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Efficacy of FK 506 in the Treatment of Recalcitrant Pyoderma Gangrenosum

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IN THIS STUDY the efficacy and safety of systemic FK 506 therapy was evaluated in four patients with severe recalcitrant pyoderma gangrenosum unresponsive to conventional therapy.

CASE MATERIAL

The clinical features in these four cases are summarized in Table 1. The patients were males between the ages of 26 and 34 years. The duration of the disease ranged from 3 to 28 years. All patients were referred to our center with well-established clinical and histopathological diagnosis of the disease. Multiple large necrotic ulcers existed in the lower extremities (n = 4), trunk (n = 2), and face (n = 2) prior to FK 506 treatment. The associated clinical conditions, which had also resisted different kinds of therapy, are summarized in Table 1. Interestingly, all four patients had concomitant inflammatory arthritis, regional enteritis (two examples), and/or connective tissue diseases (Table 1). Patient 4 was the first patient ever reported with streaking leukocyte factor syndrome, published in 1975 by Jacobs and Goetzl.[1]

FK 506 was started orally at a dose of 0.15 mg/kg twice daily. Dose adjustments were guided by FK 506 plasma levels or by clinical evidence of incomplete disease control or drug toxicity. Twelve-hour FK 506 trough plasma levels were measured with an enzyme-linked immunoassay.[2] Pre-existing steroid therapy (Table 1) was tapered in all patients after starting FK 506 and completely discontinued in three patients. Other previously used immunosuppressive agents were discontinued before initiation of FK 506 therapy.

Dermatologic and medical examinations were performed repeatedly. Assessments included pain, erythema, and drainage from pyoderma gangrenosum lesions. The arthritic manifestations were completely evaluated by a rheumatologist. Renal function, serum cholesterol, blood glucose, and electrolytes were monitored. If it developed, hyperkalemia was controlled with the mineralocorticoid fludrocortisone acetate. Hypomagnesemia was seen but did not require correction.

RESULTS

Response of the Skin Lesions

All four patients had a dramatic initial response to treatment with a marked reduction in pain, erythema, and drainage by one week. Complete clinical remission and healing of the disfiguring open sores was achieved in patients 2 through 4 within 4 to 8 weeks after initiation of FK 506 therapy (Fig 1). FK 506 plasma trough levels were maintained in these patients at 0.5 to 1.5 ng/mL.

Patient 1 was removed from the study after 4 weeks and returned to cyclosporine (CyA) because of his refusal to undergo rehabilitation for street-drug addiction. He committed suicide a few weeks later. He had been improved by FK 506. The remission has been sustained in the other three patients for 3 to 16 months. In patient 2, efforts to reduce FK 506 dosage by half resulted in low drug plasma

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Table 1. Patients With Pyoderma Gangrenosum Treated With FK 506*

No.	Age/Sex (y)	Duration of Disease (y)	Associated Clinical Disease	Previous Treatment	Date FK 506 Started	Remission	Creatinine (mg%) Before	Creatinine (mg%) After
1	26/male	3	ulcerative colitis arthritis	steroids‡, Daposone, Azathioprine, Leukeran, CyA	12/22/89	partial†	1.5	1.7
2	29/male	11	Crohn's disease with perianal fistulae polyarthritis Sjogren syndrome	steroids‡, Dapsone, 6-mercaptopurine CyA	4/4/90	complete	0.5	1.2
3	34/male	7	ankylosing spondylitis scleritis	steroids‡, Dapsone	10/29/90	complete	0.7	1.2
4	31/male	28	erosive polyarthritis streaking leukocyte factor	Thalidomide, steroids‡, Dapsone, Tetracycline, Colchicine	5/9/91	complete	0.7	1.4

*Follow-up to August 20, 1991.
†Patient was noncompliant and stopped taking FK 506.
‡The preexisting prednisone doses were 65 ± 35 (S.D.) mg/d. In patients 2–4 the values were 40, 100, and 100 mg/d. These were reduced to 0.0 and 5 mg/d after 2 to 3 weeks.

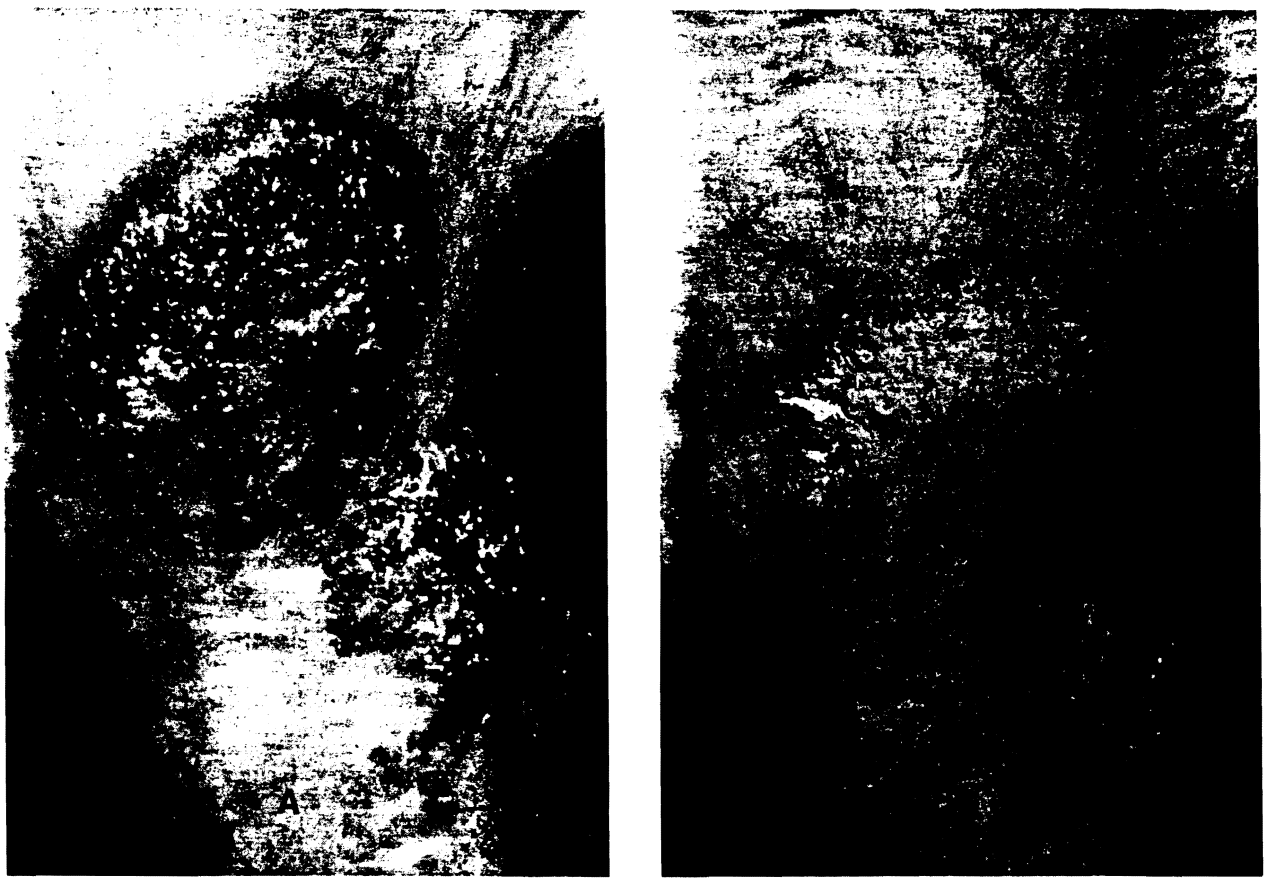

Fig 1. **(A)** This picture shows a large necrotic ulcer on the medial aspect of the left knee region of patient 2 before starting FK 506 therapy. **(B)** Marked improvement and healing of the ulcer was noted within 1 week after initiation of FK 506 treatment.

levels and consequently in beginning reappearance of the skin lesions and the arthritis, which completely disappeared after returning to the full dose. Overall, the productivity and the quality of life of patients 2–4 were significantly improved.

Effect on Extra-Dermal Lesions

Improvement of arthritis occurred simultaneously in patients 2 through 4. Discontinuance of steroids was considered a godsend by all patients and was particularly important for patient 4, who has osteoporotic lesions and bone deformity. Two patients with concomitant inflammatory bowel disease became asymptomatic within 4 weeks after FK 506 treatment. One of these patients had complete healing of multiple perianal fistulae within 6 weeks. Patient 3 had complete disappearance of scleritis within 1 week after starting FK 506 treatment.

FK 506 Adverse Effects

Toxicity, including hyperkalemia and hypomagnesemia, was similar to that in the psoriasis patients.[3] There were increases in the current serum creatinine and BUN (Table 1) despite careful dose control. None of the patients developed systemic arterial hypertension after initiation of FK 506 therapy.

DISCUSSION AND CONCLUSION

This study has shown the efficacy of FK 506 as monotherapy for patients with severe pyoderma gangrenosum. The response was complete in all three patients who continued to receive the drug. The doses and plasma levels needed to maintain remission were in the same range as those required to prevent allograft rejection. Attempts at dose reduction in one patient resulted in temporary reactivation of the skin lesions. The long-term risk/benefit ratio of FK 506 therapy remains to be determined. However, the results of the current report are unequivocally encouraging.

REFERENCES

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