Editorial

Can We Clear the Air?

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The article by DiMango et al[1] is the latest in a long series of clinical trials testing the effect of home environmental treatments on asthma.[2-8] It adds to and strengthens previous results showing that treatments to improve indoor environments have a modest impact on asthma control in patients who live there. Their conclusion is a negative one: asthma morbidity was not decreased in the treatment group despite reduced exposure to household allergens. It is not easy to accept negative or marginal results in controlled clinical trials, especially when the rationale and expectations for the treatment are rational and compelling. We try hard to pick at the study to find rational holes in the study methods or the analysis, and look for the next study to correct these problems and show that the treatment is successful. Some previous clinical trials of environmental intervention have had design flaws such as inadequate sample size, inadequate intervention methods that did not demonstrate decreased exposure, short duration that might not allow time for an effect to be seen, lack of documentation of the specific sensitivity of the population in the trial, or limited measures of asthma outcome. The DiMango trial avoided all of these.

The importance of clinical trials such as those reported in the paper by DiMango et al is that it provides both a measure of how large a change in exposure can be expected with currently recommended treatments in "real world" home environments and the morbidity effects that can be expected. Both of these measures have been disappointingly small. I have concerns with the conclusion that treatment had changed home allergen exposure. Starting allergen levels were relatively low and the changes at 32 weeks were modest, around 20%-40%. More importantly, both intervention and usual care groups showed a reduction in most allergens. For example, Mus m 1 allergen levels in the kitchen fell 39% in the treatment group, but also fell 30% in the usual care group. Bedroom Bla g 2 levels fell 40% in the treatment group and 20% in the usual care group. Surprisingly, the authors do not provide a between-group comparison of changes seen in the treatment group with those in the usual care group, but it is likely that they are not statistically significant. So there is no real support for the conclusion in the paper that "Individualized household allergen intervention lowers allergen level…." Their post hoc analysis is interesting and suggests that there might have been a clinical effect; but here too they do not provide data about measured allergen levels in the 122 subjects designated "significant reduction" group or the 125 in the comparison group without significant reduction.

Environmental intervention trials differ from drug trials in important ways. Participants in active treatment groups in environmental trials are required to make significant behavioral changes, usually several different and sometimes complex behaviors, creating a greater issue of compliance with treatment in the active arm than usually seen with medication trials. DiMango et al did not describe behavior changes in their study; but given that monitoring in other environmental studies using similar methods in inner city populations have always demonstrated good compliance,[5-8] it is unlikely that this is a large issue. However, active treatment behaviors are impossible to blind effectively. As a result, the targeted behavior changes are frequently seen in members of the control group, who may be neighbors or may sit next to others in the waiting room and have ready access to their own interventions. Unblinded participants and investigators in these studies may allow their biases to change the clinical outcomes.

Another issue in clinical trials of home allergen control is the assessment of significant exposure. Brief exposures in other settings (work, school, and other homes) are enough to cause symptoms that might confuse investigators looking at the effects of home interventions. For example, Almqvist et al.[9] showed that the airborne cat allergen introduced to school rooms on the clothing of children whose families owned cats was sufficient to be associated with increased respiratory symptoms in children sensitized to cats.

The importance of indoor allergen exposure has long been accepted[10] and efforts are now focused to understand the dose-response relationship of environmental exposure and asthma morbidity. Epidemiologic studies have suggested that a threshold exists below which sensitization and morbidity are significantly reduced.[7,11,12] Recently, evidence has been published suggesting that in sensitized individuals the dose response is linear, with substantial changes in morbidity for every 10-fold change in allergen exposure.[13] Still others have reported a more complex relationship, in which sensitization and morbidity are actually reduced at the highest exposure doses.[14,15] These differences are important not only to the design of any clinical trial of environmental control, but also to where we put our clinical priorities in treating allergic patients. If there is a threshold, then that target must be achieved to expect a clinical effect; exposures and reductions in the DiMango paper were all below suggested thresholds. If the response is linear, then every increment of exposure reduction should have a clinical effect. In their post hoc analysis, DiMango et al found evidence supporting a dose

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response with a threshold in that the group with any reduction in mouse allergen had significantly less morbidity. Finally, the idea of high-dose suppression creates a major challenge for allergen reduction trials; in this case, those with the highest exposure (high enough to suppress morbidity) would actually be made worse when allergen exposure is reduced by the treatment. So, it will be important for future research to more carefully examine the dose response to inhalant allergen.

DiMango et al suggest that there is "…a need to perform prospective clinical studies targeting mouse allergen in the inner city." I would suggest that we should first concentrate on more effective methods to reduce indoor allergen exposure. Our current methods include cockroach extermination and cleaning, mouse extermination and cleaning, fitting impervious mattress and pillow encasings, or running an air filter. In clinical trials, all of these methods have been found to change indoor allergen levels, either in settled dust or room air modestly; the changes seen in the DiMango trial are typical. The only intervention shown to substantially reduce home levels of any major allergen was reported by Wood et al.,[16] where median settled dust Fel d 1 levels fell from 61.2 to 0.7 U/g at 32 weeks after removing a cat from a house. On the other hand, keeping the cat and treating the bedroom with a high-efficiency particle arrest air cleaner and a shut door only reduced median air levels from 3.1 to 1.7 ng/M^3 (45%) and did not change settled dust allergen levels at all.[17] Until we develop methods that can reduce exposure to a greater extent, perhaps by 90% or more, it is unlikely that asthma symptoms will be shown to be decrease convincingly in clinical trials. Without evidence of more convincing improvement, we will have to follow the evidence in treating our patients and give controller medications greater priority.

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