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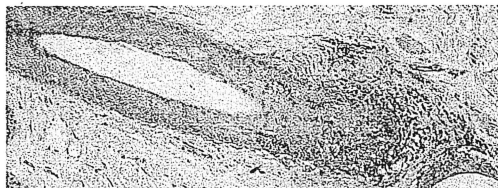
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Perifollicular lymphocytic reaction. See page 770.

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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

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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

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