patients. The most frequent laboratory abnormalities that appeared to be causally related to the test drug were abnormal changes in blood urea nitrogen (BUN), which occurred in 4 of 17 cases (23.5%) in the de novo group and in 6 of 30 cases (20.0%) in the switched group (Table 5).

Trough Blood Level of Ciclosporin

The mean dosage level of MEPC in the de novo group was tapered (ie, 4.6, 4.3, 4.2, 4.1, and 4.0 mg/kg per day at weeks 2, 4, 8, 12, and 16, respectively). Consequently, the mean trough blood level of ciclosporin in this group also tended to decrease, falling to 168.4 ± 84.4, 178.7 ± 102.7, 129.1 ± 65.8, 157.3 ± 58.7, and 135.0 ± 46.6 ng/mL at weeks 2, 4, 8, 12, and 16, respectively. The dosage of MEPC in 8 of 17 patients was reduced because of high trough blood levels of ciclosporin. The mean dosage levels of MEPC in the switched group were almost the same throughout the study period. The dose on the day of the switch to MEPC was 3.5 mg/kg per day, and was followed by 3.5, 3.5, 3.4, 3.4, and 3.3 mg/kg per day at weeks 1, 2, 4, 8, and 12, respectively. The mean trough blood level of ciclosporin in this group rose after the switch, but tended to decline thereafter because of the subsequent dose reductions. The trough blood level on the day of the switch was 84.0 ± 43.7 ng/mL, and was followed by 119.7 ± 72.6, 103.2 ± 69.4, 99.7 ± 61.4, 102.9 ± 69.8, and 88.9 ± 50.3 ng/mL at weeks 1, 2, 4, 8, and 12, respectively. The dosage of MEPC in 2 of the 30 patients was reduced because of high trough blood levels of ciclosporin. The dosage of MEPC was never increased in any of the patients in either group.

Overall Safety

In the overall safety rating of the 17 de novo cases, the test treatment was rated as "safe" in 4 cases, "almost completely safe" in 11 cases, and "safety problem exists" in 2 cases. Those rated as "safety problem exists" consisted of 1 case of onset of neuro-Behçet's

Jpn J Ophthalmol
Vol 43: 318–326, 1999

Table 4. Summary of Adverse Reactions

Adverse Reactions	No. of Cases With Adverse Reaction (%)	
	De novo (n = 17)	Switched (n = 30)
Diarrhea	2 (11.8)	2 (6.7)
Abdominal pain	1 (5.9)	1 (3.3)
Nausea[a]	1 (5.9)	
Anorexia	1 (5.9)	
Unable to ingest food	1 (5.9)	
Gastralgia	1 (5.9)	
Intestinal Behçet's disease	1 (5.9)	
Neuro-Behçet's disease	1 (5.9)	
Numbness of fingers	1 (5.9)	
Blood pressure elevation	1 (5.9)	1 (3.3)

[a]Two events in a single case.

disease and 1 case of blood pressure elevation concurrent with intestinal Behçet's disease. In the overall safety rating of the 30 cases in which therapy was switched, the test treatment was rated as "safe" in 18 cases, "almost completely safe" in 11 cases, and "safety problem exists" in 1 case. In the case rated "safety problem exists," the trial was discontinued because the patient was transferred to another hospital because of exacerbation of extraocular symptoms. Although this adverse event was unrelated to the study drug, laboratory tests performed at the other hospital revealed abnormalities of renal function (elevation of serum creatinine, BUN, and plasma β^2-microglobulin) and impairment of liver function (elevation of serum glutamine-oxaloacetic transaminase and glutamic-pyruvic transaminase). After switching to the conventional formulation with subsequent dose reduction and temporary withdrawal of the drug, the patient's condition improved. All the adverse events and abnormal laboratory changes observed in the present study have previously been reported with the conventional formulation of ciclosporin, and none of these events or changes seemed to be cause for concern.

Usefulness

Upon completion or discontinuation of the test treatment, the usefulness of MEPC was evaluated in the de novo group by integrating the global improvement rating and the safety rating. The results showed that the test treatment was "useful" or "more useful" in 13 of the 16 patients (81.3%), and "slightly useful," "not useful," or "undesirable" in one case each (6.3%).

Discussion

The efficacy of ciclosporin in the treatment of Behçet's disease has already been documented in reports of double-blind controlled trials of the current formulation versus colchicine. The improvement rate (determined by integrating "improved" and "markedly improved") in the study with ciclosporin oral solution was 74.5% (35 of 47 cases)[17] and the improvement rate ("moderately" and "markedly" improved) in the study with ciclosporin capsules was 80.0% (4 of 5 cases).[18] In the present study, visual acuity improved in 71.4% (20 of 28 cases) of the de novo patients, and the frequency of their ocular attacks also decreased significantly. Based on improvement rate (percent of cases with "improved" or better therapeutic responses), the efficacy of MEPC in the de novo patients in the present study was 81.3% (13 of 16 cases). Although the initial dosage in the present study was the recommended initial dosage of MEPC, ie, 5 mg/kg per day, and lower than the initial dosage in previous studies (10 mg/kg per day[17]), similar efficacy was obtained. Thus, the present data corroborated the usefulness of MEPC in the treatment of Behçet's disease. However, the dosage of MEPC was reduced during the course of treatment in some of the cases in the present study because of high trough blood levels of ciclosporin. This indicates that the dosage should be adjusted according to the trough blood level, as is the case with the conventional formulation.

Of the patients in the de novo group, 68.8% (11 of 16 patients) had been treated with colchicine previously, and in view of this, we assessed the cases previously treated with colchicine separately. Although the small sample size hardly permits comparative evaluation, the ocular manifestations improved after the study treatment in 8 (72.7%) of the 11 patients who had been treated with colchicine, suggesting that ciclosporin therapy, whether in combination with colchicine or not, may provide a greater clinical benefit than colchicine alone. No adverse events sus-

Table 5. Abnormal Changes in Laboratory Values

	No. of Cases With "Unclear or Worse" Changes (%)	
Laboratory Data	De novo (n = 17)	Switched (n = 30)
Hematology		
RBC	1/17 (5.9)	
Hemoglobin	2/17 (11.8)	1/30 (3.3)
Hematocrit	2/17 (11.8)	1/30 (3.3)
Serum biochemistry		
GOT	2/17 (11.8)	3/30 (10.0)
GPT	2/17 (11.8)	3/30 (10.0)
γ-GTP	2/17 (11.8)	4/30 (13.3)
ALP	1/17 (5.9)	1/30 (3.3)
Total bilirubin	1/17 (5.9)	
CPK	2/17 (11.8)	2/30 (6.7)
Mg	3/17 (17.6)	
Triglycerides	1/17 (5.9)	3/30 (10.0)
Total cholesterol	3/17 (17.6)	
Uric acid	2/17 (11.8)	2/30 (6.7)
CRP	1/17 (5.9)	1/30 (3.3)
β_2-microglobulin	3/17 (17.6)	2/28 (7.1)
Serum creatinine	1/17 (5.9)	2/30 (6.7)
BUN	4/17 (23.5)	6/30 (20.0)
Urinalysis		
Protein	1/14 (7.1)	1/28 (3.6)
β_2-microglobulin	1/14 (7.1)	1/29 (3.4)

RBC: red blood cell count; GOT: glutamine-oxaloacetic transaminase; GPT: glutamic-pyruvic transaminase; γ-GTP: gamma guanosine triphosphate; ALP: alkaline phosphatase; CPK: creatine phosphokinase; Mg: magnesium; CRP: C-reactive protein; BUN: blood urea nitrogen.

pected of having a causal relationship with the study medication occurred in any of the four patients who received MEPC alone, but a causal relation was suspected for adverse events observed in two of the eight patients who received concomitant colchicine medication. All these reactions involved the gastrointestinal system and posed no problems of clinical concern. None of the clinical laboratory test parameters revealed any significant bias in the distribution of abnormal values between MEPC therapy and combined MEPC-colchicine therapy. Nevertheless, reports suggesting an increased incidence of myopathy and gastrointestinal adverse events during concomitant therapy with ciclosporin and colchicine seem to arouse concern about such untoward reactions.[19,20]

The frequency of ocular attacks also significantly decreased in 16 of 30 patients in the switched group. This indicates that the clinical benefits of ciclosporin remained unchanged even after the switch to MEPC. Although the pharmacokinetics in the present series are unknown because the area under the time-concentration curve (AUC) of ciclosporin was not determined, the trough blood ciclosporin level significantly increased in some patients in the switched group, despite maintenance of the previous dose level. In a comparison between the pharmacokinetics of MEPC and the currently available formulation, Kahan et al[15] reported a decrease in T_{max}, an increase in C_{max}, and an increase in AUC in 55 renal transplant patients upon switching to MEPC from the current formulation. Also, according to Erkko et al,[13] the C_{max} and AUC increased when patients were on MEPC during sequential therapy with MEPC and the current formulation for 4 weeks and 2 weeks, respectively. Thus, available reports suggest that MEPC has a shorter T_{max}, higher C_{max}, and greater AUC than the current formulation. Our present study also implies that this pharmaceutical profile of MEPC contributed to improving absorption and elevating the plasma concentration, and as a result provided better efficacy in some of the cases.

MEPC was rated as "safe" in 23.5% (4 of 17 cases) of the present de novo patients, compared with 12.8% (6 of 47 cases) in previous double-blind controlled trials of ciclosporin versus colchicine (initial dose level of ciclosporin: 10 mg/kg per day).[17] All the adverse events and abnormal laboratory values observed in this study have been reported with the conventional formulation, and there were no new find-

Jpn J Ophthalmol
Vol 43: 318–326, 1999

ings of clinical concern. MEPC may, therefore, be used in the same way as the conventional formulation. MEPC therapy was rated as "almost completely safe" or "safe" in 29 of the 30 patients (96.7%) in the switched group, and the adverse events and abnormal laboratory values that occurred could be controlled without any treatment or by dose reduction.

The data obtained in this study have demonstrated that MEPC can be used in the same way as the conventional formulation of ciclosporin and that the conventional formulation can be switched to MEPC at the same dosage. However, since MEPC may increase the plasma AUC of ciclosporin, this may lead to an increase in adverse events. Therefore, regular monitoring of blood trough levels of ciclosporin, clinical manifestations, and laboratory parameters is important, and the dose should be adjusted according to the ocular symptoms whenever necessary.

References

1. Nussenblatt RB. Cyclosporine A. Inhibition of experimental autoimmune uveitis in Lewis rat. J Clin Invest 1981;67:1228–31.
2. Nussenblatt RB, Palestine AG, Chan CC. Cyclosporin A therapy in the treatment of intraocular inflammatory disease resistant to systemic corticosteroids and cytotoxic agents. Am J Ophthalmol 1983;96:275–82.
3. Nussenblatt RB, Palestine AG, Chan CC, Mochizuki M, Yancy K. Effectiveness of cyclosporin therapy for Behçet's disease. Arthritis Rheum 1985;28:671–9.
4. Masuda K, Nakajima A, Urayama A, Nakae K, Kogure M, Inaba G. Double-masked trial of cyclosporin versus colchicine and long-term open study of cyclosporin in Behçet's disease. Lancet 1989;8647:1093–5.
5. Masuda K, Sakane T. Guide for the treatment of ciclosporine on Behçet's disease. In: Annual Reports of Behçet's Disease Research Committee, Japan, Ministry of Health and Welfare, 1993:245–9.
6. Lemaire M, Fahr A, Maurer G. Pharmacokinetics of cyclosporine: inter- and intra-individual variations and metabolic pathways. Transplant Proc 1990;22:1110–2.
7. Mochizuki M, Katabami T, Hayashi K. Trough level of ciclosporin in Behçet's disease. Transplant Now 1992;5(Suppl) 1:73–8.
8. Yuasa T, Nakagawa Y, Haruta Y, Ohji M. Long-term administration of ciclosporin in Behçet's disease and survey of noneffective cases. In: Annual Reports of Behçet's Disease Research Committee, Japan, Ministry of Health and Welfare, 1991:137–9.
9. Friman S, Backman L. A new microemulsion formulation of cyclosporin. Pharmacokinetic and clinical features. Clin Pharmacokinet 1996;30:181–93.
10. Kovarik JM, Meuller EA, van Bree JB. Reduced inter- and intraindividual variability in cyclosporine pharmacokinetics from a microemulsion formulation. J Pharm Sci 1994;83:444–6.
11. Bourke JF, Berth-Jones J, Holder J, Graham-Brown RA. A new microemulsion formulation of cyclosporin (Neoral) is effective in the treatment of cyclosporin-resistant dermatoses. Br J Dermatol 1996;134:777–9.
12. Berth-Jones J, Henderson CA, Munro CS, et al. Treatment of psoriasis with intermittent short course cyclosporin (Neoral). A multicentre study. Br J Dermatol 1997;136:527–30.
13. Erkko P, Granlund H, Nuutinen M, Reitamo S. Comparison of cyclosporin A pharmacokinetics of a new microemulsion formulation and standard oral preparation in patients with psoriasis. Br J Dermatol 1997;136:82–8.
14. van de Borne BE, Landewe RB, Goei The HS, Mattie H, Breedveld FC, Dijkmans BA. Relative bioavailability of a new oral form of cyclosporin A in patients with rheumatoid arthritis. Br J Clin Pharmacol 1995;39:172–5.
15. Kahan BD, Dunn J, Fitts C, et al. The neoral formulation: improved correlation between cyclosporine trough concentrations and exposure in stable renal transplant recipients. Transplant Proc 1994;26:2940–3.
16. Mueller EA, Kally Z, Kovarik JM, et al. Bile-independent absorption of cyclosporine from a microemulsion formulation in liver transplant patients. Transplantion 1995;60:515–7.
17. Masuda K, Nakazima A, Urayama A, Nakae K, Kogure M, Inaba G. A double-masked controlled study of the treatment of Behçet's disease with ciclosporin. Rinsho Hyoka (Clin Eval) 1986;14:437–61.
18. Inaba G, Nakazima A, Ohno S, Kogure M. Clinical experience with ciclosporin soft gelatin capsules for treatment of ocular lesions of Behçet's disease. Shinyaku To Rinsho 1989;38:10–6.
19. Rieger EH, Halasz NA, Wahlstrom HE. Colchicine neuromyopathy after renal transplantation. Transplantation 1990;49: 1196–8.
20. Kotake S, Ichiishi A, Kosaka S, Yoshikawa K, Minagawa R, Matsuda H. Low dose cyclosporin treatment for ocular lesions of Behçet's disease. Nippon Ganka Gakkai Zasshi (Acta Soc Ophthalmol Jpn) 1992;96:1290–4.