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Treatment of ocular cicatricial pemphigoid with tacrolimus (FK 506)

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Abstract *Purpose:* To evaluate the efficacy of tacrolimus (FK 506) therapy in patients with ocular cicatricial pemphigoid (OCP). *Methods:* In a cohort study, six patients with OCP, in whom the disease was not controlled by conventional immunosuppressive agents administered in high doses for an appropriate period of time, were treated with FK 506. The FK 506 was administered orally at the daily dose of 8 mg. Final clinical response to FK 506 was divided into three categories based on the difference between severity of conjunctival inflammation before and after FK 506 therapy. "Total control" of disease activity was defined as residual inflammatory activity of 0.5 or less in the final examination and an inflammation decrement of at least 0.5 between initial and final examination. "Partial control" was defined as final disease activity 1.0 or 1.5 and at least 0.5 decrement of disease activity between initial and final examination. "Uncontrolled inflammation" was defined as final disease activity above 1.5 or no improvement between initial and final activity. *Results:* The average age of the patients was 67.5 years (range 50–75 years). Male to female ratio was 1:1. The average duration of OCP prior to beginning of FK 506 treatment was 6.25 years (range 3–12.5 years). The average duration of treatment with FK 506 was 11 months (range 5–18 months). The average disease activity prior to the administration of FK 506 was 2.6 (range 2.0–3.0). The average disease activity at the time when FK 506 was stopped was 2.0 (range 1.0–2.5). In four patients (67%) FK 506 failed to control activity of OCP, and in two patients (33%) the activity was controlled partially. *Conclusions:* Although FK 506 was not used in a prospective randomized trial and although we used the drug only in patients with OCP refractory to conventional immunosuppressive agents, it is likely that FK 506 is incapable of controlling the activity of OCP and inducing a remission.

Introduction

Ocular cicatricial pemphigoid (OCP) is a systemic autoimmune disease characterized by the presence of circulating autoantibodies in serum [1], elevated serum levels of proinflammatory cytokines [2], and dysregulation of T lymphocytes [3]. OCP primarily affects the conjunctiva, causing chronic cicatrizing conjunctivitis that ultimately results in blindness. In addition to the eye, OCP can also affect the skin and oral, nasopharyngeal, laryngeal, esophageal, genital, and anal mucosae [4].

Topical therapy, originally used in treatment of OCP, is ineffective in controlling the disease. As with other autoimmune disorders, immunomodulatory drugs have been employed in treatment of OCP. Therapy of OCP with systemic steroids [1] and immunosuppressive agents such as dapsone [5], methotrexate [5], azathioprine [6], and cyclophosphamide [6] is described in the

literature. Recently, intravenous immunoglobulin therapy was reported in patients with OCP recalcitrant to conventional immunomodulators [7].

Tacrolimus (FK 506) is an effective immunosuppressive agent whose mechanism of action is similar to that of cyclosporin A (CSA). FK 506 acts primarily on T-helper lymphocytes by inhibiting the production of lymphokines, principally interleukin-2 (IL-2). The clinical use of FK 506 has been recently reviewed [8]. To date, there are no reports on use of FK 506 for treating OCP.

We present a group of patients with OCP in whom the disease was not controlled by conventional therapeutic agents administered in high doses for an appropriate period of time. These patients were then treated with FK 506, which was also ineffective in controlling the disease activity and inducing a remission.

Patients and methods

Six patients were treated with FK 506 (Prograf, Fujisawa Pharmaceuticals, Osaka, Japan). All suffered from chronic cicatrizing conjunctivitis. Immunohistochemical analysis of biopsied inflamed conjunctiva disclosed immunoglobulin and/or complement deposition at the epithelial basement membrane zone of each patient. All patients had circulating autoantibodies which bound to the epithelial BMZ of normal human conjunctiva [9] and to the epidermal side of salt-split skin preparations on indirect immunofluorescence [10]. The circulating autoantibodies recognized a 205-kDa protein, previously identified as β4-integrin, in an immunoblot assay using normal human conjunctival lysates [11].

The following information was collected for each patient: age at onset of cicatrizing conjunctivitis, sex, duration of the disease prior to FK 506 therapy, previous systemic treatment, involvement of other mucosae or skin, and conjunctival injection before and after the FK 506 therapy (Table 1).

Previous treatment

Prior to the beginning of FK 506 therapy each patient had been treated with at least two systemic immunomodulators. Neither remission nor a significant clinical response was observed when using either of these drugs. In addition, some patients developed clinically significant side effects necessitating withdrawal of the medication. Thus, FK 506 therapy was started in this group of patients.

Disease activity

The severity of the eye disease was detected based on the conjunctival injection as previously described [5]. A single observer

Table 1 Clinical data on six patients with OCP refractory to conventional immunosuppressive drugs treated with FK 506

Patient	Sex	Age at onset (years)	Previous treatment	Other mucosae involved	Duration of OCP prior to FK 506 (years)	Activity prior to FK 506[a]	Duration of FK 506 Rx (months)	Activity at the end of FK 506[a]	Side effects	Reason to discontinue FK 506	Final clinical response to FK 506
1	F	60	Prednisone, Dapsone, Ara-C, MTX	None	12.5	3+	18	2+	Elevated BUN, worsenning of DM	Persistent inflammation	Uncontrolled inflammation
2	M	74	Dapsone, CTX, Imuran, Ara-C, MTX	None	3.5	2+	5	2+	Anemia, thrombocytopenia	Persistent inflammation	Uncontrolled inflammation
3	F	50	Prednisone, dapsone	Mouth, pharynx, larynx, esophagus, nose, vagina	3	2.5+	15	1.5+	Nausea	Persistent inflammation	Partial control
4	M	75	Prednisone, dapsone, CTX, Ara-C	None	9.5	2+	9	l+	None	Persistent inflammation	Partial control
5	M	74	Dapsone, MTX, Cytoxan, Ara-C	None	6	3+	11	3+	None	Persistent inflammation	Uncontrolled inflammation
6	F	72	Prednisone, dapsone	Mouth	3	3+	8	2.5+	Tremor	Persistent inflammation	Uncontrolled inflammation

[a] Conjunctival injection

(C.S.F.) had graded the degree of disease activity, i.e., conjunctival injection, using a scale of zero to four in increments of 0.5.

Because OCP is sometimes asymmetric, each patient was graded according to the eye with the higher degree of inflammation.

Clinical response

Final clinical response to FK 506 was divided into three categories based on the difference in severity of conjunctival inflammation before and after FK 506 therapy [12]. "Total control" of disease activity was defined as residual inflammatory activity of 0.5 or less in the final examination and an inflammation decrement of at least 0.5 between initial and final examination. "Partial control" was defined as final disease activity of 1.0 or 1.5 and at least 0.5 decrement of disease activity between initial and final examination. "Uncontrolled inflammation" was defined as final disease activity above 1.5 or no improvement between initial and final activity.

Administration and monitoring of FK 506 therapy

The FK 506 therapy was started in all patients after previous conventional immunosuppressive treatment had failed. The FK 506 was administered orally at the daily dose of 8 mg. A complete eye examination along with monitoring of CBC, serum levels of creatinine and BUN, and clinical manifestation of adverse side effects was performed regularly every 6 weeks in each patient.

Results

The average age of the patients was 67.5 years (range 50–75 years). The male to female ratio was 1:1. The average duration of OCP prior to beginning of FK 506 treatment was 6.25 years (range 3–12.5 years). The average duration of treatment with FK 506 was 11 months (range 5–18 months).

Previous treatment

Prednisone was used in four patients. All of them responded well to a dose of 60–80 mg daily. However, recurrences occurred when the dose was tapered. In addition, decompensation of diabetes mellitus was recorded in one patient.

Dapsone was employed in the treatment of five patients. The activity of OCP was partially reduced in four patients. In one patient no clinical response was noted. Two patients developed clinically significant hemolytic anemia.

Methotrexate was used in three patients. In none of them was significant clinical improvement noted. In addition, one patient developed mouth sores despite the use of folic acid.

Azathioprine was administered in one patient. No satisfactory clinical response was observed and therefore the drug was stopped.

Cyclophosphamide was employed in the care of three patients. One patient developed anemia and leukopenia that necessitated withdrawal of the drug. Cyclophosphamide produced clinically significant reduction of conjunctival inflammation in two patients, but recurrence occurred when the drug was discontinued after 1 year of therapy. The recurrent inflammation did not respond to retreatment with cyclophosphamide.

Cytosine arabinoside (Ara-C) was used in treatment of four patients. No significant clinical response was noted in any of them.

Subconjunctival injections of dexamethasone sodium phosphate (1 mg) and mitomycin C (0.1 mg) failed to produce more than a transient reduction in conjunctival inflammation in all six patients.

Disease activity and clinical response

The average disease activity prior to the administration of FK 506 was 2.6 (range 2.0–3.0). The average disease activity at the time when FK 506 was stopped was 2.0 (range 1.0–2.5). In four patients (67%) FK 506 failed to control activity of OCP, and in two patients (33%) the activity was controlled partially.

Discussion

We present preliminary results of FK 506 therapy in six patients with OCP. We turned to FK 506 in this group of patients because previous immunosuppressive therapy had failed to produce a satisfactory clinical response or had induced significant side effects that necessitated withdrawal of the drug. Despite the fact that the highest recommended oral dose of FK 506 was used at least for 5 months, FK 506 failed to adequately control ocular inflammation and induce remission in any patient. In two patients the disease activity was controlled partially. OCP is a classic systemic autoimmune disease that requires prolonged systemic immunosuppressive therapy in order to achieve control of disease activity and induce remission. As for other autoimmune diseases, corticosteroids and a spectrum of immunosuppressive agents were employed in treatment of OCP. Previous studies showed that systemic corticosteroids alone are less effective than immunosuppressive drugs in halting the scarring ocular process [12, 13]. Chronic use of prednisone for OCP is unacceptable because of adverse side effects such as aseptic hip necrosis, uncontrolled diabetes mellitus, and hypertension [12, 14].

Successful treatment of progressive OCP with immunosuppressive agents, particularly with azathioprine, was initially reported by Dave and Vickers in 1974 [15]. Brody and Pirozzi were the first to employ cyclophosphamide in the treatment of OCP [16]. Since then, the safety and efficacy of systemic immunosuppressive therapy for this autoimmune disease have been confirmed in two prospective clinical trials [3, 17] and in other studies [5, 6].

The efficacy and safety of FK 506 therapy has been demonstrated when used for prevention of solid organ

transplant rejection [18, 19] and in treatment of autoimmune diseases such as psoriasis [20], uveitis [21], type I diabetes mellitus [22], pediatric autoimmune enteropathy [23], and Crohn's disease [24]. FK 506 is an effective immunosuppressive agent which acts primarily on CD4+ T-helper lymphocytes by inhibiting the production of lymphokines, principally IL-2, at the transcriptional level. It is 10–100 times more potent than CSA in its ability to inhibit IL-2 mRNA synthesis [25]. Moreover, like CSA, FK 506 inhibits mediator release from basophils and mast cells, which may also contribute to its range of therapeutic effects [26, 27]. It is noteworthy that we previously noticed a failure of cyclosporine therapy in patients with OCP [5]. The mechanism of action of FK 506 and cyclosporine is similar. Both drugs selectively inhibit the transcription of the IL-2 gene, as well as macrophage colony stimulating factor (GM-CSF), and c-myc in activated human peripheral T cells [28]. Based on the fact that neither FK 506 nor CSA have been shown to be effective in controlling the activity of OCP, one can hypothesize that the major pathogenetic pathway in this disease involves immune mediators other than those inhibited by FK 506 or CSA.

In conclusion, although FK 506 was not used in a prospective randomized trial and although we used the drug only in patients with OCP refractory to conventional immunosuppressive agents, it is likely that FK 506, just like CSA, is incapable of controlling the activity of OCP and inducing remission.

References

1. Mohimen A, Neumann R, Foster CS, Ahmed AR (1993) Detection and partial characterization of ocular cicatricial pemphigoid antigens on COLO and SCABER tumor cell lines. Curr Eye Res 12:741–752
2. Lee SJ, Li Z, Sherman B, Foster CS (1993) Serum levels of tumor necrosis factor-alpha and interieukin-6 in ocular cicatricial pemphigoid. Invest Ophthalmol Vis Sci 34:3522–3525
3. Foster CS (1986) Cicatricial pemphigoid. Trans Am Ophthalmol Soc 84:527–663
4. Ahmed AR, Kurgis BS, Rogers RS, et al (1991) Cicatricial pemphigoid. J Am Acad Dermatol 24:987–1000
5. Foster CS, Neumann R, Tauber J (1992) Long term results of systemic chemotherapy for ocular cicatricial pemphigoid. Doc Ophthalmol 82:223–229
6. Foster CS, Wilson LA, Ekins MB (1982) Immunosuppressive therapy for progressive ocular cicatricial pemphigoid. Ophthalmology 89:340–353
7. Foster CS, Ahmed RA (1999) Intravenous immunoglobulin therapy for ocular cicatricial pemphigoid. A preliminary study. Ophthalmology 106:2136–43
8. Letko E, Bhol K, Pinar V et al (1999) Tacrolimus (FK 506). Ann Allergy Asthma Immunol 83:179–192
9. Ahmed AR, Khan KN, Wells PA, et al (1989) Preliminary serological studies comparing immunofluorescence assay with radioimmunoassay. Curr Eye Res 8:1011–1019
10. Chan RY, Bhol K, Tesavibul N, et al (1999) The role of antibody to human β4-integrin in conjunctival basement membrane separation: possible in vitro model for ocular cicatricial pemphigoid. Invest Ophthalmol Vis Sci 40:2283–90
11. Bhol K, Mohimen A, Neumann R, et al (1996) Differences in the antibasement membrane zone antibodies in ocular cicatricial pemphigoid and pseudo-ocular cicatricial pemphigoid. Curr Eye Res 15:521–523
12. Neumann R, Tauber J, Foster CS (1991) Remission and recurrence after withdrawal of therapy for ocular cicatricial pemphigoid. Ophthalmology 98:858–862
13. Mondino BJ (1990) Cicatricial pemphigoid and erythema multiforme. Ophthalmology 97:939–952
14. Hardy KM, Perry HO, Pingree GC, et al (1971) Benign mucous membrane pemphigoid. Arch Dermatol 104:467–475
15. Dave VK, Vicars CFH (1974) Azathioprine and the treatment of muco-cutaneous pemphigoid. Br J Dermatol 90:183–186
16. Brody HI, Pirozzi DJ (1977) Benign mucous membrane pemphigoid: response to therapy with cyclophosphamide. Arch Dermatol 113:1598–1599
17. Mondino BJ, Brown SI (1983) Immunosuppressive therapy in ocular cicatricial pemphigoid. Am J Ophthalmol 96:453–459
18. The U.S. Multicenter FK 506 Liver Study Group (1994) A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation. N Engl J Med 331:1110–1115
19. Jensik SC and the FK 506 Kidney Transplant Study Group (1998) Tacrolimus in kidney transplantation: three-year survival results of the US multicenter, randomized, comparative trial. Transplant Proc 30:1216–1218
20. The European FK 506 Multicenter Psoriasis Study Group (1996) Systemic tacrolimus (FK 506) is effective for the treatment of psoriasis in a double-blind, placebo-controlled study. Arch Dermatol 132:419–423
21. Mochizuki M, Masuda K, Sakane T, et al (1993) A clinical trial of FK506 in refractory uveitis. Am J Ophthalmol 5:763–769
22. Carroll PB, Tzakis AG, Ricordi C, et al (1991) The use of FK 506 in new-onset type I diabetes in man. Transplant Proc 23:3351–3353
23. Bousvaros A, Leichtner AM, Book L, et al (1996) Treatment of pediatric autoimmune enteropathy with tacrolimus (FK506). Gastroenterology 111:237–243
24. Sandborn WJ (1997) Preliminary report on the use of oral tacrolimus (FK506) in the treatment of complicated proximal small bowel and fistulizing Crohn's disease. Am J Gastroenterol 92:876–879
25. Tocci MJ, Matkovich DA, Collier KA, et al (1989) The immunosuppressant FK506 selectively inhibits expression of early T cell activation genes. J Immunol 143:718–726
26. Hultsch T, Albers MW, Schreiber SL, et al (1991) Immunoglobulin ligands demonstrate common features of signal transduction leading to exocytosis or transcription. Proc Nati Acad Sci USA 88:6229–6233
27. de Paulis A, Cirillo R, Ciccarelli A, et al (1991) FK-506, a potent novel inhibitor of the release of proinflammatory mediators from human Fc epsilon RI+ cells. J Immunol 146:2374–2381
28. Schreiber SL, Crabtree GR (1992) The mechanism of action of cyclosporin A and FK506. Immunol Today 13:136–142