Published in final edited form as:
Arch Dermatol. 1992 June ; 128(6): 781–785.

Tacrolimus (FK 506)—A New Therapeutic Agent for Severe Recalcitrant Psoriasis

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Abstract

Background—Psoriasis, a disease of unknown etiology, is in some patients severe, extremely debilitating, and unresponsive to conventional therapies, including UV-B, oral psoralen with long-wave UV radiation in the A range (PUVA), oral retinoids, and methotrexate. We report the results from our study of seven patients with refractory psoriasis who were treated with the new immunosuppressive drug, tacrolimus (FK 506).

Observations—All seven patients showed a dramatic resolution of psoriasis that remained in remission as long as they received full-dose therapy. Serial skin biopsy specimens demonstrated a rapid disappearance of the inflammatory infiltrate and a slower resolution of the epidermal changes. Tacrolimus was well tolerated during the 5.5 to 14 months of observation. Side effects, including nephrotoxicity and hypertension, were controlled by appropriate modification of drug dosage.

Conclusions—Tacrolimus, a new immunosuppressive agent, is effective in treating patients with severe recalcitrant psoriasis. The mechanism of its action in psoriasis is unknown, but it may be related to its ability to modulate immune function. Further studies will establish criteria for patient selection and drug dosage, to maximize efficacy of this agent in psoriasis, while minimizing its toxicity.

Psoriasis, a common heritable disease that affects the skin, the joints, or both, has many characteristics of an immunologically mediated disease. Included, among these characteristics are a variable HLA association, lymphocytic infiltration of skin lesions, and evidence of cytokine activity or increased expression of new antigens during exacerbations.[1,2] Circumstantial evidence for an immune etiology is the striking remission of psoriatic lesions that can be achieved with cyclosporine,[3–6] an immunosuppressive drug whose use for this purpose has been limited its by nephrotoxicity, hypertension, and other dose-related side effects. We report our experience with tacrolimus (FK 506), another immunosuppressive drug that is unrelated chemically to cyclosporine but also inhibits helper T-lymphocyte activation and the synthesis and expression of cytokines.[6,7] Encouraging results with tacrolimus have been reported in trials of whole organ transplantation.[8–10]

PATIENTS AND METHODS

Clinical features are summarized in Table 1. Amelioration of psoriasis in four patients was incidental to the primary objective, preventing organ rejection of heart (one patient) or liver transplantation (three patients). The liver disease in one of the latter patients was caused by

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high-dose methotrexate sodium treatment for psoriasis during a 2-year period. The other three patients had severe recalcitrant psoriasis that had resisted the therapies listed in Table 1.

Psoriasis Evaluation

The severity of psoriasis was quantitated using the Psoriasis Area and Severity Index.[5,11] The assessment is performed by measuring the extent of skin involvement and the amount of erythema, infiltration, and desquamation using a scale of 0 to 4 (0 indicates none; 1, slight; 2, moderate; 3, severe; and 4, very severe). Each of the above clinical signs was given an appropriate score and a composite additive number obtained that represents the Psoriasis Area and Severity Index. In the three patients whose primary diagnosis was psoriasis, biopsy specimens were obtained before instituting treatment, 2 weeks later, and when they were clinically free of lesions.

Dose Control

Oral tacrolimus therapy was started at 0.15 mg/kg, twice daily, in the patients who did not receive organ transplants and the dosage was adjusted, as necessary, according to tacrolimus plasma levels. Plasma levels were measured at a 12-hour trough using an enzyme-linked immunoassay.[12] Similar dosage adjustments were made when clinical evidence indicated incomplete disease control or toxic reactions. No other antipsoriatic therapy was used. The transplant recipients were initially administered intravenous doses of 0.075 or 0.10 mg/kg tacrolimus per day and converted to therapy with oral medications when they could begin oral feeding. Patients who had received transplants also received prednisone initially, doses of which were tapered to levels shown in Table 2 at the time of their last follow-up visit.

Side Effect Surveillance

Extensive medical examinations, including complete neurologic assessments, were performed repeatedly. Results of renal function tests and levels of serum cholesterol, uric acid, blood glucose, serum magnesium, and other electrolytes were carefully monitored. Development of high blood pressure (if present) was quantitated by the number of antihypertensive drugs required to maintain a normotensive state. Hyperkalemia, if it occurred, was treated with the mineralocorticoid, fludrocortisone acetate. Hypomagnesemia seen in some patients did not require correction.

RESULTS

Effect on Psoriasis

There was a marked reduction in erythema and scale in all seven patients at the end of 1 week and complete clinical remission within 4 weeks (Fig 1). The remissions have been sustained in all patients. Our follow-up periods range from 5.5 to 14 months. Interpretation of the beneficial effect of tacrolimus was straightforward in the three patients whose primary diagnosis was psoriasis (Table 3) because they were not given systemic corticosteroids or other antipsoriatic medications. Improvement of psoriatic arthritis, with reduction in stiffness, pain on movement, and swelling, also occurred simultaneously in all three patients. Serial skin biopsy specimens obtained from the active plaques of psoriasis demonstrated a rapid disappearance of the inflammatory infiltrate in the dermis and the neutrophils in the stratum corneum (Fig 2). The hyperkeratosis and epidermal acanthosis took longer to revert to normal (Table 3). Efforts to reduce tacrolimus dosage in these three patients resulted in the rapid reappearance of early psoriatic skin lesions, which promptly resolved on returning to the immediately prior dose of tacrolimus.

The four patients who had organ transplants received systemic prednisone therapy postoperatively, but their remission persisted after lowering (patient 3) or stopping (patients 1, 2, and 4) the corticosteroid therapy (Table 2). Several months postoperatively, when there was no evidence of graft dysfunction, the liver recipient whose end-stage hepatic disease was caused by methotrexate therapy (patient 2) had small psoriatic plaques develop near the exit site of his T tube. These psoriatic plaques disappeared with a minor increase in tacrolimus dose.

Toxicity and Metabolic Changes

Tacrolimus dosage, plasma levels, and surveillance measurements were similar in patients who had and did not have transplants. Transient trembling, paresthesias, and insomnia not requiring tacrolimus dose changes were noted in three patients. Increases of serum creatinine or serum urea nitrogen levels signaled the need for downward dose adjustments. Most patients required a decrease of 10% to 25% of the total dose. Despite careful monitoring of dosage, serum creatinine and serum urea nitrogen levels increased at our check points (Table 2). Although generally stable, the final levels of these measures were higher in all patients when compared with pretreatment values. Three patients had development of arterial hypertension that was controlled with single antihypertensive drug therapy; one patient who initially required two antihypertensive drugs was later normotensive with no drugs, and one patient with preexisting hypertension requiring one drug for control had no change while receiving tacrolimus therapy.

COMMENT

Tacrolimus caused a complete remission of psoriasis in all seven treated patients. Improvement was always evident within a few days. In the patients who did not have transplants, tacrolimus dose and plasma levels needed to maintain remission of psoriasis were in the same range as those required to prevent allograft rejection. Efforts to reduce the dose of tacrolimus in these patients resulted in reactivation of the psoriasis. In one liver recipient (patient 2), dose reduction caused a minor recurrence of psoriasis without evidence of graft rejection.

Whether the reward of complete control of psoriasis will be worth the risk of long-term therapy with this powerful drug can be judged only after future studies. The first administration of tacrolimus to a human to prevent organ rejection occurred only 29 months ago.[8] Our patients with psoriasis, whose cases are reported herein, have been treated with tacrolimus for 5.5 to 14 months. The results are very encouraging. The only potentially serious side effect was nephrotoxicity. In patients with psoriasis as their primary disease, serum creatinine levels increased 27% to 111% (mean, 68%) above baseline early in their course, but later stabilized at 66% to 74% (mean, 68%) above pretreatment levels. In the patients with psoriasis who also underwent organ transplantation, serum creatinine levels increased 100% to 200% (mean, 152%) above baseline, but later stabilized at 83% to 200% (mean, 166%) above pretreatment values. Patients who are candidates for organ transplantation usually have some degree of incipient renal compromise, which may have predisposed them to greater tacrolimus nephrotoxic reactions.

Elevations in serum creatinine and serum urea nitrogen levels responded to dose reduction and reached an increased but stable state at the surveillance check points. No patient has had an infection. The patients with psoriasis who did not have transplants who were accepted for our study were those who had severe, widespread treatment-resistant disease that completely ruined their quality of life. Patients with less severe disease are not candidates for treatment with tacrolimus until further experience regarding the severity and long-term effects of nephrotoxic reactions are understood.

The remarkable efficacy of tacrolimus in psoriasis is attributable to its effect on immune modulation. However, this may not be the sole explanation for its effect. It is known that the cytosolic receptors for this drug (called “FK binding protein”) as well as the distinct cyclosporine-binding site (cyclophilin) are part of a previously unrecognized class of small molecular weight proteins collectively called “immunophilins.” These proteins are found in the cytoplasm of essentially all eukaryotic cells, including those of the skin, from the lowest to highest species, including man.[13] The binding of these immunophilins with cyclosporine, tacrolimus, and presumably other drugs can affect signal transduction in nonimmunologic as well as immunoregulatory cells. Thus, an array of metabolic consequences could result affecting growth control as has been demonstrated in the liver.[14] Growth control in the skin cannot be excluded as a target of such nonimmunologic effects.

Acknowledgments

This investigation was aided by research grants from the Veterans Administration and project grant DK 29961 from the National Institutes of Health, Bethesda, Md.

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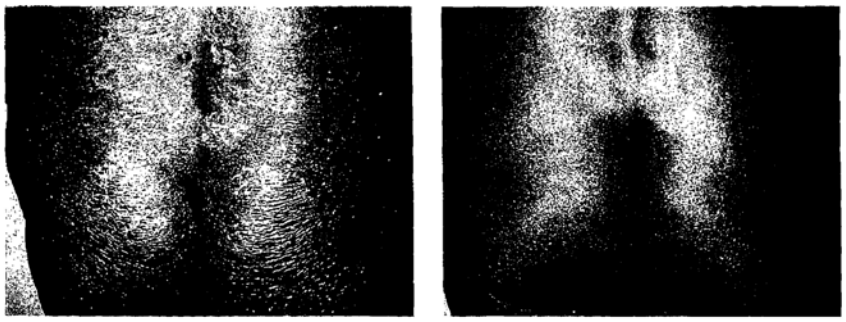

Fig 1.
Left, Generalized erythrodermic psoriasis in patient 5 before tacrolimus (FK 506) treatment; right, complete resolution after 3 weeks of tacrolimus treatment.

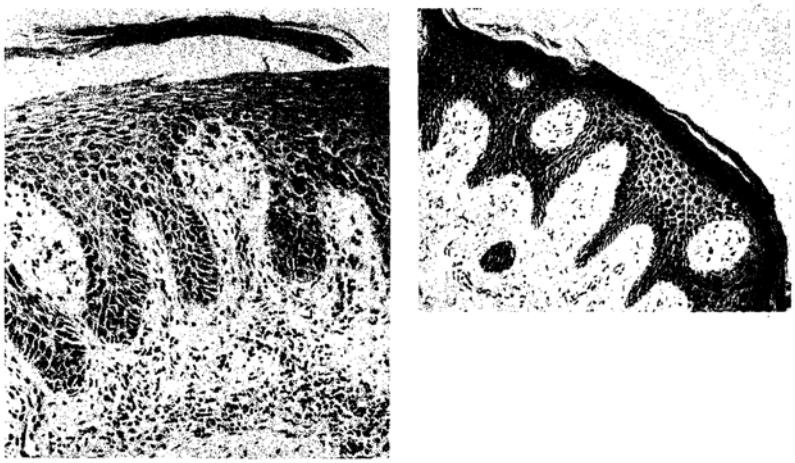

Fig 2.

Left, Histopathologic findings of patient in Fig 1 showing typical changes of psoriasis before tacrolimus (FK 506) treatment; right, 2 weeks later. Note persistence of epidermal acanthosis, but almost complete resolution of dermal and epidermal inflammation (hematoxylin-eosin, X100).

Table 1

Clinical Features*

No./Age, y/Sex	Transplant Type	Disease Duration, y (Psoriasis)	Previous Therapy	Arthritis
Transplant recipients				
1/36/F	Heart	12	Topical steroids; UV-B+tar	−
2†/40/M	Liver	22	UV-B+tar; methotrexate	+
3/33/F	Liver	25	PUVA; topical steroids; intralesional steroids; methotrexate	−
4/28/F	Liver	5	Topical steroids; systemic steroids	−
Psoriasis only				
5/49/F	–	6	PUVA, UV-B; topical steroids; etretinate	+
6/30/M	–	6	UV-B+tar; topical steroids; gold intramuscularly; methotrexate	+
7/32/F	–	9	UV-B+tar; topical steroids; methotrexate	+

*PUVA indicates oral psoralen with long-wave UV radiation in the A range (320 to 400 mm); UV-B, ultraviolet B (280 to 320 mm). Minus indicates absent; plus, present.

†End-stage liver disease was secondary to methotrexate therapy.

Table 2

Adverse Reaction Surveillance to June 6

	Patient						
	1	**2**	**3**	**4**	**5**	**6**	**7**
Date tacrolimus therapy started	2/14/90	6/30/90	7/13/90	8/8/90	5/24/90	7/16/90	8/27/90
FK doses, mg/kg per day							
At start	0.27	0.30	0.35	0.25	0.28	0.29	0.2
3 mo	0.33	0.20	0.40	0.18	0.10	0.30	0.32
Now	0.21	0.13	0.29	0.18	0.30	0.40	0.32
FK plasma, ng/mL							
1 wk	1.4	2.5	4.3	3.4	1.1	2.0	0.8
3 mo	1.5	1.0	0.9	1.2	0.4	0.4	0.9
Now	1.1	0.8	0.5	1.4	1.3	0.7	1.2
Steroid dose, mg/d							
At start	20	20	20	20	0	0	0
3 mo	10	0	10	0	0	0	0
Now	0	0	15	0	0	0	0
Creatinine, μmol/L							
At start	62	53	53	53	88	80	71
3 mo	141	150	150	106	106	133	150
Now	176	159	159	97	159	159	124
Serum urea nitrogen, mmol/L							
At start	2.5	3.6	4.3	2.5	2.1	3.2	3.6
3 mo	15.7	7.1	13.2	9.6	2.5	7.5	10.4

	Patient						
	1	2	3	4	5	6	7
Now	9.3	11.8	12.8	10.4	10.4	7.1	6.8
Fasting blood glucose, mmol/L							
At start	4.7	4.7	5.7	5.1	5.9	5.1	4.4
3 mo	4.9	5.3	6.7	5.4	5.7	4.3	5.8
Now	5.7	4.0	5.0	5.5	5.5	5.5	5.2
Uric acid, μmol/L							
At start	636	369	214	280	517	321	357
3 mo	565	434	428	464	399	297	410
Now	494	571	476	458	476	303	428
Magnesium, μmol/L							
At start	0.86	0.58	0.66	0.62	0.58	0.62	0.58
3 mo	0.49	0.49	0.66	0.74	0.58	0.49	0.49
Now	0.58	0.62	...	0.70	0.45	0.45	0.49
Potassium, mmol/L							
At start	4.1	3.2	3.5	3.9	4.3	4.8	4.5
3 mo	4.1	4.1	3.3	5.2	3.8	4.8	4.5
Now	4.6	4.8	4.3	5.2	4.6	5.0	4.1
Cholesterol, μmol/L							
At start	4.3	1.7	6.3	3.3	4.5	4.7	3.5
3 mo	5.3	3.9	5.6	2.9	6.6	3.6	3.6
Now	4.7	4.7	5.4	...	6.1	3.7	3.6

Table 3

Psoriasis End Points in Three Nontransplant Patients

Clinical (PASI* Scores)	Baseline	Week 2	Week 4	Week 6	Now
Patient					
5	67.5	27	2.8	0	0
6	43.4	5.7	0	0	0
7	68.4	34.2	9.8	0	0
Histopathologic†					
Epidermal acanthosis	+++	+++	+	+	−
Munro/Micro-abscesses	+++	−	−	−	−
Active dermal inflammation	++++	+	−	−	−

*PASI indicates Psoriasis Area and Severity Index.

†One plus indicates minimal; three pluses, moderately severe; four pluses, severe; and minus, absent.

Arch Dermatol. Author manuscript; available in PMC 2011 November 4.