



JOURNAL of the **AMERICAN ACADEMY OF** **DERMATOLOGY**

Univ. of Minn.
Bio-Medical
Library

6 01 93

Index issue
VOLUME 28 NUMBER 6

june 1993

CME article

Androgen biology as a basis for the diagnosis and treatment of androgenic disorders in women. II.

LTC LEONARD C. SPERLING, MC, USA, and CPT(P) WILLIAM L. HEIMER II, MC, USA Washington, D.C.

CME examination for volume 27

PUBLISHED BY
ST. LOUIS,

Dr. Reddy's Laboratories, Ltd., et al.
v.
Galderma Laboratories, Inc.
IPR2015-_____
Exhibit 1065



JOURNAL of the **AMERICAN ACADEMY OF** **DERMATOLOGY**

Univ. of Minn.
Bio-Medical
Library

6 01 93

Index issue
VOLUME 28 NUMBER 6

june 1993

CME article

Androgen biology as a basis for the diagnosis and treatment of androgenic disorders in women. II.

LTC LEONARD C. SPERLING, MC, USA, and CPT(P) WILLIAM L. HEIMER II, MC, USA Washington, D.C.

CME examination for volume 27

PUBLISHED BY MOSBY
ST. LOUIS, MISSOURI 63146

ISSN 0190-9622



Editor

Richard L. Dobson, MD

Associate Editor

Bruce H. Thiers, MD

Editorial Office

Department of Dermatology
Medical University of South Carolina
171 Ashley Ave.
Charleston, SC 29425-2215
803-792-9155

Assistant Editors

Philip C. Anderson, MD
Columbia, Missouri

Walter H. C. Burgdorf, MD
Albuquerque, New Mexico

Philip M. Catalano, MD
Bradenton, Florida

P. Haines Ely, MD
Grass Valley, California

Pearl E. Grimes, MD
Culver City, California

W. Clark Lambert, MD
Newark, New Jersey

Alfred T. Lane, MD
Stanford, California

W. Mitchell Sams, Jr., MD
Birmingham, Alabama

Daniel N. Sauder, MD
Hamilton, Ontario

Maria L. Chanco Turner, MD
Washington, D.C.

Ronald G. Wheeland, MD
Sacramento, California

Founding Editor

J. Graham Smith, Jr., MD
Mobile, Alabama

Vol. 28, No. 6, June 1993, the Journal of the American Academy of Dermatology (ISSN 0190-9622) is published monthly (six issues per volume, two volumes per year) by Mosby, 11830 Westline Industrial Dr., St. Louis, MO 63146-3318. Second class postage paid at St. Louis, Missouri, and additional mailing offices. Postmaster: Send address changes to Journal of the American Academy of Dermatology, Mosby, 11830 Westline Industrial Dr., St. Louis, MO 63146-3318. Annual subscription rates: \$103.00 for individuals, \$172.00 for institutions. Printed in the U.S.A. Copyright © 1993 by the American Academy of Dermatology, Inc., P.O. Box 4014, Schaumburg, IL 60168-4014.

CONTENTS June 1993

CONTINUING MEDICAL EDUCATION

- Androgen biology as a basis for the diagnosis and treatment of androgenic disorders in women. II.** 901

LTC Leonard C. Sperling, MC, USA, and
CPT(P) William L. Heimer II, MC, USA
Washington, D.C.

- Answers to CME examination (Identification No. 893-105), May 1993 issue of the JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY** 916

- CME examination** 917

CLINICAL AND LABORATORY STUDIES

- Nodular lesions of erythema elevatum diutinum in patients infected with the human immunodeficiency virus** 919

Philip E. LeBoit, MD, and
Clay J. Cockerell, MD
*San Francisco, California,
and Dallas, Texas*

- Amplified surface microscopy** 923

Douglas Puppin, Jr., MD,
Denis Salomon, MD, and
Jean-Hilaire Saurat, MD
Geneva, Switzerland

- Mucocutaneous leishmaniasis: A clinicopathologic classification** 927

Omar P. Sanguenza, MD, Julio M. Sanguenza, MD, Mathew J. Stiller, MD, and Pastor Sanguenza, MD
New York, New York, and La Paz, Bolivia

Continued on page 7A

Treatment of pemphigus and linear IgA dermatosis with nicotinamide and tetracycline: A review of 13 cases

Marsha L. Chaffins, MD,^a Daniel Collison, MD,^b and David P. Fivenson, MD^a
Detroit, Michigan, and Hanover, New Hampshire

Pemphigus usually requires long-term therapy with oral corticosteroids, which can cause significant morbidity.^{1,2} Several immunomodulating drugs, such as cyclophosphamide, azathioprine, and gold have proved beneficial as steroid-sparing agents.^{3,4} However, these agents also have limited long-term utility because of their potential to induce renal and hepatic dysfunction and bone marrow suppression.

Nicotinamide in combination with tetracycline has been reported to be effective for bullous pemphigoid (BP) and linear IgA bullous dermatosis (LABD).^{5,6} This regimen has the advantage of lower toxicity compared with corticosteroids and immunosuppressant regimens. We have treated 11 cases of pemphigus and two cases of LABD with nicotinamide and tetracycline and report our experience.

MATERIAL AND METHODS

Eleven patients with pemphigus (six with pemphigus vulgaris [PV], three with pemphigus foliaceus [PF], two with pemphigus erythematosus [PE]) and two patients with LABD were treated with nicotinamide, 1.5 gm/day, and tetracycline, 2 gm/day, with or without oral corticosteroids as summarized in Table I. The clinical diagnosis was confirmed in all cases by routine histopathology and immunofluorescence studies.

Therapeutic responses were graded by the degree of clinical improvement after 8 weeks of treatment. Responses were recorded as follows: complete response (CR) = total clearing of lesions; partial response (PR) = clearing of more than 50% of lesions; and no response (NR) = clearing less than 50% of lesions or worsening of the disease.

A complete blood cell count as well as levels of serum electrolytes, glucose, serum glutamic oxaloacetic transferase, serum glutamic pyruvate transferase, γ -glutamyl transferase, and bilirubin were determined on all patients before beginning therapy, after 4 to 8 weeks of treatment, and periodically thereafter. In four patients pemphigus autoantibodies were determined by indirect immunofluorescence on monkey esophagus at the time of diagnosis and after at least 8 weeks of treatment.

RESULTS

The therapeutic responses of the patients are summarized in Table I. When evaluated as a group, 7 of 13 patients experienced CR. Four patients had PR, and two patients failed to respond. Of the six patients with PV, three had CR, two had PR, and one had NR. Only two patients with PV were able to be treated with nicotinamide and tetracycline alone; the four other patients required a mean daily dose of 8 mg of prednisone to control disease activity. Patient 3 was also treated with 150 mg of azathioprine per day. The follow-up period for these patients ranged from 6 to 13 months (mean 9 months).

Of the five patients with superficial pemphigus, two had CR, two had PR, and one patient did not respond. Only one patient (patient 10) required a mean daily dose of 7.5 mg of prednisone for 10 months. For the last 5 months his disease has been controlled with tetracycline and nicotinamide alone. The follow-up period for these patients ranges from 11 to 41 months (mean 22 months).

Three of four patients had a significant reduction in pemphigus antibody titers during treatment. Patients 1 and 2 had a twofold decrease. Patient 10 had an initial titer of 1:2560 that became negative during treatment.

Both patients with LABD achieved rapid and complete clearing. However, patient 12 discontinued therapy after 2 months because of persistent headaches. He has subsequently remained clear

From the Departments of Dermatology, Henry Ford Hospital, Detroit^a; and Dartmouth University, Hanover.^b

Reprint requests: Marsha L. Chaffins, MD, Henry Ford Hospital, 2799 W. Grand Blvd., Detroit, MI 48202.

J AM ACAD DERMATOL 1993;28:998-1000.

Copyright © 1993 by the American Academy of Dermatology, Inc.
0190-9622/93 \$1.00 + .10 16/54/43729

Table I. History and therapeutic response of patients treated with nicotinamide and tetracycline for autoimmune bullous diseases

Patient	Age (yr)/ Sex	Diagnosis	Concurrent treatment	Response*	Follow-up period (mo)
1	34/M	PV	Topical steroids	CR	8
2	47/F	PV	Prednisone, 5 mg q.o.d.-30 mg q.d.	PR	6
3	71/F	PV	Prednisone, 5 mg/day Azathioprine, 150 mg/day	PR	10
4	81/M	PV	Topical steroids	CR	9
5	57/F	PV, oral	Prednisone, 2.5 mg/day	CR	14
6	41/F	PV, oral	Prednisone, 10 mg/day	NR	
7	60/F	PF	None	CR	24
8	51/M	PF	Topical steroids	CR	41
9	50/M	PF	Topical steroids	PR	11
10	28/F	PE	Prednisone, 7.5-0 mg/day	PR	13
11	73/M	PE	None	NR	
12	70/M	LABD	Antihistamines, topical steroids	CR	2 mo w/ medication, 11 mo clear
13	69/F	LABD	Topical steroids	CR	19

LABD, Linear IgA bullous dermatosis; PE, pemphigus erythematosus; PF, pemphigus foliaceus; PV, pemphigus vulgaris.

*Responses graded as: CR = complete response (all lesions resolved) after 8 weeks of nicotinamide/tetracycline; PR = partial response (>50% of lesions resolved) after 8 weeks of nicotinamide/tetracycline; NR = no response (<50% of lesions resolved) or worsening of disease after 8 weeks of nicotinamide/tetracycline.

with topical steroid therapy for approximately 1 year. Patient 13 (previously reported in Peoples and Fivenson⁵) has remained clear for more than 2 years with nicotinamide and tetracycline therapy.

Eight of the 13 patients reported no adverse effects. There were no abnormalities in any patient's serum chemical or hematologic findings. Four patients experienced nausea, abdominal discomfort, and mild diarrhea. Gastrointestinal symptoms were relieved in three patients when minocycline, 100 mg twice a day, was substituted for tetracycline and in the fourth patient when the dose of tetracycline was reduced to 1.5 gm/day. Patient 10 developed a generalized morbilliform eruption that was believed to be caused by tetracycline but was able to tolerate minocycline, 100 mg twice a day. Patient 12 experienced headaches with nicotinamide and tetracycline, as well as with nicotinamide and minocycline.

DISCUSSION

Although this is an uncontrolled study with a limited follow-up period, the preliminary results appear promising. Six of 11 patients with pemphigus and two patients with LABD were able to be controlled with nicotinamide and tetracycline as their only oral agents. We should emphasize that this combination was adequate therapy in only two

of six patients with PV. The role of these agents in PV appears to be that of a steroid-sparing adjuvant, rather than a steroid alternative. The combination of nicotinamide and tetracycline was found to be an effective alternative to steroids in superficial pemphigus (PE and PF) and LABD in six of seven patients.

The primary advantage nicotinamide and tetracycline offer over corticosteroids and immunosuppressive agents is a broader safety profile. The most common side effect in our patients was gastrointestinal upset. In higher doses, nicotinamide has been reported to produce flushing, pruritus, headache, vomiting, and a flu-like syndrome.⁷⁻⁹ Acanthosis nigricans, ichthyosiform skin changes, and hepatotoxicity have also been reported.^{8, 10, 11} The side effects of tetracycline are well known and have been reviewed elsewhere.^{12, 13}

Because this study is uncontrolled, it is possible that a selection bias towards patients with a tendency toward milder disease or spontaneous remission may have occurred. However, the fact that several of our patients (7, 8, 10, and 13) had recurrences when nicotinamide and tetracycline were discontinued argues against this explanation for the therapeutic results.

The mechanism of action of nicotinamide and

tetracycline in the treatment of autoimmune bullous disorders is unknown.⁶ Nicotinamide inhibits polymorphonuclear cell (PMN) and eosinophil chemotaxis and blocks IgE-mediated histamine release and mast cell degranulation.¹⁴⁻¹⁷ The infiltrate in both pemphigus and BP is rich in eosinophils; thus eosinophil inhibition may be part of the mechanism of action for the observed efficacy in these disorders. Similarly, inhibition of PMNs may contribute to the results observed in LABD.

Another likely explanation for the therapeutic results are the effects that nicotinamide and tetracycline have on lymphocyte function. Both agents inhibit lymphocyte blast transformation in vitro.¹⁷⁻¹⁹ This effect combined with the inhibition of PMN and eosinophil chemotaxis could serve to downgrade both the afferent and efferent limbs of humoral immune responses. The decrease in intercellular substance antibody titer observed in some patients after treatment with nicotinamide and tetracycline supports this suppression of lymphocyte (B cell) activity.

REFERENCES

1. Rosenberg FR, Sanders S, Nelson CT. Pemphigus: a 20 year review of 107 patients treated with corticosteroids. *Arch Dermatol* 1976;112:962-70.
2. Ahmed AR, Moy R. Death in pemphigus. *J AM ACAD DERMATOL* 1982;7:221-8.
3. Jablonska S, Chorzelski TP, Blaszczyk M. Immunosuppressants in the treatment of pemphigus. *Br J Dermatol* 1970;83:315-22.
4. McDonald CJ. Use of cytotoxic drugs in dermatologic diseases. I and II. *J AM ACAD DERMATOL* 1985;12:753-2, 965-75.
5. Peoples D, Fivenson DP. Linear IgA bullous dermatosis: successful treatment with tetracycline and niacinamide. *J AM ACAD DERMATOL* 1992;26:498-9.
6. Berk MA, Lorincz AL. The treatment of bullous pemphigoid with tetracycline and nicotinamide: a preliminary report. *Arch Dermatol* 1986;122:670-4.
7. Parsons WB Jr. Treatment of hypercholesterolemia by nicotinic acid: progress report with review of studies regarding mechanism of action. *Arch Intern Med* 1951;4:736-7.
8. Zackheim HS, Vasily DB, Westphal ML, et al. Reactions to nicotinamide [Letter]. *J AM ACAD DERMATOL* 1981;4:736-7.
9. Hoffer A. Safety, side-effects, and relative lack of toxicity of nicotinic acid and nicotinamide. *Schizophrenia* 1969;1:78-9.
10. Brown J, Winkelman RK. Acanthosis nigricans: a study of 90 cases. *Medicine* 1968;47:33-51.
11. Winter SL, Boyer JL. Hepatic toxicity from large doses of vitamin B₃ (nicotinamide). *N Engl J Med* 1973;289:1180-2.
12. Bruce S, Wolf JE. Antibacterial agents. In: Wolverton SE, Wilkin JK, eds. *Systemic drugs for skin disease*. Philadelphia: WB Saunders, 1991.
13. Wright AL, Colver GB. Tetracyclines: How safe are they? *Clin Exp Dermatol* 1988;13:57-61.
14. Cohen BM. A niacinamide-theophylline compound (RC-C-144): human and blood level studies. *J Asthma Res* 1966;4:75-9.
15. Cohen BM. A niacinamide-theophylline compound (RC-C-144): clinical and spirometric effects. *J Asthma Res* 1966;4:81-7.
16. Berkier E, Masinski C. Antihistaminic action of nicotinamide. *Agents Action* 1974;4:196.
17. Burger DR, Vandenbark AA, Daves D, et al. Nicotinamide: suppression of lymphocyte transformation with a component identified in human transfer factor. *J Immunol* 1976;117:797-801.
18. Thong YH, Ferrante A. Inhibition of mitogen induced human lymphocyte proliferative responses to tetracycline analogues. *Clin Exp Immunol* 1979;35:443-6.
19. Banck G, Forsgren A. Antibiotics and suppression of lymphocyte function in vitro. *Antimicrob Agents Chemother* 1979;16:554-60.