

life saving in affected patients and their families.

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Improvement of Noninfectious Uveitis With Fumaric Acid Esters: Results of a Pilot Study

Noninfectious endogenous uveitis often improves under corticosteroid therapy, second-line immuno-

suppressing drugs, or “biologicals.” Although they are very helpful, their use might be limited by their adverse effects.

The aim of this pilot study was to investigate the effect of fumaric acid esters (FAEs), which are used for the treatment of psoriasis on endogenous noninfectious intermediate or posterior uveitis. Besides the clinical response, treatment-related modulation of the peripheral blood mononuclear cells was investigated.

Methods. Inclusion criteria were noninfectious endogenous uveitis and vision-threatening complications without inflammatory quiescence under current systemic steroid medication or a maintenance dosage that would otherwise be an indication for a second-line immunosuppressive medication. Visual acuity was above 20/200 in the better eye. The study design complied with the Declaration of Helsinki ethical standards. The local ethics committees approved the study. Informed consent was obtained from the patients. Overall, 4 patients with bilateral uveitis were treated with FAEs and were followed up prospectively (**Table 1**).

After we established the diagnosis, all patients were first treated with systemic steroids with an initial dosage of approximately 1 mg per kilogram of body weight. After achieving quiescence of inflammation, the steroid dosage was tapered off. When inflammation recurred (a cell increase of >2 steps in the aqueous humor or the vitreous) or deterioration of visual acuity (>2 Snellen lines) or cystoid macular edema occurred, treatment with FAEs was started. The increase of FAE dosage was performed every week in accordance with recommended guidelines.¹

All patients were seen at baseline; after 2, 6, and 12 weeks; and then at 3-month intervals. At each follow-up visit, we performed a routine clinical examination, including optical coherence tomography and fluorescein angiography. Blood tests, including assessments of leukocytes, lymphocytes, and subpopulations, were performed according to generally accepted protocols.

Results. The epidemiological data and the previous and current anti-inflammatory therapy of the patients are summarized in Table 1. In 3 patients, the FAE dose could be increased to the maximal effective dose. One patient developed gastrointestinal adverse effects, so the maintenance dose was reduced. Two patients were able to stop additional steroid medication under a maintenance dose of FAEs. In the patient treated with a lower FAE dose, the systemic steroids could be reduced from 20 mg (0.3 mg/kg) to 5 mg (0.08 mg/kg). In another patient with intermediate uveitis, prednisone was tapered down from 20 mg (0.28 mg/kg) daily to 6 mg (0.09 mg/kg). Tapering off the oral steroids was, in general, possible after the 12-week visit. At this point, a clinical improvement was also evident in all 4 patients.

The clinical course of uveitis noted under treatment is summarized in **Table 2**. Vision improved over time in all patients who had reduced visual acuity at the baseline visit. Cystoid macular edema was present at the last visit only in 1 eye by angiographic means, but this was not detectable by optical coherence tomography. In the other patients, cystoid macular edema was no longer detected (**Figure 1**). No significant numbers of anterior chamber cells were seen in any patient during the whole follow-up period. Uveitis did not recur in any of the patients under therapy. Fumaric acid ester therapy was continued in all patients, and no additional complications from uveitis developed during the follow-up period.

Compared with the baseline before FAE institution, average \pm SD leukocyte counts dropped from 100% before FAE treatment to 79.9% \pm 13.6 ($P = .03$) and the lymphocyte count to 77.2% \pm 25.6 ($P = .08$) after 3 months of treatment. **Figure 2A** shows the pattern of peripheral blood leukocytes, lymphocytes, and their subpopulations of all patients. Additionally, **Figure 2B** describes a shift in T lymphocytes with an increased CD4⁺/CD8⁺ ratio.

No significant change in the liver enzyme, creatinine, or urea levels occurred during the whole treatment

Table 1. Epidemiological Data for Patients Treated for Uveitis With Fumaric Acid Esters

Patient No./Sex/Age, y	Uveitis Type/Any Associated Disease	Duration of Uveitis Before FAE Therapy, mo	Therapy Before FAEs	Follow-up of FAE Therapy, mo	FAE Maintenance Dose	Final Prednisone Therapy	FAE Adverse Effects
1/M/37	Intermediate uveitis	18	Oral prednisone	12	600 mg/d	5 mg	Flush, GIT
2/F/46	Birdshot chorioretinopathy/ unspecified CNS tumor	24	Oral prednisone	15	1200 mg/d	No	Flush
3/F/39	Intermediate uveitis	12	Oral prednisone	12	1200 mg/d	No	Flush
4/F/29	Intermediate uveitis	15	Oral prednisone	12	1200 mg/d	6 mg	Flush

Abbreviations: CNS, central nervous system; FAE, fumaric acid ester; GIT, gastrointestinal disturbance.

Table 2. Clinical Data With Assessment of CME by Fluorescein Angiography and Optical Coherence Tomography*

Characteristic	Patient 1		Patient 2		Patient 3		Patient 4	
	OD	OS	OD	OS	OD	OS	OD	OS
	Before FAE Therapy							
BCVA	20/50	20/32	20/20	20/20	20/200	20/50	20/20	20/20
CME (angiogram)	+	+	-	-	+	-	+	-
CME (OCT)	+	+	-	-	+	-	-	-
Vitreous opacities	++	+	++	++	++	+	++	+
	Last Visit							
BCVA	20/40	20/25	20/20	20/20	20/63	20/32	20/20	20/20
CME (angiogram)	-	-	-	-	-	-	+	-
CME (OCT)	-	-	-	-	-	-	-	-
Vitreous opacities	-	-	-	-	+	-	-	-

Abbreviations: BCVA, best-corrected visual acuity; CME, cystoid macular edema; FAE, fumaric acid ester; OCT, optical coherence tomography.

*Cystoid macular edema was graded as present (+) or absent (-) by angiography and optical coherence tomography. Vitreous opacities were graded according to Nussenblatt et al (1985).²

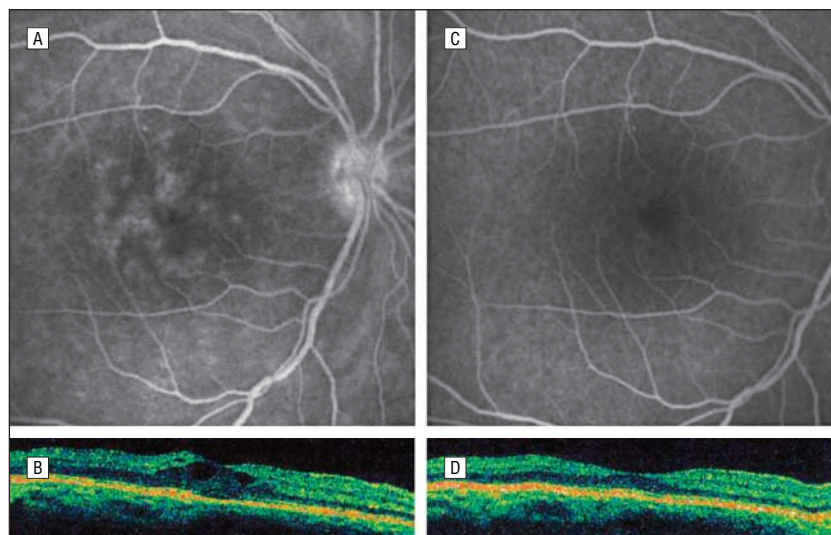


Figure 1. Representative course of cystoid macular edema of patient 3 by angiography and optical coherence tomography at the beginning of fumaric acid ester treatment (A and B) and 3 months after institution of therapy (C and D). The angiogram was taken 3 minutes after fluorescein injection.

period in any of the patients. As the main adverse effect, dermal flush occurred in all patients immediately after institution of the therapy, and gastrointestinal disturbance was noticed

in patient 1 after 3 months of FAE therapy.

Comment. Since 1994, a mixture of FAEs has been commercially avail-

able as Fumaderm (Fumapharm AG, Lucerne, Switzerland) and is used for the systemic therapy for severe psoriasis,³ which is a T-cell-mediated autoimmune disease. Double-blind, placebo-controlled studies revealed high efficacy as an anti-psoriasis medication.⁴ A phase 2 study for multiple sclerosis and a phase 3 study for psoriasis are currently being conducted with a new FAE formulation.

Fumaric acid ester treatment was necessary in all of the patients herein despite their relatively good visual acuity because all patients had adverse effects owing to systemic steroid therapy, or had a dosage above the acceptable level, and because they had vision-threatening complications. The improvement of vitreous opacities reflects the reduction of inflammation. Furthermore, FAE treatment also resulted in an improvement of cystoid macular edema in 4 patients. In this study, FAEs offered the opportunity to reduce or even to stop the steroid treatment in

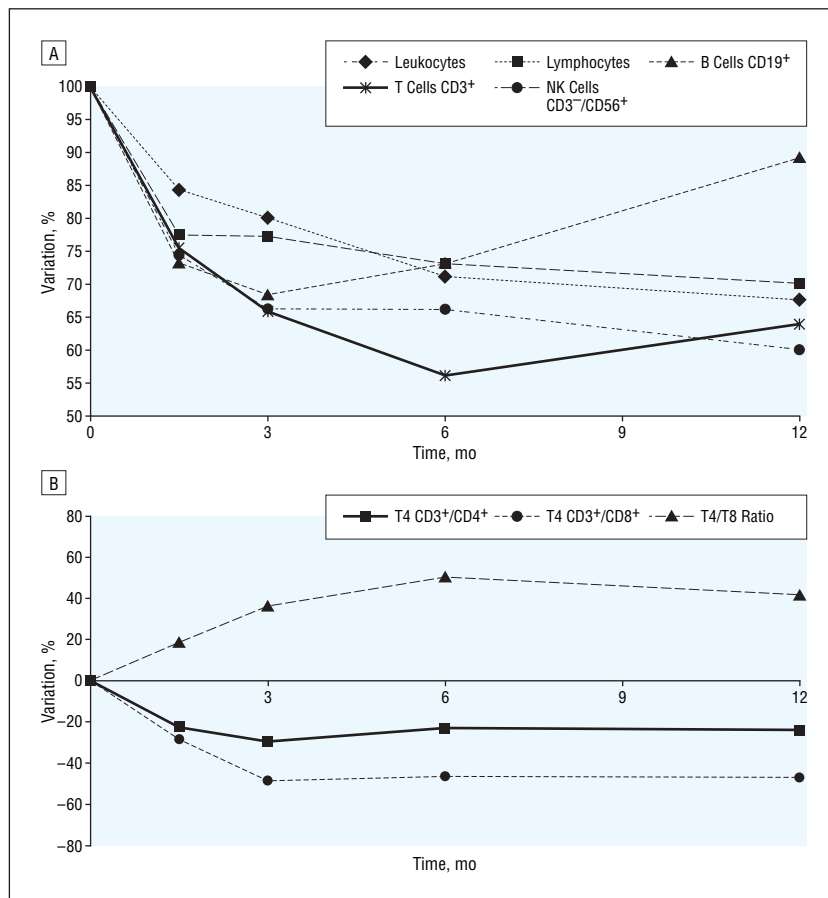


Figure 2. Individual changes in percentage of variation of patient 2 in peripheral blood white cells and the subpopulations (A) and in T cells and the CD4/CD8 ratio (B). NK indicates natural killer; T4, T helper lymphocytes; T8, T suppressor cells.

all 4 patients. The immunosuppressive effect of FAEs on the white blood cells seen in our patients was similar to those in psoriasis patients.⁵

In intermediate uveitis, an increased number of peripheral blood T cells was found. It has been shown that FAEs can modulate the immune response by a predominant reduction of CD8⁺ T lymphocytes⁵ and a shift of the T cell response to a T helper 2 subtype.⁶ In experimental autoimmune uveoretinitis, it has been shown that suppression of T helper 1 response successfully reduced the degree of inflammation. These preliminary data suggest that improvement of uveitis was associated with reduced T cell subsets.

One major problem with FAEs seems to be the adverse effects, mainly gastrointestinal disturbance (1 patient) and dermal flushing (all patients).⁴ No serious ad-

verse effects, especially opportunistic infections, occurred. However, as no carcinogenic effect of FAEs is yet known, it may also be used in patients with malignancies or unspecified tumors.

This pilot study offers a promising perspective on FAEs, a new therapeutic agent treating selected patients with noninfectious uveitis with a chronic clinical course. Further prospective case-control investigations with larger study populations are required to define the role of FAEs in the treatment of uveitis in more detail.

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Acetazolamide in the Treatment of X-Linked Retinoschisis Maculopathy

Macular schisis cavities observed in patients with X-linked retinoschisis are not associated with leakage on fluorescein angiogram as seen in other forms of cystoid macular edema. We report a case in which a young patient with this condition showed a reproducible clinical response to oral acetazolamide therapy with normalization of both macular anatomy and visual acuity.

Report of a Case. An 8-year-old boy was evaluated for reduced central vision. At age 4 years, pigmentary changes were noted in his left fundus, and he had been treated for amblyopia with hyperopic correction and patching. Best-corrected visual acuities in each eye had varied between 20/60 and 20/30.

He had no other significant medical history and received no medications, and the family ophthalmic history was positive only for amblyopia in a great-uncle. Snellen visual acuities were OU 20/70 with equally reactive pupils. Dilated examination