Clinical trials of allergen avoidance in established asthma

In its review of asthma management guidelines in 1997, the National Asthma Education and Prevention Program expert panel expressed a belief that available data justified a recommendation that all patients with persistent asthma be evaluated for allergy and that allergen avoidance be included in their management when appropriate.[1] The panel had a surprisingly small number of published reports to consider; in contrast, there were hundreds of randomized, controlled clinical trials that support the use of pharmacologic treatment. In fact, a meta-analysis published just a year later found only 27 studies and concluded that the evidence suggested that environmental control measures had no effect on established asthma.[2] These conclusions have been challenged because the meta-analysis included a number of trials with ineffective mite avoidance and used criteria that excluded 2 trials with a striking effect on both exposure and disease activity.[3] The early clinical trials were conducted before we knew enough about the basic elements of mite allergen avoidance. We now know that bedding is the most important route of exposure; installation of mattress and pillow cases, together with frequent laundering of the bedding and decreased humidity, can reduce exposure sufficiently to decrease asthma morbidity.[4-6] We also know that acaracides are minimally effective in reducing house dust mite allergen in carpeting[5,6]; interventions that included acaracide treatment of carpeting have not affected the outcomes in clinical trials.[7,8] At this point, we have less understanding of how to reduce cockroach, cat, dog, and mold allergen exposure, and the impression remains that allergen avoidance in established asthma has a minor effect in comparison with pharmacotherapy.

The article by Carter et al[9] in this month's issue of the Journal represents an important step. Not only is it one of the first clinical trials to deal with cockroach allergen avoidance; it is the first to examine the effect of combined intervention for dust mite and cockroach in an inner-city population exposed and sensitized to both allergens. Although the authors concluded that the measures tested (mattress and pillow encasings, pesticide bait stations, and cleaning education for participating families) were effective, the effects were small and were only seen in a subgroup with successful allergen exposure reduction. The most striking outcome differences were seen between the untreated controls and both of the treated groups, the active and the placebo-treated. The authors recognize that this was an example of the "Hawthorne effect," in that attention in general affects patient behavior and can have a marked effect on outcomes of an intervention. Mite and cockroach allergen declined to a similar extent in both groups, perhaps because the authors were unable to blind the cleaning procedures and both groups adapted effective cleaning measures. The article thus provides an important illustration of the difficulties of conducting trials of environmental interventions and the compromises that must enter into the planning and execution of such trials. It might not be that the treatment is not efficacious; rather, it might be that methods for testing this efficacy need to be developed.

In a widely used reference for clinical trial design and management, Meinert[10] describes a clinical trial as a "planned experiment designed to assess the efficacy of a treatment in man by comparing the outcomes in a group of patients treated with the test treatment with those observed in a comparable group of patients receiving a control treatment, where patients in both groups are enrolled, treated and followed over the same time period." Meinert emphasizes several principles that are vital to a successful trial; they are discussed in the paragraphs that follow.

Test and control treatments

Treatments must be chosen that are effective, acceptable to the patient, distinguishable from one another, and able to be administered equally to all patients in the trial. Although this is easily accomplished in pharmacologic trials with placebos, environmental allergen avoidance is not so easy. Even when a treatment has been shown to be effective, it is difficult to blind, because it involves behavioral changes on the patients' part. Carter et al tried to create placebo mattress covers and cockroach traps, but they were clearly not able to blind the recommended laundering or household cleaning procedures. Another important decision was to use cockroach pesticide bait traps for cockroach control; minimal reduction in cockroach allergen was seen, supporting earlier studies that bait traps are in general less effective than professional pesticide applications in allergen reduction.[11,12]

After 3 decades of clinical trials, we now know that the benefit of environmental avoidance treatment is seen gradually, most successful trials lasting 3 months or more.[4,6] This may be said regarding mite avoidance; mite populations and allergen levels decreased by 90% or more within a month of placing mattress and pillow cov-

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ers and treating bedding.[4,13] It is likely that trials of cockroach and cat allergen avoidance must last longer than 6 months. Fel d 1 requires 3 to 6 months to decrease by this amount after a cat is removed,[14] and cockroach allergen declines even more slowly after successful extermination.[12] In addition to the logistic problems of keeping a trial going for so long, patient retention becomes a real problem; Carter et al report a dropout rate of 30%, which is similar to rates in other environmental control trials. Furthermore, treatment effects can be altered drastically if a patient moves during the intervention (eg, from a cockroach-free home to an infested one), so the new home must be visited, evaluated, and treated; such a patient would be expected to have a different clinical outcome than if he or she had not moved.

In pharmacologic trials it is expected that most treated patients will take their medications and that adherence can be increased by appropriate education and surveillance. Again, compliance with environmental controls is poor and has been reported to be 50% or less.[15] In many early trials, participants' homes were not inspected, so adherence was not evaluated. The repeated inspections that Carter et al performed certainly contributed to the Hawthorne (attention) effect and made both the treatment and placebo groups less likely to have acute-care needs.

An important confounding issue is the medications that patients might have been using during the trial. In pharmaceutical trials, it is customary to limit medication changes or allow them only by carefully administered protocols. Most environmental trials do not involve sufficient staff to assume full clinical responsibility for medication management, and a decision is made to record medication changes in follow-up questionnaires. Carter et al report that both active and placebo patients visited emergency departments (EDs) and clinics for acute asthma several times during the study. If inhaled steroids were begun after these visits, it would have had a substantial effect on any outcome, including subsequent ED use, and it is possible that the introduction of such therapy could occur more often in one treatment group than in the other.

Outcome measures

Outcomes must be chosen that are easy to observe, free of measurement errors, capable of being observed independently of treatment assignment, and chosen at the start of data collection. In clinical trials of asthma, multiple outcomes are usually chosen, including symptom measures (quality of life scores, periodic questionnaires regarding symptoms and medication use in the last 2 to 4 weeks), periodic pulmonary function tests (FEV_1, methacholine challenge tests), and records of acute asthma attacks (office visits, ED visits, hospitalizations). In trials of allergen avoidance, daily symptoms and medication use, as well as bronchial hyperresponsiveness, are the outcomes that change most consistently.[6,7,13] So as to use an objective independent outcome measure that could be obtained from patients' clinic charts, Carter et al examined only acute care for asthma.

Allergen avoidance trials have a unique measure, allergen concentration, that might be considered an intervening variable. Conceptually, if allergen exposure is not changed, clinical changes are not believable or attributable. There remains some uncertainty regarding the most appropriate measure of exposure, but apparently it may be said to be site-specific—for instance, dust mite changes in the kitchen are unlikely to be explained by installing a mattress and pillow cover and are just as unlikely to induce symptoms.

Comparable study groups

Establishing comparable study groups is usually accomplished by setting carefully defined inclusion criteria before the trial is started and then comparing important demographic and treatment variables at baseline. Once an eligible patient has agreed to enroll, the treatment assignment must be free of selection by the patient or clinic personnel. In the case of avoidance trials, the presence of sensitization to the target allergen, the exposure intensity at the beginning of the trial, and the presence of other, untreated sensitivities and medication regimens should be comparable at baseline. These requirements make it much more difficult to recruit patients for an environmental avoidance trial, because half of the participants who are otherwise eligible cannot enter the study. In the Carter trial, 70% of the children were exposed to cockroach allergen and 56% were sensitive to cockroach; only about half were both sensitive and exposed. We do not know whether the 2 treatment groups had comparable numbers of children who were both sensitized and exposed. By waiting until the end of the study to make this determination, the investigators effectively cut the number of participants that could logically be included in the analysis by half.

Masking and bias control

Ideally, so that individual biases cannot influence the outcome, treatments should be concealed (masked, blinded) and not capable of being identified by either clinician or participant. This is almost impossible in an environmental trial, because treatments involve patient behaviors. In this case, it is important to try to mask data collection—ie, an objective outcome must be chosen that is not accessible to the participants or the study staff. Carter et al chose to review patient charts for acute severe attacks; this allowed them to collect outcome data that were relatively independent of bias. Another approach is to have outcomes collected by staff who are not involved in patient care or in the administration of the intervention.

Sample size and power estimates

Once outcomes have been chosen, one or two of them should be considered the primary outcome measures and estimates should be made to determine how many participants need to be enrolled to prove that the treatment did—or did not—have an effect. This is a critical measure

but one that is not generally described in environmental clinical trials. In the report by Carter et al, for example, it is not mentioned, and the trial turned out to contain too few subjects to have real certainty. Depending on whether house dust mite allergen or cockroach allergen was examined, 15 to 20 children in each group could have benefitted—eg, if 56% were sensitive to cockroach allergen and 43% were sensitive and exposed, then only 10 to 12 children in each group were susceptible to treatment. Given that repeated measures of settled dust allergen measures have a SD of 0.35 $\log_{10}$ units,[16] it can be calculated that 50 patients are needed in each treatment group to detect a 38% change in allergen levels.

I do not intend by these comments to detract from the value of the Carter trial; it was well conceived and conducted, and it provided a positive test of dust mite avoidance. Instead, I want to emphasize the challenges faced in conducting such trials and to point toward some solutions to these challenges. Allergen avoidance provides a really promising approach in allergic asthma, with benefit potentially gained in chronic symptom control and medication reduction. Cockroach allergen control might provide an important and feasible public health measure in urban populations. In addition to providing an adjunct to pharmacologic management of asthma, allergen avoidance could provide a unique benefit. Current pharmacologic treatment must be maintained indefinitely; as soon as a patient stops treatment disease activity returns.[17,18] In contrast, environmental allergen avoidance is likely to continue for as long as the covers stay on the bed.

As physicians caring for asthma, it is incumbent on us to continue these trials and to improve the effectiveness of this form of treatment.

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