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Treatment of Chronic Erythema Nodosum Leprosum with Cyclosporine A Produces Clinical and Immunohistologic Remission[1]

Richard A. Miller, Jen-Yee Shen, Thomas H. Rea, and James P. Harnisch[2]

Erythema nodosum leprosum (ENL) is a potentially serious immunologic complication of leprosy ([24]). Acute attacks can involve high fevers, disabling polyarthralgia, and painful neuritis. Chronic ENL is associated with secondary amyloidosis and renal failure ([13]). The management of ENL is complicated by the unpredictable course of the disease and the toxicities of the immunosuppressive drugs used for the control of acute episodes or as chronic suppressants. Thalidomide remains the drug of choice for ENL ([27]) but its use is absolutely contraindicated in fertile women, and there is continuing concern over its association with sensory polyneuropathy ([29]). Another problem with thalidomide is the development of tolerance to its effects. Finally, one of only two pharmaceutical firms in the world which produced thalidomide recently announced that it was halting production, raising the possibility of shortages of thalidomide on the world market ([29]). Corticosteroids are useful in both acute and chronic ENL, but the large doses required (60 mg to 200 mg daily of prednisone for acute attacks and 20 mg to 40 mg daily for chronic ENL) lead to serious morbidity in many patients. Clofazimine is of no benefit in acute ENL because of its delayed onset of action, but it is moderately effective in suppressing chronic reactions in some patients. Other modalities which have been tried with variable success in ENL include antimalarials, cytotoxic agents (cyclophosphamide and azathioprine), and plasmapheresis, all of which are associated with serious adverse effects and expense.

An understanding of the unique efficacy of thalidomide in ENL is essential to the rational selection of new agents for clinical trials. Early studies implicated immune complexes in the pathogenesis of ENL, and postulated that the clinical illness reflected an Arthus phenomenon ([34]). However, thalidomide was not active in an animal model of an Arthus reaction or in human illnesses associated with immune complex deposition, such as systemic lupus erythematosus ([30]). Thalidomide is known to produce imbalances in circulating T-lymphocyte subpopulations. Specifically, the ratio of helper (T4 positive cells) to suppressor (T8 positive cells) T cells is decreased through an absolute and relative decrease in the number of helper T cells ([6, 18]). B-cell populations are relatively unaffected.

Another drug which acts on the T4 positive lymphocyte population is cyclosporine A (CsA) ([28]). CsA and thalidomide are both active in Behçet's disease ([2, 5, 25]), and both are effective in preventing graft versus host disease after allogeneic marrow transplantation ([4, 8, 33]). The hypothetical efficacy of CsA in the treatment of ENL was first proposed by Mshana in 1982 ([19]), and it was subsequently demonstrated by other investigators that CsA corrected some of the *in vitro* abnormalities in lymphocyte function during ENL ([31]). The similarities between the *in vitro* activities and the clinical applications of thalidomide and CsA led us

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[2] R. A. Miller, M.D., Division of Infectious Diseases, Immunology Research Laboratory, Department of Medicine, Pacific Medical Center and the University of Washington, Seattle, Washington, U.S.A. J.-Y. Shen, M.D., Ph.D., and T. H. Rea, M.D., Division of Dermatology, Department of Medicine, University of Southern California School of Medicine, Los Angeles, California, U.S.A. J. P. Harnisch, M.D., Division of Dermatology, Department of Medicine, Pacific Medical Center and the University of Washington, Seattle, Washington, U.S.A.

Reprint requests to Dr. R. A. Miller, Immunology Research Laboratory, Pacific Medical Center, 1200 12th Avenue South, Seattle, Washington 98144, U.S.A.

to study the efficacy of CsA in the control of chronic ENL.

MATERIALS AND METHODS

This study and the informed consent forms used were approved by the Institutional Review Boards of the University of Washington and of the University of Southern California, following the guidelines of the U.S. Department of Health and Human Services. Informed consent was obtained from all patients.

Patients regularly followed at the Seattle Hansen's disease clinic were considered eligible for a trial of CsA therapy if they had biopsy-confirmed chronic ENL which had proven difficult to control with currently available therapeutic agents. Concurrent therapy with cytotoxic chemotherapeutic agents was considered an absolute contraindication for CsA therapy because of the associated increased risk of neoplasms. The first three consecutive patients meeting these criteria after May 1985 were enrolled. One patient from the Los Angeles County/University of Southern California Medical Center was also enrolled, but this patient failed to complete the protocol. The following studies were performed prior to starting CsA: Complete blood count; erythrocyte sedimentation rate; marker studies on circulating lymphocytes to enumerate B cells, T cells, and T4, T8, Leu7, and Leu11a lymphocyte subsets; renal and liver function studies; 24-hr renal creatinine clearance; C1q assay (for circulating immune complexes); anti-phenolic glycolipid antibody IgM level (a *Mycobacterium leprae*-specific antigen) ([33]); anti-mycobacterial arabinomannan IgG level (a crossreactive mycobacterial antigen) ([14]); and a skin biopsy of an active lesion(s). Oral CsA therapy was begun with 10 mg/kg daily (patients 1 and 2) or 7 mg/kg daily (patient 3). CsA trough levels in whole blood were measured on days 4, 7, 11, 14, 21, and as needed thereafter. The dose was adjusted to maintain trough whole blood levels between 150 and 300 ng/ml. A repeat skin biopsy and determination of 24-hr creatinine clearance were performed after 2 to 3 months of therapy. Treatment with anti-mycobacterial agents was continued throughout the period of treatment with CsA, but an attempt was made to decrease or eliminate the dose of prednisone each patient was receiving. All patients remained ambulatory and were treated as outpatients, with clinic visits twice a week for the first 2 weeks, then weekly for the next 2 weeks, then monthly.

Skin biopsy specimens were obtained with a 5-mm skin punch and processed with routine histologic stains and with Fite's tissue acid-fast stain. Portions of each biopsy specimen were placed in OCT, snap-frozen in liquid nitrogen, then stored at −70°C until sectioned and stained as previously described ([17, 23]). Briefly, application of the desired primary monoclonal antibody was followed either by peroxidase conjugated goat antimouse immunoglobulin or by biotinylated horse antimouse immunoglobulin and avidin-biotin-peroxidase complexes. Aminoethylcarbizol was then applied as the chromogenic substrate. The specificities sought, antibodies used, and dilutions employed as determined by checkerboard titration included: pan T (Leu4, 1:60); T-helper/inducer subset (Leu3a, 1:60); T-suppressor/cytotoxic subset (Leu2a, 1:100); Langerhans' cell (OKT 6, 1:50); interleukin 2 (IL-2) (Genzyme, 1:50); IL-2 receptor (antiTac, Dr. T. A. Waldman, National Cancer Institute, 1:5000); and HLA-DR(Ia) framework antigen (H4, Dr. R. Billing, University of California in San Francisco, 1:2000). Six site smears for bacterial and morphological indices were performed at least twice during the study on each patient.

CASE REPORTS

Case 1. The first case is a 38-year-old Filipino male whose borderline lepromatous Hansen's disease was diagnosed in March 1979. He was begun on dapsone and rifampin but developed tender skin nodules, polyarthralgia, and neuritis after 21 months of therapy. ENL was confirmed by biopsy, and prednisone was begun. There was only a limited clinical response, so thalidomide was added with rapid and complete resolution. The ENL was well controlled with thalidomide alone for 13 months, when a severe flare of ENL developed that failed to respond to an increase in the dose of thalidomide to 400 mg daily. Control was finally achieved with prednisone, and the thalidomide was discontinued. The ENL le-

sions, neuritis, and polyarthralgia flared whenever the prednisone dose dropped below 30 mg daily. Trials of thalidomide were again unsuccessful and clofazimine was begun. Over the next 2½ years, clofazimine and prednisone were continued, but the ENL flared whenever the prednisone dose dropped below 20 mg per day. Attempts to institute an every-other-day steroid regimen were unsuccessful, even when supplemented with ibuprofen on the alternate days. Recurrent ENL and increasing steroid toxicity prompted a trial of plasmapheresis with limited success.

After several months of moderate control, new ENL lesions began to appear despite administration of 20 mg daily of prednisone. CsA therapy was begun at an initial dose of 10 mg/kg daily. Therapy with prednisone, dapsone, and clofazimine was continued. Established skin lesions began to fade after 2 days on CsA, and no new lesions were noted. Arthralgia of the left ankle improved rapidly. The steroid dose was slowly tapered (because of concern about adrenal suppression) to 5 mg daily over the next 5 months, with continued excellent control of the ENL. This was the lowest dose of prednisone this patient had been on in the previous 4 years. Asymptomatic nodules that were palpable but not tender appeared once or twice a week and persisted for 12 to 24 hr, but arthralgia, myalgia, and neuritis were completely suppressed. Prednisone was discontinued after 6 months, but within 2 days pain developed in the left knee and leg associated with low-grade fever and new, tender skin nodules. CsA therapy was continued and the ENL flare responded rapidly to reinstitution of prednisone at 40 mg daily (contrasted with the 60 to 120 mg daily required to control ENL flares prior to CsA therapy). Subsequently, the dose of prednisone was decreased to 10 mg every other day with good control of the ENL.

Case 2. An otherwise healthy, 51-year-old Vietnamese male had borderline lepromatous Hansen's disease diagnosed by biopsy in December 1981, and therapy was begun with dapsone and rifampin. Biopsy-confirmed ENL developed 3 months later and responded rapidly to thalidomide, which was discontinued after 6 months. Three months later the ENL flared, finally coming under control with clofazimine and high-dose prednisone after thalidomide failed. ENL activity waxed and waned over the next 2½ years, relapsing when the prednisone dose was decreased below 20 mg daily.

Following a severe relapse with extensive skin nodules, polyarthralgia, and myalgia, therapy with 700 mg daily of CsA (10 mg/kg) was begun. Dapsone and clofazimine were continued. Prednisone was inadvertently discontinued by the patient on the same day. After 3 days on CsA, the cutaneous nodules had begun to regress and the patient noted he was able to climb stairs without pain. However, he complained of lower abdominal cramps and watery diarrhea. The CsA dose was decreased to 350 mg daily (6 mg/kg), and the prednisone was restarted at 10 mg every other day. The gastrointestinal complaints decreased on the lower dose, although loose stools persisted. After 4 weeks, the patient ran out of CsA. Recurrent ENL lesions developed 4 days later, but responded to reinitiation of CsA and an increase in the prednisone dose to 20 mg every other day. Over the next 3 months the prednisone was tapered and discontinued. The rationale behind this slow steroid wean was the concern over adrenal suppression in this patient who had received moderate- and high-dose steroids for over 3 years. The patient is now doing well on clofazimine and 350 mg daily of CsA with no arthralgia, neuritis, or myalgia, and minimal cutaneous evidence of ENL.

Case 3. This 31-year-old Filipino woman had multibacillary Hansen's disease diagnosed in April 1983, and therapy with dapsone and rifampin was begun. Four months later she acutely developed painful nodular skin lesions, polyarthralgia, and migratory arthritis. ENL was confirmed by skin biopsy, and she was treated with prednisone with an incomplete response. She refused clofazimine and obtained a 3-month supply of thalidomide (from sources outside the U.S.) which suppressed the reactional state.

When first seen in our clinic 14 months later, she had chronic ENL manifesting as red, tender skin nodules, ulnar neuritis, ankle arthritis, and fever despite low-dose prednisone. Her prednisone dose was increased to 40 mg daily, the rifampin was

TABLE 1. *Hematologic values prior to and during cyclosporine A (CsA) therapy.*

Patient	HCT (%)		WBC (mm^3)		ESR (mm/hr)	
	Pre-CsA[a]	On CsA[b]	Pre-CsA[a]	On CsA[b]	Pre-CsA[a]	On CsA[c]
1	41.6	35.0	11.1	7.7	5	21
2	45.2	35.7	8.8	7.9	15	41
3	34.8	32.9	18.7	22.2	58	94

[a] Arithmetic mean of 10–18 measurements per patient over 12 months prior to cyclosporine A (CsA).

[b] Arithmetic mean of 4–10 measurements per patient.

[c] Arithmetic mean of 8–16 measurements per patient after maintenance prednisone dose lowered to 10 mg or less daily.

discontinued, and clofazimine begun. The ENL responded, but relapsed when the steroid dose was tapered. Hydroxychloroquine was added, but urticaria developed and the hydroxychloroquine was discontinued. The ENL worsened, leading to hospitalization and a successful trial of azathioprine. Subsequently, the ENL remained under fair control on 20 mg daily of prednisone. A major flare of the ENL 6 months later required higher doses of prednisone and resumption of azathioprine therapy. Low-grade ENL activity persisted over the next 5 months despite 20 mg daily of prednisone and 75 mg daily of azathioprine.

After 5 months, the azathioprine was discontinued and CsA 7 mg/kg per day (400 mg) was prescribed. This dose was well tolerated, but blood levels of CsA were subtherapeutic. Attempts on two occasions to increase the dose to 450 mg or 500 mg resulted in epigastric pain, nausea, and watery diarrhea. Scattered, minimally tender cutaneous lesions persisted on 400 mg daily of CsA and 10 mg daily of prednisone (the lowest maintenance prednisone dose she had received for 14 months), but the neuritis and polyarthralgia were controlled.

RESULTS

CsA blood levels. Blood levels of CsA are affected both by erratic absorption after oral administration and by the rate of metabolism of the drug. Several drugs which activate the hepatic cytochrome P450 enzyme system, including rifampin, are known to accelerate CsA metabolism ([1]), but nothing is known concerning any interactions between dapsone or clofazimine and CsA. Patient 1 had whole blood trough CsA levels ranging between 192 and 261 ng/ml while receiving 10 mg/kg daily, and the second patient had levels between 130 and 173 ng/ml while on 6 mg/kg daily. These blood levels are within the ranges predicted from the administered dose (data supplied by Sandoz, Inc., East Hanover, New Jersey, U.S.A.), and suggest that dapsone and clofazimine have little, if any, effect on CsA absorption or metabolism. The levels in the third patient varied from 50 to 124 ng/ml while on 7 mg/kg daily, but patient compliance was known to be erratic.

Hematologic studies. CsA therapy had a minimal effect on the white blood cell count (Table 1) or on the relative distribution of lymphocytes among the various lymphocyte subpopulations as defined by monoclonal antibody probes (Table 2). The relative frequency of Leu7 and Leu11a positive cells, a group which includes natural-killer cells ([11]), was markedly elevated before and during therapy. The hematocrit dropped significantly in the first two patients during the first 4 weeks of therapy, but then stabilized. Values for the erythrocyte sedimentation rate increased in all three patients after the prednisone dosage was dropped to 10 mg or less daily (Table 1).

Humoral immunity studies. Levels of circulating immune complexes as determined by liquid phase C1q binding were in the normal range in all three patients at the time CsA therapy was begun and remained normal throughout the study (although all three patients had had very high levels of circulating complexes when they initially presented with acute ENL). Antibody levels to the mycobacterial antigens phenolic glycolipid-I (PGL-I) and arabinomannan were determined for 10 pre-treatment sera collected from each of the first two patients over the year prior to the start of CsA therapy, and for 6 (patient 1) or 4 (patient 2) sera collected at approximately monthly intervals while on CsA. Levels of IgM antibodies to PGL-I were modestly elevated in patients 1 and 2 prior to CsA therapy (A_{492} = 0.22 and 0.34, respectively; normal $\leq$ 0.09) and remained in the same range while on CsA in patient 1 (A_{492} = 0.24). In patient

TABLE 2. *Lymphocyte subpopulations in peripheral blood prior to and during cyclosporine A (CsA) therapy.*

Patient	Lymphocytes reacting with monoclonal probe (%)											
	pan-B		T4		T8		Leu7		Leu11a		T4:T8 ratio	
	Pre-CsA[a]	On CsA[a]	Pre-CsA	On CsA	Pre-CsA	On CsA	Pre-CsA	On CsA	Pre-CsA	On CsA	Pre-CsA	On CsA
1	4.4	4.9	19.3	31.2	23.3	42.9	23.9	34.0	17.4	24.7	0.8	0.7
2	9.0	11.1	22.8	25.8	31.4	39.5	47.0	45.7	42.7	35.1	0.7	0.7

[a] Single determinations for all lymphocyte marker studies.

2, levels dropped into the normal range after 2 months on therapy. Levels of IgG antibody to arabinomannan were very high in patient 1 and remained elevated while on CsA therapy (A_{492} = 0.90 pre-treatment, 0.87 on treatment; normal ≤ 0.30). Levels of antibody to arabinomannan were borderline in patient 2 and were unaffected by CsA (A_{492} = 0.30 and 0.33, respectively).

Results of skin biopsy and slit-skin smear examinations. Six site smears obtained from patients 1 and 2 after two or more months of therapy had bacterial indices which were slightly lower than on the respective pre-treatment smears. The morphological indices remained essentially zero.

On immunoperoxidase studies, pre-treatment tissues showed the T-helper/inducer predominance (Table 3) previously reported to be present during ENL ([16, 21]), and the post-treatment tissues manifested the T-suppressor/cytotoxic predominance associated with LL not in reaction ([11, 17, 20, 32]). The distribution of cells bearing the IL-2 receptor, Tac, was similar in both groups, as was the number of epidermal Langerhans' cells (data not shown). Epidermal keratinocytes strongly expressed the Ia antigen in pre-treatment specimens, but this was absent in the post-treatment biopsy specimens.

Adverse effects. The only symptomatic adverse effect observed was gastrointestinal distress, manifested as nausea, abdominal cramps, and watery diarrhea in patients 2 and 3. Patient 1 also noted transient diarrhea when he inadvertently increased his dose above 700 mg daily on one occasion. These gastrointestinal side effects were controlled by decreasing the dosage in all three cases.

As noted above, anemia developed in two patients. Reticulocyte counts were elevated and the Coombs' tests were negative in both. There was no evidence of gastrointestinal blood loss. Transient mild hyperbilirubinemia (maximum level 1.5 mg/dl) developed in one patient but resolved spontaneously. No deterioration in renal function as assessed by serial determinations of BUN, serum creatinine, and renal creatinine clearance was detected in any patient.

DISCUSSION

Administration of CsA resulted in very good control of chronic ENL reactions in two of the three patients treated. The third patient had only a partial response, allowing a decrease in her prednisone dose from 20 mg to 10 mg daily, but it is perhaps relevant that satisfactory levels of CsA were never achieved in this case because of dose-related

TABLE 3. *Mean percentages and ratios of T-lymphocyte subsets in skin lesions before and after cyclosporine A (CsA) treatment.*[a]

	No.	% Leu4+ (mean ± S.D.)	% Leu3a+ (mean ± S.D.)	% Leu2a+ (mean ± S.D.)	Leu3a/Leu2a (mean ± S.D.)
Pre-treatment	4	34 ± 4	28 ± 10	14 ± 4	2.0 ± 0.2
Post-treatment	2	30 ± 10	8 ± 8	28 ± 3	0.3 ± 0.3

[a] Percentages of T lymphocytes were estimated as compared to the total number of cells in the granulomas. Leu4, pan T-cell marker; Leu2a, suppressor/cytotoxic cell marker; Leu3a, helper/inducer cell marker.

gastrointestinal toxicity and poor compliance. Two of our three patients experienced significant gastrointestinal toxicity at moderate doses of CsA. In contrast, the reported incidence of diarrhea, nausea, or vomiting in renal transplant patients receiving CsA has ranged between 2% and 4%. All of our patients were receiving 100 mg or 200 mg of clofazimine per day. Clofazimine is known to accumulate in the intestinal epithelial cells and is associated with nausea, vomiting, and diarrhea when given in large doses. It is possible that alterations in the gastrointestinal mucosa induced by long-term clofazimine use predisposed our patients to gastrointestinal toxicity when CsA was given. This may be a limiting factor in the treatment of chronic ENL patients with CsA since the majority of these patients will be receiving clofazimine. The known nephrotoxicity of CsA is also of concern, particularly since patients with chronic ENL are at risk of developing amyloidosis ([13]) with resultant glomerular damage. The fact that the renal functional studies remained unchanged in our patients is reassuring, but we did not perform renal biopsies to screen for more subtle or pre-clinical abnormalities. The risk of using CsA in these patients must be carefully weighed against the significant risks associated with prolonged steroid therapy, thalidomide, or cytotoxic agents. The etiology of the mild anemia in our patients is unclear, but none of the patients developed symptoms attributable to the anemia or required transfusions. Anemia is a reported but uncommon complication of CsA therapy (occurring in less than 2% of patients). The increase in sedimentation rates in all three patients despite decreasing disease activity reflects the decrease in (or elimination of) the dosage of prednisone, which, unlike CsA, is known to inhibit the acute-phase reactants primarily responsible for the high sedimentation rates in inflammatory conditions.

The activity of CsA in controlling chronic ENL provides insight into the pathogenesis of this condition. Modlin, *et al.* have demonstrated an increase in the ratio of helper T cells to suppressor T cells in the cutaneous lesions of lepromatous leprosy patients with ENL when compared with lesions from lepromatous patients without ENL ([15]). CsA, like prednisone and thalidomide, produces effects on several different cell types involved in the host immune response. Its most consistent effects at therapeutic blood levels are an inhibition of IL-2 production and a decrease in the number of IL-2 receptors on helper T cells ([28]). Activation of helper T cells is also depressed by glucocorticosteroids and thalidomide. On the other hand, suppressor T-cell activation, monocyte-macrophage function, B-cell function, and neutrophil activity are all unaffected or only slightly affected by one or more of these three agents. As predicted by prior studies on the mechanism of action of CsA, we observed no consistent effects on B-cell function as measured by circulating immune complex levels, as well as specific antibody levels to two mycobacterial antigens, one of which elicits primarily an IgM response ([36]) and one which induces host IgG ([14]). Thus, the activity of these immunosuppressive agents in the treatment of ENL appears to be related to their inhibition of helper T-cell activation. Aberrant activation of helper T cells, or of a subset of helper T cells, is therefore an essential step in the pathogenesis of ENL. The low T4:T8 ratio in the peripheral blood of our patients was unexpected but was unaffected by CsA therapy, emphasizing the importance of the changes observed in tissue sections. Normal ratios have been reported in patients with acute ENL ([15]), but there are no comparable studies from patients with chronic ENL.

As judged by immunoperoxidase staining, CsA therapy was associated with several biological effects. The change from a T-helper/inducer to a T-suppressor/cytotoxic predominance is consistent with the known suppressor cell sparing effects of CsA ([7]). Keratinocyte Ia expression has been recently recognized as common in ENL tissues ([23]), and probably represents a response to interferon-gamma, as is believed to be the case in tuberculin skin tests ([26]), graft versus host reactions ([9]), and allergic contact dermatitis ([12]). Interferon-gamma is known to induce Ia in keratinocytes both *in vitro* ([34]) and *in vivo* ([22]). The abolition of keratinocyte Ia expression in association with CsA therapy is most easily explained as an

interruption of the cell-mediated immune cytokine cascade, eventually resulting in cessation of interferon-gamma production.

CsA is expensive both in absolute cost and in relation to the established first line therapeutic agents used in the treatment of ENL. If our results on the efficacy of CsA in the treatment of ENL are confirmed in larger studies, the expense of CsA in conjunction with its toxicity will still restrict its use to highly selected cases in developed countries. More important to the long-range goal of developing safe and effective therapeutic agents for ENL is the indirect evidence that helper T-cell function is fundamental in producing this reactional state. Future efforts should focus on immunopharmacologic interventions which are specific for the helper T-cell subset involved in ENL.

SUMMARY

We have treated three leprosy patients suffering from chronic, steroid-dependent erythema nodosum leprosum (ENL) with cyclosporine A (CsA). Excellent results were obtained in two patients. Extra-cutaneous manifestations of the reactional state were completely suppressed, and the development of new skin lesions was sharply curtailed. Immunohistologic abnormalities characteristic of active ENL were corrected. Lymphocyte subpopulations and anti-mycobacterial antibody levels in peripheral blood were unaffected. The third patient showed only a partial response to CsA, but satisfactory blood levels were never obtained in this individual because of dose-related gastrointestinal toxicity. The effectiveness of CsA in the treatment of ENL is consistent with the hypothesis that aberrant activation of a subset of T-helper cells is involved in the pathogenesis of this reaction. CsA may have a role in the treatment of chronic ENL that has failed to respond to conventional therapeutic modalities.

RESUMEN

Se trataron 3 pacientes con lepra y eritema nodoso leproso crónico, dependiente de esteroides, con ciclosporina A (CsA). En 2 pacientes se obtuvieron resultados excelentes. Las manifestaciones extracutáneas fueron suprimidas completamente y se impidió el desarrollo de nuevas lesiones en la piel de manera muy clara. Las anormalidades inmunohistológicas características del ENL también se corrigieron. El tercer paciente mostró sólo una respuesta parcial a la CsA pero nunca se obtuvieron niveles sanguíneos satisfactorios de la droga debido a cierta toxicidad gastrointestinal relacionada con la dosis usada. La efectividad de la CsA en el tratamiento del ENL es consistente con la hipótesis de que en la patogénesis de ésta reacción, está involucrada la activación aberrante de una subclase de células T cooperadoras. La CsA puede resultar útil en el tratamiento del ENL crónico que no ha respondido a las formas convencionales de tratamiento.

RÉSUMÉ

Trois malades de la lèpre souffrant d'une érythème noueux lépreux (ENL) chronique, stéroide-dépendant, ont été traités par la cyclosporine A (CsA). D'excellents résultats ont été obtenus. Les manifestations extracutanées de l'état réactionnel ont été complètement supprimées, et le développement de nouvelles lésions cutanées a été drastiquement empêchée. Les anomalies immuno-histologiques caractéristiques de l'ENL actif ont été corrigées. Les sous-populations de lymphocytes, de même que les taux d'anticorps anti-mycobactériens dans le sang périphérique, n'ont pas été affectés. Un des trois malades n'a présenté qu'une réponse partielle à la cyclosporine A; toutefois, des taux sanguins satisfaisants n'ont jamais pu être atteints chez cet individu, par suite d'une toxicité gastrointestinale en relation avec la dose administrée. L'efficacité de la cyclosporine A dans le traitement de l'ENL confirme l'hypothèse qui veut que l'activation abérrante d'une sous-population de cellules T adjuvantes (helper) intervient dans la pathogénèse de cette réaction. La cyclosporine A peut avoir une place dans le traitement de l'ENL chronique, lorsque celui-ci n'a pas répondu aux schémas thérapeutiques conventionnels.

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