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PSORIASIS AND OTHER SKIN DISORDERS

FK 506: A New Therapeutic Agent for Severe Recalcitrant Psoriasis

K. Abu-Elmagd, D. Van Thiel, B.V. Jegasothy, C.D. Ackerman, S. Todo, J.J. Fung, A.W. Thomson, and T.E. Starzl

BETWEEN 12 and 18 months ago we treated three patients with FK 506 who had severe psoriasis that was refractory to conventional therapy and four patients with widespread incidental psoriasis before undergoing heart or liver transplantation under FK 506. All had dramatic resolution of psoriasis, which remained in remission as long as full-dose therapy was provided. Serial skin biopsies had a rapid disappearance of the inflammatory infiltrate and slower resolution of epidermal changes. FK 506 was well tolerated with only minor side effects during the 12 to 18 months of observation.

Circumstantial evidence for an autoimmune etiology of psoriasis is the striking remission of psoriatic lesions, which can be achieved with cyclosporine,[1-3] an immunosuppressive drug whose use for this purpose has been limited by nephrotoxicity, hypertension, and other dose-related side effects. We report here the use of the chemically unrelated drug, FK 506, which also inhibits T helper lymphocyte activation and the synthesis and expression of cytokines.[4,5]

METHODS

Clinical features are summarized in Table 1. Amelioration of psoriasis in four patients was incidental to the primary objective of heart (one) or liver transplantation (three). The liver disease in one of the latter patients was caused by methotrexate treatment for psoriasis over a period of 2 years. The other three patients had severe recalcitrant psoriasis that had resisted the therapies listed in Table 1.

Table 2. Psoriasis Endpoints in Three Nontransplant Patients

	Baseline	Week 2	Week 4	Week 6	Now
Clinical (PASI Scores)					
Patient 5	67.5	27	2.8	0	0
Patient 6	43.4	5.7	0	0	0
Patient 7	68.4	34.2	9.8	0	0
Histopathologic					
Epidermal acanthosis	+++	++		-	
Munro's microabscesses	+++	-		-	
Active dermal inflammation	++++	-		-	

The patients were scored for their psoriasis severity using the Psoriasis Area and Severity Index (PASI).[3] The severity of the psoriasis was determined (Table 2) by measuring the amount of erythema, infiltration, and desquamation using a scale of 0–4 (0 = none, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe). In

From the Departments of Surgery (K.A.-E., D.V., S.T., J.J.F., A.W.T., T.E.S.) and Dermatology (B.V.J., C.D.A.), University Health Center of Pittsburgh, University of Pittsburgh, and the Veterans Administration Medical Center, Pittsburgh, PA.

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Address reprint requests to Thomas E. Starzl, MD, Dept. of Surgery, 3601 Fifth Ave., University of Pittsburgh, Pittsburgh, PA 15213.

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Table 1. Clinical Features

No.	Age/Sex	Transplant	Disease Duration (psoriasis/y)	Previous Therapy	Arthritis
Transplant Recipients					
1	36/F	heart	12	Topical steroids; UVB + tar	—
2*	40/M	liver	22	UVB + 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, UVB; topical steroids etretinate	+
6	30/M	—	6	UVB + tar; topical steroids gold I.M.; methotrexate	+
7	32/F	—	9	UVB + tar; topical steroids methotrexate	+

Abbreviations: PUVA = Psoralen and Ultraviolet A (320–400 nm); UVB = Ultraviolet B (280–320 nm).
*End stage liver disease was secondary to methotrexate therapy.

Table 3. Adverse Reaction Surveillance to End of January 1991*

Date FK 506 Started		1 2/14/90	2 6/30/90	3 7/13/90	4 8/8/90	5 5/24/90	6 7/16/90	7 8/27/90
FK doses	at start	0.27	0.30	0.35	0.25	0.28	0.29	0.2
(mg/kg/d)	3 months	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	1 week	1.4	2.5	4.3	3.4	1.1	2.0	0.8
(ng/mL)	3 months	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	at start	20	20	20	20	0	0	0
(mg/d)	3 months	10	0	10	0	0	0	0
	now	0	0	15	0	0	0	0
Creatinine	at start	62	53	53	53	88	80	71
(μmol/L)	3 months	141	159	150	106	106	133	150
	now	176	159	159	97	159	159	124
BUN	at start	2.5	3.6	4.3	2.5	2.1	3.2	3.6
(mmol/L)	3 months	15.7	7.1	13.2	9.6	2.5	7.5	10.4
	now	9.3	11.8	12.8	10.4	10.4	7.1	6.8
FBS	at start	4.7	4.7	5.7	5.1	5.9	5.1	4.4
(mmol/L)	3 months	4.9	5.3	6.7	5.4	5.7	4.3	5.6
	now	5.7	4.0	5.0	5.5	5.5	5.5	5.2
Uric acid	at start	636	369	214	280	517	321	357
(μ mol/L)	3 months	565	434	428	464	399	297	410
	now	494	571	476	458	476	303	428
Mg	at start	0.86	0.58	0.66	0.62	0.58	0.62	0.58
(mmol/L)	3 months	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
K	at start	4.1	3.2	3.5	3.9	4.3	4.8	4.5
(mmol/L)	3 months	4.1	4.1	3.3	5.2	3.8	4.8	4.4
	now	4.6	4.8	4.3†	5.2	4.6	5.0†	4.1
Cholest	at start	4.3	1.7	6.3	3.3	4.5	4.7	3.5
(mmol/L)	3 months	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
BP drugs	at start	0	0	0	2	0	0	1
number	3 months	0	1	0	0	1	0	1
	now	0	1	1	0	1	0	1

*Parameters essensaly unchanged in August 1991.
†Fludrocortisone acetate (a mineralocorticoid) (Florinef).

the three patients whose primary diagnosis was psoriasis, biopsies were taken before instituting treatment, 2 weeks later, and when they were clinically free of lesions.

Oral FK 506 was started at 0.15 mg/kg twice daily in the nontransplant patients and adjusted down or up according to the FK 506 plasma levels (measured at 12 hour trough with an enzyme-linked immunoassay) or when there was clinical evidence of incomplete disease control or toxicity. No other drugs were used. The transplant recipients were started on 0.075 or 0.10 intravenous FK 506/d and converted to oral dosing when they could eat. Transplant patients also had prednisone initially, which was tapered to the levels shown in Table 3 by 1 February 1991. These levels have not changed substantially in the ensuing half year.

Complete medical examinations including neurologic assessment were performed repeatedly. Renal function, serum cholesterol, uric acid, blood glucose, magnesium, and other electrolytes were monitored. A detailed report of these parameters in a larger group of psoriasis patients is reported elsewhere in this symposium.[6]

Development of high blood pressure was quantitated (if present) by the number of antihypertensive drugs required to maintain a normotensive state. Hyperkalemia was treated with the mineralocorticoid fludrocortisone acetate. Hypomagnesemia was seen but did not require correction.

RESULTS

Effect on Psoriasis

There was a marked reduction in erythema and scale in all seven patients by 1 week and complete clinical remission by 3 weeks (Table 2). The remission has been sustained

with follow-ups of 12 to 18 months. The three patients whose primary diagnosis was psoriasis (Table 2) were not given steroids or other medications. Improvement of arthritis from which they also suffered occurred simultaneously.

Serial skin biopsies taken from the active plaques of psoriasis demonstrated a rapid clearance of the inflammatory infiltrate in the dermis and the neutrophils in the stratum corneum. The effect of FK 506 on the skin infiltrate is described elsewhere in this symposium.[7] The hyperkeratosis and epidermal acanthosis took longer to resolve (Table 2). In these three patients, efforts to reduce FK 506 dosage resulted in beginning reappearance of the skin lesions, which promptly disappeared after returning to the prior dose.

The four patients who had organ transplants received systemic prednisone postoperatively, but their remission persisted after lowering (one case) or stopping the steroids (three cases) (Table 3). 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) developed small psoriatric plaques near the exit site of his T-tube. These disappeared with a minor increase in FK 506 dose.

Toxicity and Metabolic Changes

FK 506 doses, plasma levels, and surveillance parameters were similar in both nontransplant and transplant patients. Temporary trembling, parathesias, and insomnia not requiring dose changes were noted in three patients. Increases of serum creatinine or BUN signaled the need for downward adjustments, and because of careful attention to dose control, there were no alarming patterns of toxicity at the check points (Table 3). While stable, the ultimate level of these measures was higher in all patients than at the outset. Hirsutism and gingival hyperplasia sometimes associated with cyclosporine were not observed with FK 506.

DISCUSSION

Complete remission of psoriasis induced by FK 506 was evident more quickly than has been observed with other immunosuppressive regimens. In the nontransplant patients, the FK 506 doses and plasma levels needed to maintain remission were in the same range as required to prevent allograft rejection. Efforts to give less FK 506 to these patients resulted in reactivation of the psoriasis. In one liver recipient a dose reduction caused a minor recurrence of psoriasis rather than graft rejection.

Whether the reward of complete control of psoriasis will be worth the risk of long-term therapy with this powerful drug will be judged with further observations. In our psoriasis series herein reported, follow-ups have been 12 to 18 months. However, what was seen so far is encouraging. The only potentially serious side effect was nephrotoxicity with rises in creatinine and BUN, which responded so quickly to dose reduction that they had reached a stable although slightly elevated state at the surveillance check points. No patient has had an infection. Patients with widespread lesions (often with psoriatic arthritis) that ruin the quality of life have been eager to take the risk. Patients with less severe disease should be discouraged from candidacy and treated with less drastic means.

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