

Treatment Of Atopic Dermatitis With Antihistamines: Lessons From A Single-Patient, Randomized Clinical Trial

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Abstract: *Background:* Single-patient randomized clinical trials (RCTs) can be utilized to maintain methodologic precision in the analysis of treatment effect in individual patients. We describe the results of a single-patient RCT in a patient with atopic dermatitis and review practical considerations regarding the use of antihistamines.

Methods: Using double-blind, crossover techniques, the patient was randomly allocated to four 2-week treatment periods with the following regimens: chlorpheniramine, 8 mg twice daily; chlorpheniramine, 12 mg twice daily; terfenadine, 120 mg twice daily; and placebo (phase 1). The drug that produced superior results from phase 1 (chlorpheniramine, 8 mg) was subsequently compared with astemizole, 10 mg/d, during phase 2, consisting of four 4-week, double-blind, crossover trial periods with random allocation of study drugs. Daily symptom scores, as well as end of treatment period summary impressions by patient and investigator, were analyzed.

Results: In both phases, chlorpheniramine produced the most noticeable positive therapeutic effect on the patient's mild but most disturbing symptoms (pruritus and eye irritation) associated with atopic dermatitis. Drowsiness was reported with chlorpheniramine. Tolerance to this side effect, however, developed quickly.

Conclusions: A single-patient RCT with different antihistamines in a patient with chronic atopic dermatitis was a useful tool in achieving a favorable balance among efficacy, toxicity, and cost of therapy. (J Am Board Fam Pract 1992; 5:137-42.)

Atopic dermatitis is a genetically conferred hyperirritable skin disease manifested by variable degrees of xerosis, lichenification, pruritus, and white dermographism. Exacerbations occur throughout life, often resulting from physical or emotional stress.¹ Systemic antihistamines are commonly prescribed for pruritic symptoms.¹ Traditional antihistamines (e.g., diphenhydramine, chlorpheniramine, and hydroxyzine), although potentially effective at relieving pruritus, often produce bothersome sedative effects.² Newer, more selective antihistamines (e.g., terfenadine and astemizole) cause less sedation and interference with cholinergic muscarinic receptors,¹ in part because they are less lipophilic

and subsequently less able to penetrate the blood-brain barrier.³ The antipruritic efficacy of these newer agents has not been proved superior to traditional antihistamines.⁴ Furthermore, the newer agents are significantly more expensive.⁵

Before prescribing a daily course of these medications for atopic dermatitis, a prudent physician may want to know the comparative efficacy for these drugs, including potential for adverse effects. Randomized clinical trials (RCTs) are usually required to establish valid evidence of drug efficacy. In some clinical situations, however, treatment decisions cannot be guided by such trials. One obvious example is the treatment of a disease in which RCTs have not been conducted. More commonly, even when an RCT has shown that a treatment is effective, the result of that RCT may not apply to the individual patient. If the patient does not meet the eligibility criteria, generalization may be unwarranted. Regardless of the overall trial results, some patients appear to benefit from the otherwise effective therapy and some do not.⁶⁻⁸

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To maintain the methodological precision provided by RCTs and to avoid the disadvantages of large-sample multicenter studies, methods for examination of the treatment effect in individual patients have been developed.⁶⁻⁸ Single-patient RCTs are especially useful in assessing the efficacy of treatment for chronic conditions. We report the results of a single-patient RCT and review practical considerations regarding the use of antihistamines in such a chronic disease as atopic dermatitis.

Case Report

A 32-year-old man had a lifelong complaint of classic atopic dermatitis. His main manifestations were diffuse pruritus, a dry lichenified dermatitis in the distribution of his hands and flexure creases of elbows and knees, and red swollen eyelids. Nondrug modalities and moderate strength topical corticosteroids effectively controlled the rash; however, pruritus and eye complaints persisted. He had tried a variety of antihistamines without significant relief. Diphenhydramine caused excessive sedation. Hydroxyzine caused a severe dysphoric reaction. He was taking terfenadine, 60 mg twice daily, with minimal relief.

Methods

Single-Patient Randomized Clinical Trial

During an explanatory interview with the patient, outcome variables were developed consistent with his most significant complaints and possible antihistamine adverse effects. These outcomes were scored by the patient using Likert scales and re-

Daily Symptoms Log

RANDOMIZED TRIAL IN INDIVIDUAL PATIENTS:
Antihistamines for Atopic Dermatitis

Date: _____ Time of day: _____ Treatment period: _____

Note:
Regarding the current treatment for your condition, circle the number that best describes how you have felt during the last 24 hours.

1. Rate the severity of itching that you experienced today.	1	2	3	4	5	6	7
	Mild			Moderate			Severe
2. Rate the severity of your eye symptoms (redness, swelling) that you experienced today.	1	2	3	4	5	6	7
	Mild			Moderate			Severe
3. Rate the severity of drowsiness you felt today.	1	2	3	4	5	6	7
	Mild			Moderate			Severe
4. How many times did you apply triamcinolone cream today?	1	2	3	4	5	6	7
5. Comments (Describe any other symptoms/circumstances related to your condition not discussed above in the space below:							

Figure 1. Patient-directed daily symptoms log for single-patient randomized clinical trial.

Data Collection Form

End of Treatment Record

RANDOMIZED TRIAL IN INDIVIDUAL PATIENTS:
Antihistamines for Atopic Dermatitis

Date: _____ Time of day: _____ Treatment period: _____

Note:
Answer the following questions regarding the treatment period just completed.

1. Was the medication effective? YES () NO ()
2. Did you experience any side effects? YES () NO ()
If YES, please explain: _____
3. Do you feel that you received active or placebo medication during this treatment period? ACTIVE ()
PLACEBO ()
4. How many pills are left in the bottle? _____
5. List any other medications that you took during this treatment period, including over-the-counter medications. _____

6. Comments: _____

Figure 2. Patient-directed end of treatment record for single-patient randomized clinical trial.

corded in a daily symptoms log (Figure 1). After giving consent, the patient underwent an initial trial (phase 1) that included four 2-week periods with the patient receiving the following regimens: (1) chlorpheniramine, 8 mg twice daily; (2) chlorpheniramine, 12 mg twice daily; (3) terfenadine, 120 mg twice daily; and (4) placebo, twice daily. The order of treatment was determined by random allocation. The patient and investigators were blinded to the treatment sequence. A pharmacist prepared all study medications to appear identical as pink capsules and maintained the drug code. The drug that produced superior results from phase 1 was subsequently compared with astemizole 10 mg/d during a second trial (phase 2) consisting of four 4-week double-blind trial periods. In addition to the daily log of symptoms, during both phases, the patient also completed a report summarizing his impressions about the trial period just completed (Figure 2).

The severity of symptoms and adverse effects of study medications measured on Likert scales were analyzed using Kruskal-Wallis one-way analysis of variance by ranks set up on CRUNCH, a statistical package for personal computers.⁹ Experience with the 7-point Likert scale in single-patient RCTs indicates that an average difference of 0.5 points shows a clinically significant difference (personal communication with Dr. E.B. Larson and with G. Guyatt, McMaster University, Ontario, Canada, 1989).

Table 1. Results of Phase 1 of Single-Patient Randomized Clinical Trial.

Symptom	Phase 1 Mean Scores				<i>P</i>
	Placebo	Terfenadine*	Chlorpheniramine*		
		120 mg	8 mg	12 mg	
Severity of itching†	1.7	0.7	0.7	1.4	0.06
Severity of eye symptoms*	2.0	2.6	3.0	1.5	0.1
Severity of drowsiness*	2.6	1.9	2.7	3.1	0.3
Topical steroid use‡	0.8	0.9	0.3	0.3	0.06
Was medicine effective?	No	No	Yes	Yes	
Compliance (%)	100	100	100	100	
Medication guess	Placebo	Placebo	Active	Active	

*Drugs were administered twice daily.

†Likert scales: 0 = none, 1 = mild, 7 = severe.

‡Number of applications per day.

Results

The results of phase 1 are shown in Table 1. During this phase, the mean severity of symptoms for all complaints never exceeded moderate, although the scores ranged from mild to severe. Itching seemed to be more severe during treatment with placebo and chlorpheniramine, 12 mg. Severity of eye symptoms (redness and swelling) was fairly consistent across all drug regimens, with chlorpheniramine, 12 mg, yielding the lowest mean score. Chlorpheniramine was also associated with less topical corticosteroid use. With regard to pruritus, the patient thought that only chlorpheniramine (either dose) was effective. There were no identifiable trends in related adverse effects, although the patient was able to guess correctly the active drug and placebo periods. Both the patient and the clinician agreed that during this treatment phase, chlorpheniramine produced the most noticeable positive therapeutic effect. Terfenadine, even at double the recommended dosage,

was not consistently effective based on symptom scores and was not judged effective by the patient.

Phase 2 results (chlorpheniramine, 8 mg twice daily, versus astemizole, 10 mg once daily) are shown in Table 2. The mean severity of symptoms for all complaints (itching, eyelid itching, and swelling) never exceeded moderate. There was little difference between the two drugs when judged by their effect on itching, but the severity of the eye complaints was much less during treatment with chlorpheniramine. There was a significant amount of drowsiness accompanying the relief of symptoms produced by chlorpheniramine. As seen in Figure 3, however, the severity of drowsiness decreased from severe to mild the longer the patient remained on chlorpheniramine.

Based on the results of both phases, chlorpheniramine was recommended for symptomatic relief except when sedation might be a liability. As of 15 months of follow-up care, the patient had

Table 2. Results of Phase 2 of Single-Patient Randomized Clinical Trial.

Symptom	Phase 2 Mean Scores		P
	Astemizole*	Chlorpheniramine*	
	10 mg	8 mg	
Severity of itching†	3.3	3.0	0.8
Severity of eye symptoms*	4.0	2.5	0.2
Severity of drowsiness*	1.4	4.6	0.01
Topical steroid use‡	5.0	5.6	0.7
Was medicine effective?	Yes	Yes	
Compliance (%)	>95	>95	
Medication guess	Unknown	Active	

*Drugs were administered twice daily (astemizole, 10 mg/d; chlorpheniramine, 16 mg/d).

†Likert scales: 0 = none, 1 = mild, 7 = severe.

‡Number of applications per day.

Drowsiness and Chlorpheniramine Therapy

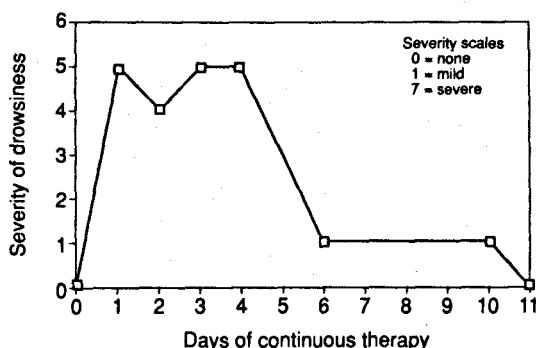


Figure 3. Severity of self-reported drowsiness (Likert scale) during chlorpheniramine therapy.

been following this treatment with good relief of symptoms.

Discussion

Single-patient RCTs can be useful to evaluate drug therapy when doubt (on the part of either the patient or the physician) exists about the efficacy of the treatment. Doubt can occur when a physician is uncertain of the risk-to-benefit ratio of a new treatment as a result of limited literature and available experience or when a patient with a chronic disease is doing poorly on a particular medication. Additionally, for patients with rare or unusual conditions, the single-patient RCT could not only benefit the patient but also add to knowledge about management of unusual conditions.

Single-patient trials are usually of most value for patients with chronic problems requiring long-term treatment. Single-patient trials of short-term treatments are less likely to have value for an individual patient unless the patient will require the short-term treatment repeatedly. The ideal treatment for single-patient RCTs has a rapid onset and offset. Thus, assessment of outcomes can be accomplished starting relatively early in the trial, and there is little or no carry-over between treatment periods. Single-patient trials are less likely to be useful for curative treatments and for long-acting treatments.

A disease with characteristics similar to atopic dermatitis lends itself to this type of evaluation. The literature on antihistamines for pruritus in atopic dermatitis does not clearly favor any one particular agent for treatment.² Further, there are substantial differences in costs and claims for side effects for the different antihistamines.⁴ Since the

marketing of terfenadine with the accompanying "no sedation" claims, the drug has become one of the most popular antihistamines prescribed in this country.¹⁰ Are the newer antihistamines worth the cost? Do they really offer significant advantage to justify a greater than 10-fold increase in cost? The results of the single-patient RCT in this patient indicate that the less expensive chlorpheniramine might be the better agent. This trial also reinforces the conventional wisdom that tolerance to the sedative side effects of traditional antihistamines develops quickly.¹⁰ Terfenadine and the other nonsedating antihistamines could have advantages for intermittent dosing when sedation is more likely to be problem. Combination therapy using nonsedating antihistamines during the day and traditional antihistamines at night could be the most economical regimen.

This study was not difficult to perform and, with the assistance of a pharmacist, could be duplicated. Although it is not appropriate to generalize from a single-patient RCT about treatment effects for other patients with the same condition, there are other general conclusions: (1) for conditions that require on-going daily administration of antihistamines, a single-patient RCT can be a useful therapeutic decision-making tool, particularly when patients do not get substantial benefit from the least expensive regimen; (2) single-patient RCTs can help clarify issues of efficacy, toxicity, and cost for a variety of comparative treatments; and (3) single-patient RCTs allow patients a greater sense of participation in the management of their disease. Further, trials can be individualized to patient-specific complaints. Daily log entries can be made by allowing patients to use their own words to emphasize their most significant symptoms or side effects.

A single-patient RCT with different antihistamines in a patient with chronic atopic dermatitis was a useful tool in choosing an effective and affordable therapeutic regimen. Further studies of this type can be done by primary care physicians seeking assurance of a favorable balance among efficacy, toxicity, and cost of therapy for patients with chronic medical problems.

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