

Immunodeficiency and other clinical immunology

Double-blind placebo-controlled study of the efficacy of oral terfenadine in the treatment of chronic fatigue syndrome

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Background: There is no established treatment for chronic fatigue syndrome (CFS), an illness characterized by disabling fatigue exacerbated by physical activity. A variety of immunologic abnormalities have been reported, including a high incidence of atopy and hypoergy or anergy.

Objective: Because of anecdotal reports and uncontrolled trials showing antihistamine efficacy in CFS, we evaluated the clinical efficacy of the antihistamine terfenadine (60 mg twice daily) in a placebo-controlled study.

Methods: Thirty patients with CFS were enrolled in a 2-month, double-blind, placebo-controlled trial of terfenadine. Participants underwent a battery of both immediate- and delayed-type hypersensitivity skin tests and completed a self-assessment questionnaire used to measure severity of symptoms, physical and social functioning, health perceptions, and mental health before each of six biweekly visits.

Results: Twenty-eight patients completed the trial. History of atopy and positive immediate skin test results were prevalent, 73% and 53%, respectively. No evidence for hypoergy or anergy after delayed-type hypersensitivity skin testing was found. No therapeutic benefit from terfenadine could be detected in terms of symptom amelioration, improved physical or social functioning, health perceptions, or mental health. A high incidence of atopy in patients with CFS was confirmed.

Conclusion: Although this trial involved a small number of patients, the results suggest that terfenadine is unlikely to be of clinical benefit in treating CFS symptoms. (*J ALLERGY CLIN IMMUNOL* 1996;97:119-26.)

Key words: Chronic fatigue syndrome, atopy, antihistamines, terfenadine, immediate skin tests, delayed skin tests

Chronic fatigue syndrome (CFS) is a syndrome characterized by disabling fatigue exacerbated by minimal physical activity and a constellation of other nonspecific symptoms or signs, including

Abbreviation used

CFS: Chronic fatigue syndrome

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complaints of cognitive dysfunction such as forgetfulness, confusion, difficulty thinking, and inability to concentrate.¹ CFS usually results in impaired functioning in social and workplace settings.² CFS predominantly affects young adult and middle-aged women and frequently follows an acute viral-like illness.³ A variety of immunologic abnormalities has been reported, including a high incidence of atopy⁴ and hypoergy or anergy.⁵ The most common premorbid condition in patients with CFS

TABLE I. Demographic features of study participants with CFS

	Placebo (n = 15)	Terfenadine (n = 15)	Total (n = 30)
Female	13	10	23 (77%)
Age in years ±(SD)	35.2 ± 11.7	37.3 ± 11.4	36.2 ± 11.4
Atopic history	13 (86.7%)	9 (60.0%)	22 (73.3%)
Immediate skin test reactivity	10 (66.7%)	6 (40.0%)	16 (53.3%)

All comparisons were not significant.

is atopy, the prevalence ranging from 43% to 65%.^{4, 6, 7} Although the pathogenesis of CFS is unknown, there is growing evidence to implicate central nervous system involvement including cytokine-induced immunologic changes, perfusion abnormalities, pituitary-adrenal axis derangements, and neurotransmitter dysfunction.⁸⁻¹⁴ Unfortunately there is no established treatment for CFS, although several symptomatic therapies have been advocated.¹⁵

Because of the theorized involvement of immunologic abnormalities in the pathogenesis of CFS, a variety of immunomodulatory agents have been tried. Two placebo-controlled, double-blind studies of intravenous gammaglobulin showed conflicting results.^{16, 17} A preliminary study of a double-stranded RNA "ampligen," an immunomodulatory compound, suggested benefit.¹⁹ Prednisone, at 15 mg every day over a 2-week period, has not been shown to be effective in fibrositis, an idiopathic disorder thought to be closely related to CFS.¹⁸ A placebo-controlled trial of low-dose prednisone is currently underway at the National Institutes of Health.

This study was stimulated by the association of allergy with CFS⁴ and a report of Jones²⁰ on a 70% success rate in an uncontrolled trial of doxepin 10 to 50 mg/hr in patients with CFS. Doxepin, a tricyclic antidepressant, is known to be a potent blocker of histamine H₁ and H₂ receptors.²¹ We were also influenced by the anecdotal reports by many of the patients with CFS in our research program that the antihistamine, terfenadine, which most were using to treat their concomitant allergies, improved their CFS symptoms. We decided to test the effect of an antihistamine on CFS symptoms and functional impairment associated with CFS in a controlled trial and selected terfenadine

because of its absence of central nervous system side effects.

METHODS

Patients

Thirty patients with CFS 18 years of age or older were recruited from the registry of the Minnesota Regional CFS Research Program established at Hennepin County Medical Center, Minneapolis, in 1988.² Study volunteers were selected from patients who responded to a letter sent to all members of the registry. All patients lived in Minnesota or neighboring communities of Wisconsin or Iowa, and most had been referred by infectious disease specialists or rheumatologists. The study was conducted in the Drug Evaluation Unit, Hennepin County Medical Center. A diagnosis of CFS was established after thorough medical, psychometric, and psychiatric evaluations did not establish another explanation for chronic fatigue and after the other criteria for a case definition of CFS were met.¹ The psychometric assessment consisted of three standardized questionnaires: Beck Depression Inventory,²³ Zung Self-Rating Anxiety Scale,²⁴ and Symptom Checklist-90.²⁵ No attempt was made to preselect patients with atopic disease.

Study design

After giving informed consent and completing a 2-week antihistamine-free period, patients with CFS were randomly assigned to receive either terfenadine 60 mg twice daily or a placebo. The study design called for 30 participants (15 per treatment group) to give a sample size sufficient to detect a 20% difference between the two groups at the two-tailed $p = 0.05$ level with a power of 80%. The study was approved by Hennepin County Medical Center's Institutional Review Board.

Treatment

Patients received either terfenadine or a placebo on a b.i.d. schedule over 2 months of the double-blind period. During the course of the study, patients were permitted to take oral contraceptives, antibiotics, vitamins, aspirin, nonsteroidal antiinflammatory drugs, β -adrenergic agonists, and other medications as prescribed by their primary physician but were not permitted to take antihistamines; decongestants; tricyclic antidepressants; or ocular, nasal, or bronchial antiinflammatory agents.

Self assessments

Each participant was asked to complete a self-assessment form within 48 hours of the baseline and five treatment visits. The form contained both generic and disease-specific measures. Patients were first asked to rate the severity of their symptoms during the previous month on a 4-point scale, ranging from none to severe. Patients also completed a modified version of the previously described Medical Outcome Study Short Form^{26, 27} and reported on physical and social functioning, health

perceptions, and mental health during the previous month. Scales for each of these dimensions were developed on the basis of face validity of the question; scale ranges included 0 (worst possible health) to 100 (best health). Results are reported as mean $\pm$ SD.

Immunologic studies

Skin puncture and intradermal skin tests with a number of common inhaled allergens were performed, including the mites *Dermatophagoides farinae* and *D. pteronyssinus*, cat, dog, cockroach, *Alternaria tenuis*, *Cladosporium cladosporioides*, birch, elm, maple, oak, June grass, timothy, short ragweed, lamb's-quarters (Hollister-Stier, Spokane, Wash.).²⁸ Codeine sulfate (20 mg/ml) and histamine phosphate (5 mg/ml) (Allermed Labs, San Diego, Calif.) served as positive puncture controls, and phosphate-buffered saline as a negative control. All testing solutions contained 0.1% phenol. Skin reactions were read at 15-minute intervals. Puncture testing was done with Dermapik (Greer Labs, Lenoir, N.C.). Intradermal tests were done by injecting 0.02 ml through a no. 27 tuberculin syringe. The wheal and erythema were outlined with a fine-tip pen. The longest diameters connecting the inner margins of the pen outlines were measured, and at the midpoint of each line, a perpendicular diameter (orthogonal diameter) was drawn. Results of puncture and intradermal skin tests were considered positive if the net mean wheal or erythema diameter (mean wheal or erythema diameter = largest + midpoint orthogonal diameter $\div$ 2) was $\geq$ 3 mm larger than the phosphate-buffered saline control.²⁹ All patients did not take antihistamines and tricyclic antidepressants for at least 30 days before testing.

Delayed-type hypersensitivity skin testing was done with a battery of five standardized antigens: tetanus (neat) (Sclavo Labs, Wayne, N.J.), mumps (neat) (Connaught, Swiftwater, Penn.), *Candida albicans* (1:100) (Miles Labs, West Haven, Conn.), *Trichophyton mentagrophytes* (1:1000) (Greer Labs, Lenoir, N.C.), tuberculin (5 T.U.) (Connaught). Intradermal tests were done by injecting 0.1 ml through a no. 27 tuberculin syringe. The tests were read 48 hours later.³⁰ Results of intradermal tests were considered positive if the net mean induration diameter (mean induration diameters $\div$ 2 was $\geq$ 5 mm).

Statistics

Descriptive statistics, including means and standard deviations or percentages, were calculated as appropriate. To compare the differences in treatments over time, a mixed-model analysis of variance was used. This model is of a mixed design; the primary interest is the interaction between groups (terfenadine vs placebo) and within groups (predrug to postdrug change) components. This design was used to assess functional status outcomes. Statistical significance was assumed if *p* was less than 0.05. All analyses were completed with SPSS software (SPSS Version 5.0.; SPSS, Inc., Chicago, Ill.).

TABLE II. Prevalence of positive immediate skin test reactivity to selected allergens in 30 study patients with CFS

Allergen	<i>n</i>	% Positive*
One or more positive	16	53.3
Total indoor allergens	14	46.7
House dust	13	43.3
<i>D. pteronyssinus</i>	11	36.7
<i>D. farinae</i>	10	33.3
Cat	9	30.0
Dog	7	23.3
Cockroach	7	23.3
Total outdoor allergens	12	40.0
June grass	10	33.3
Timothy	9	30.0
Ragweed	10	33.3
Lamb's-quarters	10	33.3
Birch	8	26.7
Oak	6	20.0
Maple	5	16.7
Elm	4	13.3
<i>Alternaria tenuis</i>	4	13.3
<i>Cladosporium cladosporioides</i>	3	10.0

*Net mean wheal or erythema diameter $\geq$ 3 mm larger than phosphate buffered saline control.

RESULTS

Demographics

The demographic features of the 30 study participants are shown in Table I. Two patients (one receiving treatment, one receiving placebo) were excluded from the evaluation of treatment efficacy because they withdrew from the study because of their perception of no improvement. Twenty-three of 30 (77%) were women. The 30 subjects ranged in age from 19 to 74 years (mean age, 36.2 years). There were no significant differences between the treatment and placebo groups with regard to age, sex, history of atopy, or immediate skin test reactivity.

Allergy

Twenty-two (73%) of the study patients had histories suggestive of atopy (seasonal and/or perennial rhinitis, bronchial asthma, urticaria, atopic dermatitis, food, drug allergy). All study patients responded appropriately to both the histamine and codeine positive skin test controls. Table II shows the distribution of immediate skin test reactivity in the patients with CFS. Sixteen (53.3%) of the study

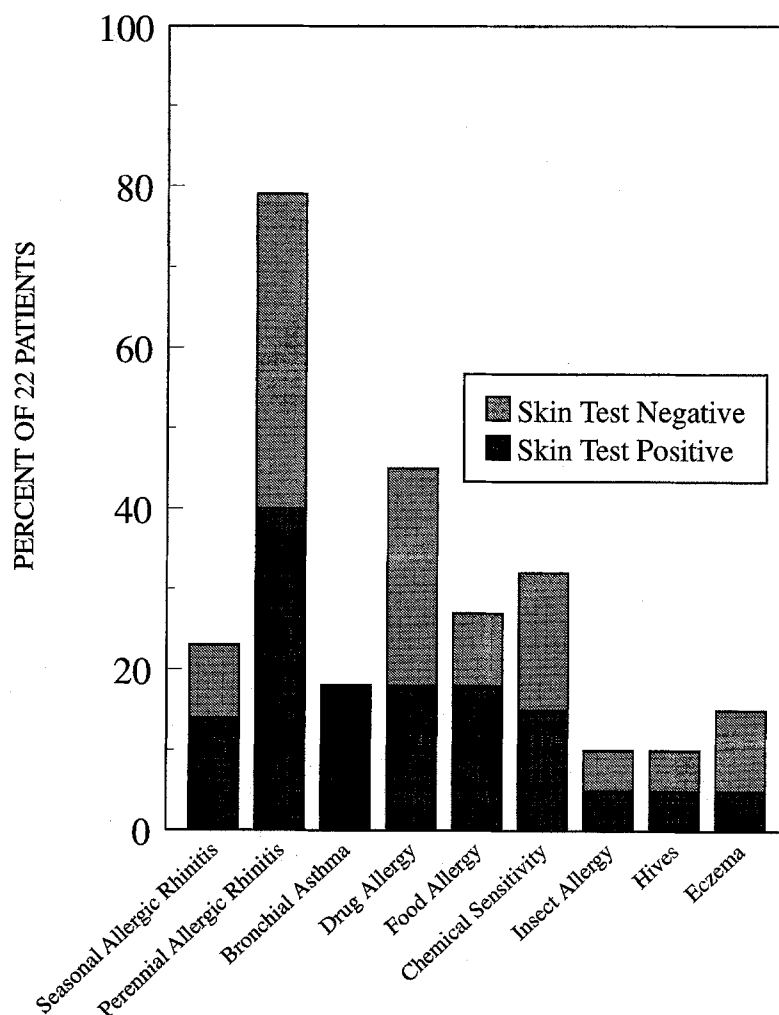


FIG. 1. Histogram showing skin test reactivity in patients with CFS and histories of allergic and related diseases.

TABLE III. Delayed-type hypersensitivity skin test reactivity in 30 patients with CFS

Antigen	Concentration	n	% Positive*
Tetanus	Neat	29	97
Mumps	Neat	25	83
<i>Candida albicans</i>	1:100	11	37
<i>Trichophyton mentagrophytes</i>	1:1000	3	10
Tuberculin	5 T.U.	1	3
One or more above	—	30	100

*Net mean induration diameter ≥ 5 mm.

patients reacted to one or more allergens. Fourteen (46.7%) reacted to indoor allergens and 12 (40.0%) to outdoor allergens. In the group with positive skin test results, reactions to defined aller-

gens, *D. pteronyssinus* and *D. farinae* (68.75% and 62.50%, respectively), were most frequently observed. No significant differences in skin test reactivity were seen between the treatment and placebo groups.

Fig. 1 shows a histogram of skin test reactivity in patients with CFS and histories of allergic and related diseases. The sensitivity and specificity between patient history and skin test reactivity were poor. Of 16 patients with positive skin test results, 11 (69%) had histories of allergies to inhalants compared with 14 patients with negative skin test results of whom 11 (79%) had positive histories. Positive skin tests were found in 11 of 22 (50%) with atopic histories and in 5 of 8 (63%) with negative histories.

Taken together, these data demonstrate that although there were no significant differences be-

TABLE IV. Effect of treatment on functional status and well-being in 30 patients with CFS

Health Measures*	Treatment group			
	Placebo (n = 14)		Terfenadine (n = 14)	
	Score		Score	
	Visit 1	Visit 5	Visit 1	Visit 5
Physical functioning	64.53 ± 17.20	69.66 ± 18.09	60.32 ± 14.27	63.10 ± 17.52
Social functioning	40.38 ± 17.54	45.83 ± 22.26	36.61 ± 11.23	34.52 ± 11.49
Health perceptions	37.44 ± 14.54	29.74 ± 12.36	33.81 ± 12.67	30.95 ± 13.49
Mental health	77.18 ± 15.74	74.62 ± 15.31	64.29 ± 14.11	63.89 ± 21.36

*A modified Medical Outcome Study Short Form was used to assess functional status, health perceptions, and mental health. On a calibrated scale, the worst possible health is equal to 0, and the best possible health is equal to 100. Values are mean ± SD. All comparisons were not significant. Visit 1 (start of treatment); visit 5 (end of treatment).

TABLE V. Effect of treatment on symptoms in 30 patients with CFS

Symptoms	Treatment group							
	Placebo (n = 14)				Terfenadine (n = 14)			
	Visit 1		Visit 5		Visit 1		Visit 5	
	No.	%	No.	%	No.	%	No.	%
Fatigue	12	86	10	71	10	71	12	86
Postexertional fatigue (prolonged)	12	86	8	57	11	79	12	86
Muscle weakness	6	43	7	50	7	50	8	57
Myalgias	7	50	6	43	8	57	9	64
Sleep disturbance	6	43	5	36	3	21	3	21
Headaches	5	36	3	21	10	71	9	64
Arthralgias	6	43	5	36	6	43	8	57

*Symptoms reported by 28 evaluable patients as moderate or severe for the 2 weeks before visit 1 (start of treatment) and for the 2 weeks before visit 5 (end of treatment). All comparisons were not significant.

tween treatment groups, history of atopy and positive immediate skin test results are highly prevalent in patients with CFS, 73% and 53%, respectively; 90% had positive histories and/or positive immediate skin test results.

Delayed hypersensitivity

All patients had positive delayed skin test responses to at least one antigen. There was a mean of 2.3 positive skin test responses per patient (range 1 to 4). There were no significant differences observed in delayed skin test reactivity between the treatment and placebo groups. The mean induration diameter was 11.7 mm. The percent positive for each antigen is shown in Table III.

Effect of treatment

Baseline symptoms for the 2 weeks before the treatment (visit 1) for the self-assessment questions measuring physical functioning, social functioning, health perceptions, and mental health in 28 evaluable patients are shown in Table IV. No significant differences between treatment and placebo groups were observed.

No differential changes during 8 weeks were observed for any of the symptoms (Table V) or measures of physical functioning, social functioning, health perceptions, and mental health between the treatment and placebo groups (Table IV) or in the subgroups with a history of atopy or with positive immediate skin test results (not shown).

No significant placebo effect of treatment was observed in the study patients.

DISCUSSION

The mean age (36 years) and female-to-male ratio (3:3) of the patients with CFS in this trial were similar to that of our entire CFS registry, 38 years and 3.7, respectively, and to that described in the literature.^{1, 31} The 90% with positive histories of allergy and/or positive immediate skin tests is also similar to the 83% observed in a CFS study group reported by Straus et al.⁴ The immediate cutaneous reactivity rate to selected allergens of 16 of 30 (53.3%) is similar to the 50% rate observed by Straus et al.⁴ and much higher than the 20% to 30% observed in unselected Caucasian adults of similar age reported in the literature.^{32, 33} Our finding of poor correlation between history of allergy and positive skin test results differs from that of Straus et al.⁴ and may be explained by the smaller number of skin tests in this study or by a higher percent of patients in our study group with nonallergic rhinoconjunctivitis or both. (Straus et al. used a larger number of skin test allergens, including 38 foods and 25 inhalants, compared with our group of 16 inhalants alone.)

The relationship between the highly prevalent objective findings of atopy and CFS is intriguing. Straus et al.⁴ have suggested that the heightened reactivity of patients to allergens that results in atopic disease may also result in CFS because of heightened response to the putative infection(s) causing CFS. Support for this hypothesis comes from the observation that antibody titers to Epstein-Barr virus antigens were significantly higher in atopic children than in control subjects.^{34, 35}

The results of the delayed skin testing are in agreement with those of Straus, using intradermal tests (personal communication), and are different from those reported by Lloyd et al., using the Multitest technique (Multitest CMI, Mérieux, France), who observed reduced delayed skin test reactivity in 19 of 57 (33%) patients and negative skin test results in 31 of 57 patients (54%).⁵ The patients with CFS we studied appear to be neither hypoergic nor anergic. We believe the differences are probably due to the test methodology. Multitest applies antigen epicutaneously rather than intradermally.³⁶ Davis et al.³⁷ found a significant decrease in the percent of positive delayed *Candida albicans* and tetanus toxoid skin tests with Multitest when both Multitest and intradermal

tests were applied simultaneously in HIV-seropositive patients.³⁷

The results of this double-blind, placebo-controlled study suggest that terfenadine is unlikely to be of clinical value in the treatment of patients with CFS symptoms themselves. When patients with histories of atopy or with positive immediate skin test results were looked at separately, the treatment group fared no better. The 30 patients with CFS enrolled in this study did not appear to differ significantly from those described in the literature.^{1, 31} However, CFS may be heterogeneous enough so that a different geographic population could react otherwise. It is of interest that no placebo treatment effect was observed in this study. Possible explanations include inability to detect small improvements because of sample size or the relentlessness of the chronic fatigue—the hallmark of the syndrome. According to the current data and sample size, we would have needed a minimal difference of 50% between groups from visit 1 to visit 5 to achieve a *p* value of less than 0.05 and a power of 80%. It was not possible to control for drugs other than those that were excluded: antihistamines; decongestants; tricyclic antidepressants; and ocular, nasal, or bronchial antiinflammatory agents. Other drugs used may have accounted for additional variability, which could dilute potential study treatment effects. The patients with CFS in our research registry have shown significantly impaired function compared with those with other chronic illnesses,^{26, 27} and in one group previously studied, 43.3% were no longer able to work.¹⁷ Terfenadine is of clinical benefit in treating symptoms of allergic rhinoconjunctivitis,³⁸ and the anecdotal improvement reported by our patients with CFS, in retrospect, could have been due to amelioration of these symptoms rather than the fatigue. Physicians might still expect an amelioration of allergic symptoms in this population, as they would in the general population.

Expanded research is needed to discover the cause (or causes) of CFS and to understand its connection with atopy. Properly controlled therapeutic trials are also needed to find effective treatments and to comprehensively assess promising treatments reported anecdotally.

In addition to expanded research on CFS to discover the cause(s), pathogenesis, and connection with atopy of this disorder, the results of this study underscore the need for additional properly controlled therapeutic trials to find an effective treatment for this disabling illness.

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