

ARCHIVES OF DERMATOLOGY

CURRENT
AWARENESS
TITLE

JUNE 1994

Univ. of Minn.
Bio-Medical
Library

06 15 94



Perifollicular lymphocytic reaction. See page 770.

DERMATOLOGY IN THE OREGON PLAN WITH IMPLICATIONS FOR HEALTH CARE PLANS IN OTHER STATES

P. S. Russell

NICOTINAMIDE AND TETRACYCLINE THERAPY OF BULLOUS PEMPHIGOID

D. P. Fivenson, D. L. Breneman, G. B. Rosen,
C. S. Hersh, S. Cardone, D. Mutasim

TOPICAL RETINOIC ACID (TRETINOIN) FOR MELASMA IN BLACK PATIENTS: A VEHICLE-CONTROLLED CLINICAL TRIAL

C. K. Kimbrough-Green, C. E. M. Griffiths,
L. J. Finkel, T. A. Hamilton, S. M. Bulengo-Ransby,
C. N. Ellis, J. J. Voorhees

FOLLICULAR DEGENERATION SYNDROME IN MEN

LTC L. C. Sperling, CAPT H. G. Skelton III,
COL K. J. Smith, COL P. Sau, K. Friedman

SPECIFIC PRURITIC DISEASES OF PREGNANCY: A PROSPECTIVE STUDY OF 3192 PREGNANT WOMEN

D. Roger, L. Vaillant, A. Fignon, F. Pierre, Y. Bacq,
J.-F. Brechot, M.-C. Grangeponde, G. Lorette

INHIBITION OF A MODEL OF IN VITRO GRANULOMA FORMATION BY TETRACYCLINES AND CIPROFLOXACIN: INVOLVEMENT OF PROTEIN KINASE C

#BXNBBCL***** 3-DIG H 554
#010460858052#130D04 9412
UNIVERSITY OF MINNESOTA
BIO-MEDICAL LIBRARY
505 ESSEX ST SE/325A DIEHL
MINNEAPOLIS MN 55455-0350

American Medical Association

Physicians dedicated to the health of America



Dr. Reddy's Laboratories, Ltd., et al.
v.
Galderma Laboratories, Inc.
IPR2015-
Exhibit 1063

ARCHIVES

CURRENT
AWARENESS
~~TITLE~~

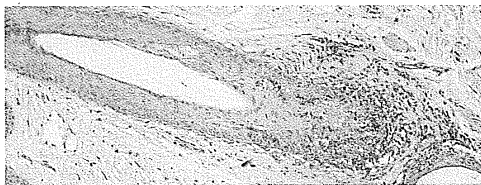
OF

DERMATOLOGY

JUNE 1994

Univ. of Minn.
Bio-Medical
Library

06 15 94



Perifollicular lymphocytic reaction. See page 770.

DERMATOLOGY IN THE OREGON PLAN WITH IMPLICATIONS FOR HEALTH CARE PLANS IN OTHER STATES

P. S. Russell

NICOTINAMIDE AND TETRACYCLINE THERAPY OF BULLOUS PEMPHIGOID

D. P. Fivenson, D. L. Breneman, G. B. Rosen,
C. S. Hersh, S. Cardone, D. Mutasim

TOPICAL RETINOIC ACID (TRETINOIN) FOR MELASMA IN BLACK PATIENTS: A VEHICLE-CONTROLLED CLINICAL TRIAL

C. K. Kimbrough-Green, C. E. M. Griffiths,
L. J. Finkel, T. A. Hamilton, S. M. Bulengo-Ransby,
C. N. Ellis, J. J. Voorhees

FOLLICULAR DEGENERATION SYNDROME IN MEN

LTC L. C. Sperling, CAPT H. G. Skelton III,
COL K. J. Smith, COL P. Sau, K. Friedman

SPECIFIC PRURITIC DISEASES OF PREGNANCY: A PROSPECTIVE STUDY OF 3192 PREGNANT WOMEN

D. Roger, L. Vaillant, A. Fignon, F. Pierre, Y. Bacq,
J.-F. Brechot, M.-C. Grangeponne, G. Lorette

INHIBITION OF A MODEL OF IN VITRO GRANULOMA FORMATION BY TETRACYCLINES AND CIPROFLOXACIN: INVOLVEMENT OF PROTEIN KINASE C

G. E. Williams

#BXNBBCL***** 3-DIG H 554
#010460858052#130D04 9412
UNIVERSITY OF MINNESOTA
BIO-MEDICAL LIBRARY
505 ESSEX ST SE/325A DIEHL
MINNEAPOLIS MN 55455-0350

American Medical Association

Physicians dedicated to the health of America



Nicotinamide and Tetracycline Therapy of Bullous Pemphigoid

David P. Fivenson, MD; Debra L. Breneman, MD; Gary B. Rosen, MD; Craig S. Hersh, MD; Scott Cardone, MD; Diya Mutasim, MD

Background and Design: The combination of nicotinamide and tetracycline has been anecdotally reported to be effective in the treatment of bullous pemphigoid. We conducted a randomized, open-labeled trial comparing the combination of 500 mg of nicotinamide, three times daily, and 500 mg of tetracycline four times daily, with prednisone therapy in 20 patients with bullous pemphigoid. The study was divided between an 8-week acute phase with fixed drug dosages and a 10-month follow-up phase in which study medications were tapered based on patient response.

Results: Eighteen of 20 patients enrolled in the study were treated, two patients were unavailable for follow-up. Twelve patients were treated with the combination of nicotinamide and tetracycline and six patients were treated with prednisone. There were five complete responses, five partial responses, one nonresponder, and one patient with disease progression in the nicotinamide and tetracycline group compared with one complete response and five partial responses in the predni-

sone group. There were no statistically significant differences in response parameters between the two groups. All five patients in the nicotinamide and tetracycline group receiving long-term follow-up remained disease free during medication tapering, while three patients in the prednisone group had repeated disease flare-ups with steroid tapering. Adverse effects in the nicotinamide and tetracycline group included gastrointestinal upset (two patients) and transient renal failure (one patient). In the prednisone group, there was one occurrence each of hypertension, erosive gastritis, multiple decubitus ulcers, osteomyelitis, deep venous thrombosis, and death related to sepsis. Two patients required insulin therapy for hyperglycemia.

Conclusions: The combination of nicotinamide and tetracycline appears to be a useful alternative to systemic steroids in the treatment of bullous pemphigoid.

(*Arch Dermatol.* 1994;130:753-758)

BULLOUS PEMPHIGOID (BP) is a chronic autoimmune blistering disease that is characterized by erythematous plaques, vesicles, and tense bullae that typically begin in the sixth or seventh decade. Traditional therapies used in BP include systemic corticosteroids and cytotoxic agents.¹ Other agents reported as efficacious include dapsone, cyclosporine, erythromycin, and tetracycline.¹⁻⁵ An effective steroid-sparing regimen could potentially benefit elderly patients with BP by helping to reduce the steroid-related side effects to which this population is prone. Recently, Berk and Lorincz⁶ presented four patients with BP treated effectively without steroids with a combination of nicotinamide and tetracycline.⁶

We have treated a series of 20 pa-

tients with BP in a nonrandomized fashion with the combination of nicotinamide and tetracycline and found it to be effective. We, therefore, initiated a randomized, open-label trial to compare the efficacy of the combination of nicotinamide and tetracycline with prednisone in the treatment of BP. In this article, we review our experience with the combination of nicotinamide and tetracycline in 20 patients enrolled in this randomized trial. The short-term and long-term effectiveness and safety of this combination therapy

*See Patients and Methods
on next page*

From the Department of Dermatology, Henry Ford Hospital, Detroit, Mich (Drs Fivenson, Rosen, and Hersh), and the Department of Dermatology, University of Cincinnati (Ohio) (Drs Breneman, Cardone, and Mutasim).

PATIENTS AND METHODS

PATIENTS

The study design was that of an open-label randomized trial comparing the combination of nicotinamide and tetracycline with prednisone in the treatment of BP. The study protocol was approved by the institutional review boards at Henry Ford Hospital, Detroit, Mich, and the University of Cincinnati (Ohio) Medical Center. Treatment was divided into two phases: an 8-week acute phase with fixed drug dosages and a 10-month follow-up period. The inclusion criteria included diagnosis of BP by clinical, histologic, and immunofluorescence findings, a minimum of eight lesions (bullae, urticaria, or erosions/crusts), and no systemic therapy within 2 weeks of enrollment. The exclusion criteria included a history of positive tuberculin skin test without treatment, cicatricial pemphigoid, or poorly controlled systemic diseases in which therapy with prednisone, nicotinamide, or tetracycline therapy was contraindicated.

Patients were randomized into one of two treatment groups: nicotinamide, 500 mg, three times daily, plus tetracycline, 500 mg, four times daily, or prednisone 40 to 80 mg/d. Minocycline, 100 mg, twice daily was substituted if excessive gastrointestinal upset was noted with tetracycline.

Patients were seen weekly for 2 weeks, then biweekly for 2 months, then monthly for the remainder of 1 year. On each visit, the number of bullous, crusted, and urticarial lesions on each patient were counted and plotted on cutaneous maps, one for lesions less than 1 cm in diameter and one for lesions more than 1 cm in diameter. The following scale was used: 0, no lesions; 1+, one to five lesions; 2+, six to 10 lesions; 3+, 11 to 20 lesions; 4+, 21 to 40 lesions; and 5+, more than 40 lesions.

Pruritus and the physician's global assessment were

also recorded at each visit. Pruritus was assessed as follows: 0, no pruritus or burning; 1, mild pruritus or burning (occasionally noticeable); 2, moderate pruritus or burning (present but did not interfere with daily activity or sleep); and 3, severe pruritus or burning (interference with daily activities and/or sleep). The physician's global assessment was rated with respect to baseline presentation as follows: -3, markedly worse; -2, somewhat worse; -1, slightly worse; 0, no change; 1+, slightly better; 2+, somewhat better; 3+, markedly better; and 4+, clinical remission.

The patient's blood pressure, complete blood cell count, and alanine aminotransferase, aspartate aminotransferase, serum electrolytes, serum urea nitrogen, and creatinine concentrations were obtained at weeks 0, 1, 2, 4, 8, and 12, and then at 3-month intervals. A chest roentgenogram and a skin anergy panel (including a tuberculin skin test antigen) were obtained prior to treatment.

Response categories were defined after 8 weeks of treatment as complete response, complete clearing of all lesions; partial response, at least 50% clearing of lesions; no response, less than 25% clearing; and worsening, progression of disease. During the follow-up period, disease recurrence was recorded if any new bullae, urticaria, or erosions and/or crusts were noted.

STATISTICAL ANALYSIS

The differences in numbers of bullous, crusted, and urticarial skin lesions of less than 1 cm or more than 1 cm were calculated between 1 week and baseline, 2 weeks and baseline, and 4 weeks and baseline, to adjust for the baseline conditions of the patients. The groups were then compared using Wilcoxon rank sum tests on the differences. Wilcoxon rank sum tests were also used to compare pruritus and global assessment between the two treatment groups. *P* values less than or equal to .01 were considered to be statistically significant. *P* values between .01 and .05 were considered to be "borderline" significant.

in the treatment of both localized and generalized BP are demonstrated.

RESULTS

Twenty patients were enrolled between the two study centers. This included six men between the ages of 69 and 89 years and 14 women between the ages of 52 and 91 years. There were 14 whites and six blacks in the study population. Fourteen patients were randomized to treatment with nicotinamide and tetracycline and six to prednisone treatment. The study was originally designed to randomize a total of 96 patients, with approximately 24 in each treatment arm at each center. The study was terminated after the 20 patients presented were enrolled; a randomized, double-blind, multicenter trial has since been initiated. During the acute phase of the trial, there were

five complete responses, five partial responses, one no response, and one worsening in the nicotinamide and tetracycline group and one complete response and five partial responses in the prednisone group. Two patients in the nicotinamide/tetracycline group were unavailable for follow-up (**Table 1**).

There was a general trend toward improvement in both groups in lesion counts, pruritus, and global assessment. Both treatment groups had rapid resolution of

See also pages 748 and 781

bullous and urticarial lesions in patients who achieved complete response or partial response. The mean pruritus score on enrollment was 2.0 for both the nicotinamide/tetracycline group and the prednisone group and de-

Table 1. Comparison of Patient Demographics and Responses to Therapy During the Acute Phase of a Randomized Trial of Nicotinamide/Tetracycline vs Prednisone in the Treatment of Bullous Pemphigoid*

Patient	Age, y/ Sex/Race	Lesions			Treatment Regimen, mg/d†	Response
		Bullous	Crusted	Urticarial		
1	77/M/W	>40	>40	>40	Prednisone 80	PR
2	82/F/B	>40	>40	0	Prednisone 80	PR
3	88/F/W	0	35	0	Prednisone 40	PR
4	70/F/B	>20	>10	20	Tetracycline/nicotinamide	Unavailable for follow-up
5	69/M/B	15	30	0	Tetracycline/nicotinamide‡	PR
6	76/M/W	>40	0	>40	Tetracycline/nicotinamide	PR
7	89/M/W	>40	>40	5	Tetracycline/nicotinamide	NR
8	90/F/W	>40	>40	0	Tetracycline/nicotinamide	CR
9	85/F/W	>40	>40	0	Tetracycline/nicotinamide	PR
10	74/M/W	5	30	>40	Tetracycline/nicotinamide	CR
11	73/F/W	3	3	18	Tetracycline/nicotinamide§	PR
12	61/F/B	15	>40	11	Prednisone 60	CR
13	90/F/W	8	3	>40	Tetracycline/nicotinamide§	CR
14	75/F/W	0	30	3	Prednisone 40	PR
15	81/M/W	11	>40	0	Tetracycline/nicotinamide	W
16	78/F/B	0	>40	8	Prednisone 60	PR
17	78/F/B	15	>40	>40	Tetracycline/nicotinamide	Unavailable for follow-up
18	52/F/W	>40	>40	>40	Tetracycline/nicotinamide	CR
19	78/F/W	18	6	3	Tetracycline/nicotinamide	PR
20	91/F/W	25	>40	>40	Tetracycline/nicotinamide	CR

*CR indicates complete response, complete clearing after 8 weeks or less; PR, partial response, at least 50% clearing after 8 weeks; NR, no response, less than 25% clearing or worse after 8 weeks; and W, worsening or disease progression after 8 weeks.

†Tetracycline, 500 mg four times daily plus nicotinamide, 500 mg three times daily, or prednisone, 40 to 80 mg/d.

‡Stopped after 4 weeks due to renal failure.

§Minocycline substituted for tetracycline due to gastrointestinal upset.

creased to 1.5 and 1.0, respectively, at 2 weeks and 1.2 and 0.2, respectively, at 4 weeks. The physician's global assessment followed a similar trend in both patient groups as well. Statistical comparison revealed no significant differences between the two treatment groups in the reduction in numbers of skin lesions (P values ranged from .13 to .96 at 1, 2, and 4 weeks of therapy). Prednisone showed borderline significance in reducing the number of bullous lesions of more than 1 cm after 1 week of treatment compared with the nicotinamide/tetracycline combination ($P=.017$). There were also no significant differences between treatment group responses for pruritus ($P=.32$, $P=.81$) or the physician's global assessment ($P=.40$, $P=.83$) at any time point in the acute phase of the trial. The **Figure** graphically demonstrates the similarity in responses to nicotinamide/tetracycline vs prednisone over time for the evaluation of skin lesions, pruritus, and the physician's global assessment.

Table 1 demonstrates that not only was the combination of tetracycline and nicotinamide efficacious in treating localized or limited BP (patients 5, 11, 13, and 19), but it was also effective in patients with extensive disease (patients 6, 8, 9, 18, and 20). Several patients with an excess of 100 bullae and/or erosions had their disease

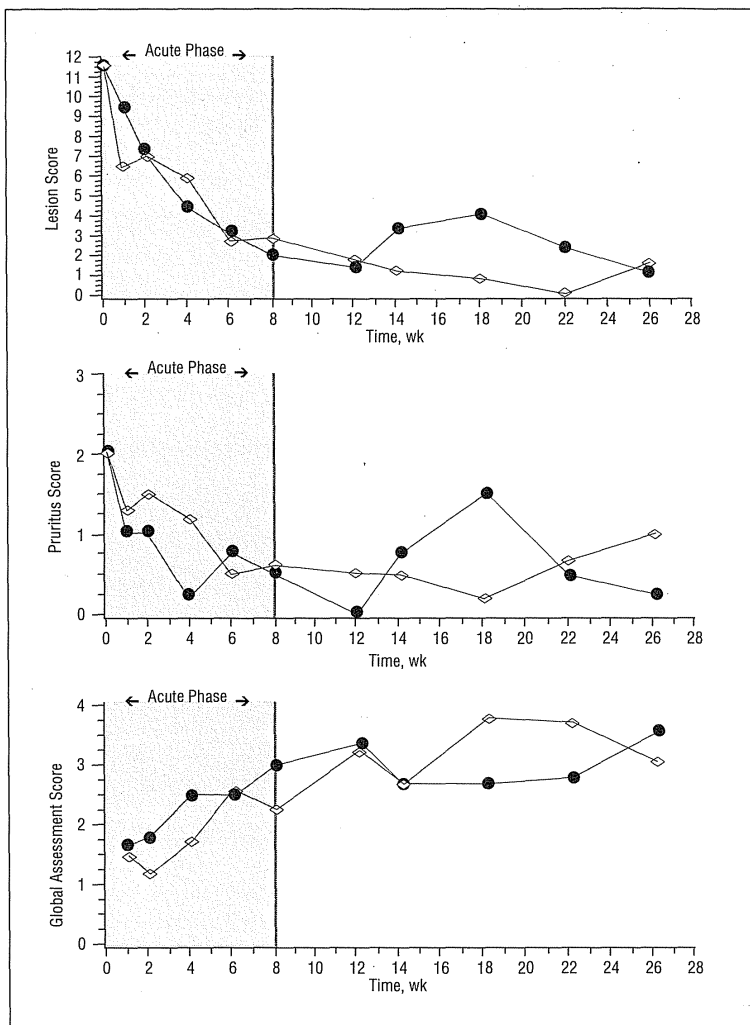
successfully controlled within 2 to 4 weeks of initiating tetracycline and nicotinamide therapy.

LONG-TERM FOLLOW-UP

The mean follow-up period was 21.3 weeks in the prednisone patients and 17.5 weeks in the nicotinamide/tetracycline patients. Eight patients maintained regular follow-up visits for 22 weeks or longer and their treatment courses and outcome are summarized in **Table 2**. Two of three prednisone-treated patients had repeated disease flare-ups with tapering of medication. Five patients in the nicotinamide and tetracycline group remained in complete response for 22, 28, 42, 50, and 54 weeks of observation while being tapered off treatment.

ADVERSE EFFECTS

Two patients in the nicotinamide and tetracycline group reported gastrointestinal upset and responded well to the substitution of minocycline at 100 mg twice daily for tetracycline. Both of these patients developed minocycline-related hyperpigmentation



Top, Mean lesion scores of bullous pemphigoid patients treated with prednisone vs the combination of nicotinamide and tetracycline in a randomized, open-label trial. Patients received a fixed dose of prednisone (solid circles) (40 to 80 mg/d [$n=6$]) or 500 mg of nicotinamide (open diamonds) twice daily plus 500 mg of tetracycline four times daily (nicotinamide/tetracycline [$n=2$]) for 8 weeks during the acute phase of the study and were then tapered individually. The lesion score represented is the mean score for each treatment group of the sum total score of bullous, urticarial, and crust lesions both less than 1 cm and more than 1 cm in diameter. Skin lesions were scored on the following scale: 0, no lesions; 1+, one to five lesions; 2+, six lesions; 3+, 11 to 20 lesions; 4+, 21 to 40 lesions; 5+, more than 40 lesions, thus the maximum score was 30 for any patient. The P values between the prednisone and nicotinamide/tetracycline groups at 1, 2, and 4 weeks were .61, .96, and .78, respectively. Center, Mean pruritus scores of the same patients as in the top part of the Figure. Pruritus was scored on the following scale: 0, no pruritus or burning; 1, mild pruritus or burning (occasionally noticeable); 2, moderate pruritus or burning (present, but not interfering with daily activities or sleep); and 3, severe pruritus or burning (interfering with daily activities and/or sleep). The P values between the prednisone (solid circles) and nicotinamide/tetracycline (open diamonds) groups at 1, 2, and 4 weeks were .81, .45, and .32, respectively. Bottom, Mean physician's global assessment scores of the same patients as in the top and center parts of the Figure. Physician's global assessment was scored on the following score: the physician's global assessment was rated with respect to baseline presentation as follows: -3, markedly worse; -2, somewhat worse; -1, slightly worse; 0, no change; 1+, slightly better; 2+, somewhat better; 3+, markedly better; and 4+, clinical remission. The P values between the prednisone (solid circles) and nicotinamide/tetracycline (open diamonds) groups at 1, 2, and 4 weeks were .83, .40, and .40, respectively.

within areas of old blisters and have been reported elsewhere.⁷ One of these patients treated with minocycline also developed tinnitus, which resolved after 1 month despite continued treatment. One patient was enrolled with elevated serum creatinine and serum urea nitrogen concentration (serum urea nitrogen, 12.9 mmol/L [3.6 to 8.9 mmol/L]; creatinine, 159 μ mol/L [<133 μ mol/L]) and developed acute tubular necrosis after 4 weeks of nicotinamide and tetracycline therapy. His peak creatinine level was 654 μ mol/L and renal function returned to baseline within 2 weeks of discontinuation of nicotinamide and tetracycline therapy. This patient was also taking nonsteroidal anti-inflammatory medications (ibuprofen and aspirin) at the time renal failure was diagnosed. No other significant serologic or hematologic abnormalities were noted in the nicotinamide and tetracycline group.

In the prednisone group, there was one occurrence each of hypertension (after week 9 of therapy), osteo-

myelitis of the toe (after week 7), multiple decubitus ulcers (after week 18), and deep venous thrombosis and erosive gastritis (after week 12). There was also one death in the prednisone group due to sepsis complicated by aspiration pneumonia. Two patients developed hyperglycemia necessitating supplemental insulin therapy.

COMMENT

Treatment of BP has historically involved systemic corticosteroids and immunosuppressive agents.¹ Because patients are often elderly, they are more prone to suffer from a number of other medical problems such as diabetes, hypertension, congestive heart failure, and osteoporosis that place them at higher risk for developing side effects from systemic corticosteroid therapy. Berk and Lorincz⁶ initially reported successful treatment of four patients with BP using the combination in 1986.⁶ In preliminary experiences at our institutions using nicotinamide and tetracycline in treating 20 patients with BP, we found this

Table 2. Long-term Follow-up Results and Complications in Patients With Bullous Pemphigoid Treated With Nicotinamide and Tetracycline vs Prednisone*

Patient	Treatment Regimen†	Follow-up Period, wk	Outcome	Complications
1	Prednisone, taper	42	PR, repeated flares of disease	Decubitus ulcers, weeks 18 and 38
8	Tetracycline/nicotinamide, taper	50	CR	None
10	Tetracycline/nicotinamide, taper	28	CR	None
11	Tetracycline/nicotinamide, taper	42	Flare week 12, add 4 week prednisone taper	Herpes zoster, week 18
12	Prednisone, taper	26	Flare, week 25	None
13	Tetracycline/nicotinamide, taper	22	CR	Gastrointestinal upset, tetracycline changed to minocycline, week 4
16	Prednisone, taper	34	PR	Hypertension, week 9
18	Tetracycline/nicotinamide, taper	54	CR	None

*CR indicates complete response, complete clearing after 8 weeks or more; PR, partial response, at least 50% clearing after 8 weeks; NR, no response, less than 25% clearing or worse after 8 weeks; and W, worsening, after 8 weeks or progression.

†Tetracycline, 500 mg four times daily plus nicotinamide, 500 mg three times daily, or prednisone, 40 to 80 mg/d.

combination an effective alternative therapy to systemic steroids in the majority of patients (unpublished observations). These uncontrolled observations led to the present randomized, open-label trial comparing nicotinamide and tetracycline with prednisone in the treatment of BP.

The results of our uncontrolled observations and this randomized trial suggest that the combination of nicotinamide and tetracycline may be a useful alternative for first-line therapy in the acute treatment of BP. Although the number of patients studied was not large, these results suggest comparable efficacy for the nicotinamide/tetracycline combination with prednisone in the treatment of BP. The efficacy of nicotinamide/tetracycline was independent of the number of lesions, as no correlation was observed between the extent of disease and the ability to respond to the nicotinamide and tetracycline combination.

In this group of patients, fewer short-term and long-term adverse effects occurred in the patients treated with the nicotinamide/tetracycline combination compared with prednisone therapy. Five of six patients randomized to prednisone developed major complications while receiving therapy including hypertension, decubitus ulcers, erosive gastritis, and serious infections, with one death due to sepsis. These underscore the potential toxic effects of corticosteroid therapy in patients with BP. In comparison, fewer significant adverse effects occurred with nicotinamide/tetracycline therapy. Those patients with gastrointestinal upset had complete amelioration with minocycline substitution for tetracycline while maintaining comparable efficacy. Only the one patient treated with this combination who developed acute tubular necrosis (patient 5) was withdrawn from the study due to a side effect. This occurrence has lead us to recommend

exclusion of patients with a serum creatinine level of more than 177 $\mu\text{mol/L}$ or a serum urea nitrogen level of more than 14.3 mmol/L from being treated with nicotinamide/tetracycline as well as avoidance of other potentially nephrotoxic drugs (eg, nonsteroidal anti-inflammatory medications). The pathophysiology of renal failure due to tetracycline in patients with baseline mild renal insufficiency involves decreased clearance of tetracycline with resulting accumulation of toxic metabolites in the renal tubules.^{8,9} Minocycline, which is metabolized in the liver prior to renal excretion, is considered a safe alternative to tetracycline in patients with mild renal insufficiency.^{8,9}

Potential adverse effects reported with nicotinamide therapy include hepatotoxicity, pruritus, and flushing; these have generally been reported in patients taking a much higher dose than those used in this study. Tetracycline has been associated with gastrointestinal upset, hepatotoxicity, and phototoxicity.⁸⁻¹⁰ Long-term systemic corticosteroid therapy is associated with osteoporosis, weight gain, cataracts, hyperglycemia, gastrointestinal ulcers, myopathy, hypertension, and psychosis in addition to the septic complications and poor wound healing seen in this study.¹¹ Thus, both the observed and expected side-effect profiles for nicotinamide/tetracycline therapy appear to be more tolerable for the elderly patient with BP than those for prednisone.

There are a variety of proposed mechanisms for the therapeutic effects of nicotinamide and tetracycline in BP. Nicotinamide may exert its therapeutic function via electron scavenging,¹² inhibition of phosphodiesterase,¹³ and/or increased tryptophan conversion to serotonin.^{14,15} Nicotinamide also has direct antihistamine receptor effects as well as effects inhibiting histamine release,¹⁶⁻²⁰ and BP has been shown to have blister fluid

characterized by increased levels of histamine.²¹ Both nicotinamide and tetracycline inhibit neutrophil and eosinophil chemotaxis and secretion.^{6,20,22-25} As BP is characterized by a subepidermal blister, often rich in eosinophils and neutrophils, inhibition of chemotaxis of these cells by nicotinamide and tetracycline is one of the more likely mechanisms of action. Other mechanisms of action include the effect of nicotinamide on gene regulation and suppression of lymphocyte transformation.²⁶⁻²⁸ Tetracycline has also been reported to experimentally increase cohesion of the epidermal basement membrane zone.²⁹

We present data from a randomized, open-label trial showing that nicotinamide combined with tetracycline is a useful alternative to systemic steroids in the treatment of BP. The mechanism of action for this combination is unknown but may involve some down-regulation of antigen-induced lymphocyte transformation, inhibition of leukocyte chemotaxis, and/or inhibition of histamine release. These findings will need to be confirmed in a randomized, double-blind study, which is currently underway. This novel and inexpensive combination may offer advantages to older patients by avoiding some of the toxic effects of systemic steroids without significant loss of efficacy.

Accepted for publication July 8, 1993.

This study was supported in part by a grant from the Food and Drug Administration-Orphan Products Development Office, Detroit, Mich (No. FDU-000651) (Dr Fivenson).

Presented in part at the American Academy of Dermatology Summer Session, June 13, 1991, Monterey, Calif, and before the annual meeting of the Ohio Dermatological Association, September 15, 1991, Columbus.

Reprint requests to the Department of Dermatology, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202 (Dr Fivenson).

REFERENCES

- Korman N. Bullous pemphigoid. *J Am Acad Dermatol*. 1987;16:907-924.
- Person JR, Rogers RS. Bullous pemphigoid responding to sulfapyridine and the sulfones. *Arch Dermatol*. 1977;113:610-615.
- Fox BJ, Odum RB, Findlay RF. Erythromycin therapy in bullous pemphigoid: possible anti-inflammatory effects. *J Am Acad Dermatol*. 1982;7:504-519.
- Thornfeldt CR, Menkes AW. Bullous pemphigoid controlled by tetracycline. *J Am Acad Dermatol*. 1987;16:305-310.
- Thomas I, Khorenian S, Arbesfeld DM. Treatment of generalized bullous pemphigoid with oral tetracycline. *J Am Acad Dermatol*. 1993;28:74-77.
- Berk NA, Lorincz AL. The treatment of bullous pemphigoid with tetracycline and niacinamide. *Arch Dermatol*. 1986;122:670-674.
- Altman DA, Fivenson DP, Lee MW. Minocycline hyperpigmentation as a model for in situ phagocytosis by factor XIIIa positive dermal dendrocytes. *J Cutan Pathol*. 1992;19:340-345.
- Dukes MNG. *Meyler's Side Effects of Drugs*. 9th ed. Princeton, NJ: Excerpta Medica; 1980.
- Cunha BA, Comer JB, Jonas M. The tetracyclines. *Med Clin North Am*. 1982;66:293-302.
- Zackheim HS, Vasily DB, Westphal MC, Hastings CW. Reactions to nicotinamide. *J Am Acad Dermatol*. 1981;6:736-737.
- Axelrod L. Glucocorticoid therapy. *Medicine*. 1976;55:39-65.
- Wilson GL, Patton NJ, McCord JM, Mullins DW, Mossman BT. Mechanisms of streptozotocin- and alloxan-induced damage in rat B cells. *Diabetologia*. 1984;27:587-591.
- Shinmoyama M, Kawai M, Hoshi Y, Veda I. Nicotinamide inhibition of 3', 5' cyclic AMP phosphodiesterase in vitro. *Biochem Biophys Res Commun*. 1972;49:1137-1141.
- Scherer B, Kromer W. Influence of niacinamide administration on brain 5-HT and a possible mode of action. *Life Sci*. 1972;11:189-195.
- Hoffer A. LSD-induced psychosis and vitamin B₃. *Am J Psychiatry*. 1972;128:1155.
- Cohen BM. A niacinamide-theophylline compound (RC-C-144), human and blood level studies. *J Asthma Res*. 1966;4:75-79.
- Cohen BM. A niacinamide-theophylline compound (RC-C-144), clinical and spirometric effects. *J Asthma Res*. 1966;4:81-87.
- Bekier E, Maslinski C. Antihistaminic action of nicotinamide. *Agents Action*. 1974;4:196.
- Wyczolkowska J, Maslinski C. Inhibition by nicotinamide of an homologous PCA reaction and antigen-induced histamine release from rat peritoneal cells. *Int Arch Allergy Appl Immunol*. 1975;49:285-292.
- Bekier E, Wyczolkowska J, Szych H, Maslinski C. The inhibitory effect of nicotinamide on asthma-like symptoms and eosinophilia in guinea pigs, anaphylactic mast cell degranulation in mice, and histamine release from rat peritoneal mast cells by compound 48/80. *Int Arch Allergy Appl Immunol*. 1974;47:737-748.
- Katayama I, Doi T, Nishioka K. High histamine level in the blister fluid of bullous pemphigoid. *Arch Dermatol Res*. 1984;276:126-127.
- Forsgren A, Schmeling D, Ouie PF. Effect of tetracycline on the phagocytic function of human leukocytes. *J Infect Dis*. 1974;130:412-415.
- Majeski JA, Alexander JW. Evaluation of tetracycline in the neutrophil chemotactic response. *J Lab Clin Med*. 1977;90:259-265.
- Esterly NB, Furey NL, Flanagan LE. The effect of antimicrobial agents on leukocyte chemotaxis. *J Invest Dermatol*. 1978;70:51-55.
- Esterly NB, Koransky JS, Furey NL, Trevisan M. Neutrophil chemotaxis in patients with acne receiving oral tetracycline therapy. *Arch Dermatol*. 1984;120:1308-1313.
- Burger DR, Vandenbark AA, Daves D, Anderson WA, Vetto RM, Finke P. Nicotinamide: suppression of lymphocytic transformation with a component identified in human transfer factor. *J Immunol*. 1976;117:797-801.
- Thong YH, Ferrante A. Inhibition of mitogen induced human lymphocyte proliferative responses to tetracycline analogues. *Clin Exp Immunol*. 1979;35:443-446.
- Banck G, Forsgren A. Antibiotics and suppression of lymphocyte function in vitro. *Antimicrob Agents Chemother*. 1979;16:554-560.
- Humbert P, Renaud A, Millet J, et al. Evaluation of the effect of heparin and tetracycline on the cohesion of the dermal-epidermal junction. *Acta Derm Venereol*. 1989;69:434-436.