

## COST-BENEFIT ANALYSIS FOR ALLERGEN IMMUNOTHERAPY

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Current medical health care reimbursements in the United States have evolved from a loosely controlled, fee-for-service system into highly regulated, managed care organizations. Physicians, patients, employers, insurance providers, and local and federal government health agencies have developed a heightened awareness of increasing health care costs in this country and of the responsible driving forces. The discipline of pharmacoeconomics is an important means for assessing the cost versus benefit of medical diagnostic procedures and therapeutic interventions. Pharmacoeconomic studies have been conducted for potential new therapeutic agents, educational programs, and diagnostic or screening procedures in almost every medical and surgical subspecialty. The modification of standard health care protocols is influenced by the demonstration that a drug, educational program or diagnostic/screening procedure improves short- and long-term medical outcomes and quality of life in a cost-effective manner. Medical specialty organizations have developed practice parameters that define consensus state-of-the-art approaches to specific clinical disorders. Whenever possible, these guidelines have incorporated pharmacoeconomic data that support current recommendations.

Pharmacoeconomics has already affected the specialty of allergy and clinical immunology. For example, the design of new investigational drug protocols for the treatment of allergic rhinitis and asthma now frequently include quality-of-life questionnaires.<sup>23</sup> These protocols also often monitor changes in end-point parameters such as days lost from school and work, which have previously been demonstrated to correlate

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with the indirect costs associated with specific disease management.<sup>24</sup> Another example of the impact of pharmacoeconomics is the development of asthma self-management programs, which are cost-effective in reducing asthma morbidity.<sup>27, 45</sup>

There are no well-controlled pharmacoeconomic studies assessing the benefits of allergen immunotherapy in the treatment of allergic rhinitis or allergic asthma. An increased amount of direct and indirect information, however, supports the cost-effectiveness of allergen immunotherapy. Allergen immunotherapy should be scrutinized because it is widely prescribed and constitutes a significant percentage of the total health care costs attributed to the treatment of allergic rhinitis and asthma.

## PREVALENCE OF ALLERGIC DISEASES

Allergic rhinitis is the most prevalent chronic disease diagnosed in adolescents 18 years or younger.<sup>32</sup> Overall, it is the fifth most prevalent chronic disease diagnosed by physicians in the United States.<sup>32</sup> One out of every five visits to a pediatrician's office is for an allergic disorder. The National Health Interview Survey distributed by the Centers for Disease Control and Prevention in 1994 indicated that 10% (26 million) of the population in the United States has allergic rhinitis, and the prevalence of allergic rhinitis seems to be increasing.<sup>3</sup> This is supported by a 23-year follow-up study of college students that revealed that the frequency of allergic rhinitis increased with age.<sup>41</sup> Table 1 summarizes the prevalence of self-diagnosed allergic rhinitis determined from a self-administered questionnaire distributed to 15,000 households representative of the US population with respect to gender, age, geographic locale, population density, and household income.<sup>33</sup> Extrapolation of the results from this survey with 1993 census data indicated that 14.2% of US population, at least 35.9 million persons, have symptoms associated with allergic rhinitis, and 31.5% of the population or approximately 79.5 million persons experience 7 days or more of nasal/ocular symptoms each year.<sup>33</sup> Figure 1 illustrates the geographic distribution of subjects from this survey reporting symptoms consistent with allergic rhinitis or experiencing nasal/ocular symptoms 7 days or more each year.<sup>33</sup> The results of this survey can be criticized on several points. The investigators did not use a validated questionnaire, they did not confirm self-reported symptoms or diagnosis of allergic rhinitis with objective testing, and they made no provision for distinguishing perennial allergic rhinitis from nonallergic rhinitis. A high nonresponder rate (33.7%) suggests that the responding cohort who completed and returned the questionnaires for analysis was skewed toward those being symptomatic.<sup>33</sup> Despite these limitations, the increased prevalence of allergic rhinitis in this survey is consistent with other studies conducted in the United States, England, and Sweden.<sup>1, 39, 51</sup>

**Table 1. PREVALENCE OF SELF-DIAGNOSED ALLERGIC RHINITIS\***

| <b>Variable</b>              | <b>Percentage (%)</b> |
|------------------------------|-----------------------|
| <b>Total</b>                 | 14.2                  |
| <b>Gender</b>                |                       |
| Male                         | 13.7                  |
| Female                       | 14.3                  |
| <b>Age (y)</b>               |                       |
| ≤17                          | 9.1                   |
| 18–34                        | 18.4                  |
| 35–49                        | 17.6                  |
| 50–64                        | 14.2                  |
| ≥65                          | 7.8                   |
| <b>Region</b>                |                       |
| Northeast                    |                       |
| New England                  | 13.2                  |
| Middle Atlantic              | 13.8                  |
| Midwest                      |                       |
| East North Central           | 11.7                  |
| West North Central           | 13.7                  |
| South                        |                       |
| South Atlantic               | 13.7                  |
| East South Central           | 12.7                  |
| West South Central           | 15.5                  |
| Pacific                      |                       |
| Mountain                     | 20.2                  |
| Pacific                      | 16.4                  |
| <b>Population Density</b>    |                       |
| Rural (<100,000)             | 12.4                  |
| Urban                        |                       |
| 100,000–499,999              | 12.6                  |
| 500,000–1,999,999            | 14.4                  |
| ≥2 million                   | 15.1                  |
| <b>Household Income (\$)</b> |                       |
| <12,500                      | 9.4                   |
| 12,500–24,999                | 12.8                  |
| 25,000–39,999                | 13.4                  |
| 40,000–59,999                | 15.8                  |
| ≥60,000                      | 15.9                  |

\*Extrapolated to the total base population of 22,285 responders.

From Nathan RA, Meltzer EO, Selner JC, et al: Prevalence of allergic rhinitis in the United States. *J Allergy Clin Immunol* 99(suppl):808–814, 1997; with permission.

## ECONOMIC IMPACT OF ALLERGIC DISEASES

The economic impact of allergic rhinitis is better appreciated when one considers that patients with this disease have a threefold increased risk for developing asthma.<sup>1</sup> A significant percentage of the approximately 4.5% of the US population who suffer from asthma (nearly 10 million individuals) experience exacerbations of their symptoms in

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**Figure 1.** Prevalence (%), by geographic area, of patients with allergic rhinitis (\*) or  $\geq 7$  days of nasal and ocular symptoms in the previous 12 months (†). (From Nathan RA, Meltzer EO, Selner JC: Prevalence of allergic rhinitis in the United States. *J Allergy Clin Immunol* 99(suppl):808–814, 1997; with permission.)

response to allergic triggers. Collectively, allergic rhinitis and asthma disorders affect approximately 40 million people in the United States or 15% of the total population. The prevalence of other comorbid conditions associated with allergic rhinitis, such as sinusitis and otitis media with effusion, increases the health and economic impact of allergic diseases in the United States.<sup>41, 43</sup>

Direct costs for disease management include physician office visits, emergency room visits, hospitalizations, pharmacologic therapy and avoidance measures. Indirect costs include lost income resulting from missed work days and the expense of school absenteeism. Table 2 itemizes the estimated direct costs for treating allergic rhinitis in the

**Table 2.** DIRECT COSTS ASSOCIATED WITH SELF-REPORTED ALLERGIC RHINITIS IN 1993

| Item              | Millions of Dollars/Year |
|-------------------|--------------------------|
| Medications       |                          |
| Prescription      | 907                      |
| Nonprescription   | 1389                     |
| Total             | 2296                     |
| Physician visits* | 1130                     |
| Total overall     | 3426                     |

\*Does not include diagnostic tests or allergy shots.

From Storms W, Meltzer EO, Nathan RA, et al: The economic impact of allergic rhinitis. *J Allergy Clin Immunol* 99(suppl):820–824, 1997; with permission.

United States, which exceed 3.4 billion dollars each year.<sup>43</sup> Indirect costs to treat allergic rhinitis are estimated to approximate the direct costs. Conservative estimates of direct costs to treat patients with allergic rhinitis who experience common complications, such as acute or chronic sinusitis and otitis media with effusion, amount to an additional 2.4 billion dollars each year.<sup>25</sup> Finally, a portion of the total annual costs (direct and indirect) to treat asthma, estimated at 6.2 billion dollars, should be included as many individuals with allergic rhinitis have concomitant allergic asthma.<sup>50</sup> Together, the total health care dollars spent to treat allergic rhinitis and other associated conditions approaches 15 billion dollars each year or approximately 2% to 3% of the total annual health care costs in the United States.

## EFFICACY OF ALLERGEN IMMUNOTHERAPY

The prevalence of allergic diseases and magnitude of their associated health care costs require that the advantages and disadvantages of the available therapeutic interventions carefully be examined. Allergen immunotherapy is defined as "the repeated administration of specific allergens to patients with IgE-mediated conditions, for the purpose of providing protection against the allergic symptoms and inflammatory reactions associated with natural exposure to these allergens."<sup>34</sup> The initial successful use of allergen immunotherapy was reported by Noon in 1911.<sup>35</sup> Since this sentinel study, many hypotheses have been proposed regarding the mechanisms of allergen immunotherapy. Although the mechanism(s) for how allergen immunotherapy works is still not completely understood, evidence suggests that it down-modulates IgE-mediated immune responses through several different pathways resulting in T-cell tolerance to specific allergens.<sup>34</sup> Thus, allergen immunotherapy ultimately attenuates the inflammatory responses associated with allergic rhinitis and allergic asthma. The inability to achieve a better understanding of allergen immunotherapy is confounded by the absence of objective biomarkers that reliably predict which patients will optimally respond to this treatment. Similarly, there are no objective tests for determining when an individual has received the optimal benefits of allergen immunotherapy. Allergen skin testing and specific IgE *in vitro* assays are useful for confirming potential triggers for an individual's symptoms but seldom are useful for determining whether the duration of allergen immunotherapy is sufficient to induce tolerance.<sup>34</sup> Therefore, the clinician is faced with the decision of initiating, continuing, and discontinuing allergy injections based solely on the presence or absence of a patient's clinical symptoms in the context of confirmatory skin tests. Helpful criteria for determining clinical improvement include: (1) reduction of symptom scores; (2) increased time interval between administration of injections (i.e., subjects who require injections once a month compared with once a week presumably have achieved a greater therapeutic response); and (3) reduction of chronic medication require-

ments once maintenance concentrations have been achieved. Clinical assessment of the therapeutic response to allergen immunotherapy, however, is often hindered by the significant placebo response that is observed with any therapeutic intervention. The lack of objective parameters available to measure the efficacy of allergen immunotherapy has necessitated that well-designed, placebo-controlled trials be conducted.<sup>34</sup>

Information is abundant in demonstrating the efficacy of allergen immunotherapy in the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma, and stinging insect hypersensitivity.<sup>34</sup> Numerous double-blind, placebo-controlled studies have shown that allergen specific immunotherapy is effective in reducing symptoms in patients with seasonal allergies to tree, grass, and ragweed pollens. One of the earliest studies demonstrated that 79% of patients with grass pollen allergic rhinitis had good to excellent results after grass immunotherapy compared with 33% of subjects who received placebo.<sup>17</sup> Subjects with grass pollen-induced asthma experienced an even better response in that 94% of these subjects had good to excellent results compared with 30% of those receiving placebo.<sup>17</sup> Studies comparing tree, grass, and ragweed allergen immunotherapy to placebo reported similar findings.<sup>6, 28, 38</sup> Cat allergen immunotherapy administered to cat-sensitive patients resulted in a significant reduction in bronchial hyper-responsiveness and attenuation in ocular and pulmonary symptoms after exposure to cats.<sup>36-37, 46</sup> Double-blind, placebo-controlled studies of dust mite allergen immunotherapy demonstrated a decrease in symptoms and nasal provocation responsiveness to dust mite allergen.<sup>11, 13</sup> *Alternaria* immunotherapy administered to *Alternaria*-sensitive asthma patients decreased the severity of the late-phase asthmatic response after *Alternaria* bronchoprovocation.<sup>18, 31</sup> *Cladosporium*-sensitive children with asthma treated with *Cladosporium* immunotherapy experienced significant reductions in seasonal symptoms.<sup>12, 29</sup> Finally, immunotherapy in individuals with Hymenoptera stinging insect-induced anaphylaxis resulted in almost complete protection against subsequent laboratory or field stings.<sup>20</sup>

Controversy exists regarding the efficacy of specific allergen immunotherapy in the treatment of asthma. In many instances, the lack of efficacy of allergen immunotherapy reflects discrepancies in study design, quality of allergen extracts used for treatment, patient selection, and severity of airway disease.<sup>44</sup> These problems are highlighted by a recent study by Adkinson et al,<sup>4</sup> who reported no additional benefit using allergen immunotherapy in children with allergic asthma compared with anti-inflammatory medications alone. The authors' conclusions were somewhat misleading in that they selected a patient population with pre-existing moderate airway obstruction, suggesting a significant component of irreversible, airway remodeling. Furthermore, the authors did not discuss whether the subject's skin test reactivity correlated with individual clinical asthma symptoms prior to enrollment into either the allergen immunotherapy or placebo group. Confirmation of specific allergen-induced bronchial hyperresponsiveness by history

and objective testing in these subjects is important because many asthma patients experience exacerbations in response to multiple allergic and nonallergic triggers. Therefore, their inability in this population to demonstrate a therapeutic advantage for allergen immunotherapy compared with pharmacologic therapy is not surprising.<sup>4</sup>

The findings of this study contrast with other trials that have demonstrated that atopic patients without asthma or with mild asthma and well-preserved lung function respond favorably to allergen immunotherapy. A meta-analysis assessing the efficacy of 20 asthma immunotherapy trials revealed the odds for symptomatic improvement increased with this treatment. Allergen immunotherapy was successful in decreasing chronic medication use and improving pulmonary function.<sup>2</sup> The strength of this analysis was striking when one considers that 33 negative immunotherapy trials for the treatment of allergic asthma would have to be reported to offset the therapeutic benefits of asthma immunotherapy trials performed until 1990.<sup>2</sup> There are now several studies that confirm that allergen immunotherapy reduces the risk of individuals with allergic rhinitis from developing asthma.<sup>21, 22</sup>

## **PROPER DIAGNOSIS AND PATIENT SELECTION FOR IMMUNOTHERAPY**

Demonstration that a specific therapeutic intervention, such as allergen immunotherapy, is effective does not necessarily prove that it offers a distinct pharmacoeconomic advantage. The decision to implement allergen immunotherapy must incorporate other factors. A primary consideration for initiating allergen immunotherapy is an accurate diagnosis of allergic rhinitis or allergic asthma. To ensure that patients selected for this treatment will benefit, a detailed physician-administered history and physical examination designed to differentiate allergic from nonallergic rhinitis or asthma is essential. Confirmation of allergic sensitivity by skin testing or, if appropriate, standardized specific IgE in vitro assays is also a necessity.<sup>9</sup> The Joint Task Force on Practice Parameter for Diagnostic Testing, sponsored by the American Academy and College of Allergy, Asthma and Immunology and the Joint Council of Allergy, has published consensus recommendations for allergen skin testing.<sup>8</sup> These guidelines highlight the fact that proper training and expertise are required to apply and interpret allergen skin tests. In spite of these recommendations, allergists continue to use a variety of techniques for testing and different scales for grading reactions. The Food and Drug Administration has developed a standardized method to ensure proficiency of skin testing for assessing new biologic agents such as allergen extracts.<sup>47</sup> Closer attention to these skin testing proficiency standards could circumvent the potential incorrect interpretation of skin testing. Inaccurate testing may result in the erroneous treatment of nonallergic

patients or alternatively deprive some allergic patients from receiving the benefits of allergen immunotherapy.

The use of allergen immunotherapy by suboptimally trained physicians may further obscure its pharmacoeconomic advantages. Studies confirm that management of patients with allergic rhinitis or allergic asthma by well-trained allergists leads to improved quality of life and cost-efficient clinical outcomes.<sup>14, 48</sup> This observation is attributed to the allergist's more expedient recognition of allergic disease, which minimizes associated inappropriate treatment and complications. Health care professionals other than allergists often use less effective methods for diagnosis and treatment of allergic respiratory disease. Insurance carriers do not typically differentiate whether a patient is receiving allergen immunotherapy prescribed by a trained allergist or from less experienced physicians practicing allergy. Pharmacoeconomic studies assessing the advantages of allergen immunotherapy should include the potential savings in health care costs that allergy subspecialists could accomplish by adherence to standardized recommendations for diagnosis of allergic diseases and administration of allergen immunotherapy.

## **APPROPRIATE INITIATION OF ALLERGEN IMMUNOTHERAPY**

Present guidelines for initiating allergen immunotherapy imply sound decision analysis based on clinical experience and knowledge of immunopathogenic mechanisms of allergic diseases.<sup>34</sup> The consensus recommendations by the Joint Task Force on Practice Parameters for initiating allergen immunotherapy are: (1) symptoms and clinical course correlating with evidence of specific IgE antibodies to clinically relevant allergens; (2) symptoms not adequately controlled with avoidance measures and appropriate medications; and (3) the absence of any significant risk for systemic allergic reactions.<sup>34</sup> Before initiation of allergen immunotherapy, patients should be provided extensive education on cost-effective, practical approaches to avoidance measures for indoor and outdoor aeroallergen triggers in the home and recreational and work environments.<sup>16, 19, 34</sup>

Environmental allergen avoidance recommendations are important in the management of allergic rhinitis and asthma and are emphasized in the United States and international treatment guidelines of these disorders. Compliance by patients with these recommendations, however, is often poor. Patients often perceive environmental avoidance measures as impractical, expensive, and having a negative impact on their quality of life. For example, patients allergic to animals often have strong emotional attachments to their pets and are unwilling to remove them from their home. Many dust mite-sensitive patients are hesitant to spend even a modest amount of money to implement dust mite avoidance measures in their home. Patients allergic to outdoor aeroallergens

require restriction of outdoor activity during peak pollinating seasons, a recommendation that is not possible for outdoor workers or acceptable for recreational enthusiasts.<sup>9, 15, 16, 19</sup>

Another shortcoming of effective avoidance counseling is the difficulty in obtaining an accurate home and work environmental history on which to base the recommendations for environmental control. An ideal approach to ensure that recommendations for avoidance measures are warranted for a specific patient would require provisions for home and work environmental surveillance. On site assessment of the workplace and home would allow the indoor ambient allergen quantification, facilitating implementation of effective appropriate avoidance measures. This approach, however, would require home visits by personnel trained in environmental sampling techniques and a reliable immunologic laboratory, which are costly and usually impractical. Avoidance measures may create family conflicts (i.e., removal of the cat from the home), which can adversely affect a patient's quality of life and result in non-compliance.<sup>10, 15</sup> It is evident that more effective strategies to improve patient compliance with avoidance measures need to be developed as allergen immunotherapy should not be construed as a substitute for avoidance. Rather, allergen immunotherapy and allergen avoidance should work synergistically to improve clinical outcomes.

The initial treatment of allergic respiratory disease also should include a medication regimen tailored to the severity of the patient's symptoms and tolerance of medications.<sup>8</sup> Although medication is often effective for symptomatic control, many patients do not accept the regular use of medications or they experience side effects that limit their use.<sup>21</sup>

**Table 3. COST COMPARISON OF IMMUNOTHERAPY AT THREE SEPARATE INSTITUTIONS TO DAILY MEDICATION USE OVER 5 YEARS IN THE UNITED STATES**

| Year        | 1      | 2      | 3      | 4      | 5      | Total 5 Years* |
|-------------|--------|--------|--------|--------|--------|----------------|
| Site 1†     | \$800  | \$290  | \$290  | \$290  | \$290  | \$1960         |
| Site 2‡     | \$762  | \$292  | \$292  | \$292  | \$292  | \$1930         |
| Site 3§     | \$890  | \$250  | \$250  | \$250  | \$250  | \$1890         |
| Medications | \$1200 | \$1200 | \$1200 | \$1200 | \$1200 | \$6000         |

\*Total costs do not include the cost of a yearly office visit to assess patient's progress on immunotherapy. Costs to administer allergy injections vary regionally around the United States. If a patient receives two injections at one time or maintenance injections more frequently than once a month, costs may double.

†Estimated costs from Emory University.

‡Estimated costs from University of Cincinnati.

§Estimated costs from the University of South Florida.

||Estimated annual costs if medications (antihistamine/decongestant pills and intranasal corticosteroid spray) used on a daily basis.

From Sullivan TJ, Selver JC, Patterson R, et al: Expert care and immunotherapy for asthma. *Am Coll Allergy, Asthma, and Immunol*, 1996, pp 1-25, with permission; and Bernstein JA: Pharmacoeconomic considerations for allergen immunotherapy. In Lockey RF, Bukantz SC (eds): *Allergens and Allergen Immunotherapy*. New York, Marcel Dekker, Inc., 1999; reprinted from reference 10, pp 445-453, by courtesy of Marcel Dekker, Inc.

## COST ANALYSIS: MEDICATION VERSUS ALLERGEN IMMUNOTHERAPY

Pharmacologic treatment of allergic rhinitis often includes combined use of a topical intranasal corticosteroid spray (approximately \$30 per canister) and an antihistamine-decongestant (approximately \$50–\$60 for a 1-month supply of nonsedating, antihistamine-decongestant pills), costing approximately \$100 per month or \$1200 per year and \$6000 for 5 years. This treatment does not include the cost of physician office visits, antibiotics for secondary sinus or otitis media infections, and indirect costs that result from missed days from school and work. The costs for treating asthma are more substantial, especially when one considers that many patients with asthma have concomitant allergic rhinitis. Treatment of asthma each month commonly includes the minimum of a short- or long-acting  $\beta_2$ -agonist bronchodilator (approximately \$30 per canister for a short-acting  $\beta_2$ -agonist and about \$50 per canister for a long-acting  $\beta_2$ -agonist) and an anti-inflammatory agent (approximately \$30–\$75 per 1–2 canisters or a 1-month supply of oral leukotriene antagonist). The combined cost of asthma medications is approximately \$1000 to \$1200 each year. The cost of these medications does not include other direct and indirect expenses.

The average cost of allergen immunotherapy over a 5-year period is less than treatment with medication alone. In *appropriately* selected patients, favorable results lead to reduced requirements or discontinuation of medications. Table 3 illustrates the costs to provide immunotherapy to a patient for 5 years in three different facilities in the United States.<sup>10, 44</sup> The average 5-year cost to administer immunotherapy is approximately \$2000 compared with \$6000 for medication alone. Assuming a conservative estimate of 50% efficacy for immunotherapy and a 50% reduction of medication, the combined total cost of allergen immunotherapy and medication compared with medication alone remains less expensive (\$5000 versus \$6000). After 5 years, however, medication alone would only have been effective in controlling symptoms and not in modifying the underlying allergic immune response, which is the major advantage of allergen immunotherapy. The disappearance of symptoms after long-term immunotherapy implies a further economic advantage.

The discussion of the pharmacoeconomic advantages of allergen immunotherapy would be incomplete without taking into consideration potential quality-of-life issues, which have not been included in the above cost analyses. Quality-of-life questionnaires have become important sources of information for assessing the impact of disease morbidity on daily life activities. The Rhinoconjunctivitis Quality-of-Life questionnaire (RQLQ) is a good example of a disease-specific instrument that has been used for assessing patients suffering from allergic rhinitis.<sup>23, 24</sup> Box 1 summarizes the quality-of-life parameters measured by the RQLQ.<sup>30</sup>

**Box 1. Quality-of-Life Parameters Measured by the RQLQ**  
Dimension (items)

|                                                          |                                  |
|----------------------------------------------------------|----------------------------------|
| Sleep                                                    | Frustrated                       |
| Lack of a good night's sleep                             | Inpatient or restless            |
| Wake during the night                                    | Embarrassed by nose/eye symptoms |
| Difficulty getting to sleep                              | Activities*                      |
| Non-hay-fever symptoms                                   | Bicycling                        |
| Tiredness                                                | Cooking                          |
| Fatigue                                                  | Dancing                          |
| Worn out                                                 | Doing home maintenance           |
| Reduced productivity                                     | Doing housework                  |
| Poor concentration                                       | Gardening                        |
| Thirst                                                   | Eating                           |
| Headache                                                 | Jogging, exercising, or running  |
| Practical problems                                       | Attending public events          |
| Need to blow nose repeatedly                             | Driving a car                    |
| Need to rub nose/eyes                                    | Watching TV or a movie           |
| Inconvenience of having to carry tissues or handkerchief | Singing                          |
| Nasal symptoms                                           | Mowing the lawn                  |
| Stuffy/blocked                                           | Playing with pets                |
| Sneezing                                                 | Doing regular social activities  |
| Runny                                                    | Talking (public speaking)        |
| Itchy                                                    | Studying or doing homework       |
| Eye symptoms                                             | Taking a test or quiz            |
| Itchy                                                    | Visiting friends or relatives    |
| Watery                                                   | Going for a walk                 |
| Swollen                                                  | Having sexual intercourse        |
| Sore                                                     | Carrying out activities at work  |
| Emotions                                                 | Reading                          |
| Irritable                                                | Playing sports                   |

\*Examples listed in the questionnaire. Subjects may provide additional activities.

From Meltzer EO, Nathan RA, Selner JC, et al: Quality of life and rhinitic symptoms: Results of a nationwide survey with the SF-36 and RQLQ questionnaires. *J Allergy Clin Immunol* 99(suppl):815-819, 1997; with permission.

Figure 2 illustrates RQLQ profiles of subjects experiencing nasal-ocular symptoms.<sup>30</sup> These individuals exhibit consistently higher scores that directly correspond to a poorer quality of life compared with normal healthy controls. Disease-specific quality-of-life questionnaires, such as the RQLQ, provide a quantitative method for approximating indirect costs associated with poorly controlled diseases, such as allergic rhinitis and allergic asthma.

## SUMMARY

Given the preponderance of evidence that demonstrates the effectiveness of allergen immunotherapy, the major question that needs to be

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**Figure 2.** Rhinoconjunctivitis quality-of-life questionnaire (RQLQ) health profiles of patients with nasal and ocular symptoms (*solid circles*,  $n = 312$ ) versus healthy controls (*open circles*,  $n = 96$ ). Higher score indicates poorer health status;  $P < 0.01$  versus control (\*). (From Meltzer EO, Nathan RA, Selner JC, et al: Quality of life and rhinitic symptoms: Results of a nationwide survey with the SF-36 and RQLQ questionnaires. *J Allergy Clin Immunol* 99(suppl):815–819, 1997; with permission.)

addressed is not whether immunotherapy should be implemented in the treatment of allergic rhinitis and allergic asthma but rather at what point during the course of disease should it be initiated. One of the earliest studies indicated that children with allergic rhinitis treated with immunotherapy had significantly reduced chances of later developing asthma.<sup>22</sup> A more recent study conducted in Europe confirmed this observation as allergen immunotherapy was found to significantly reduce the incidence of asthma.<sup>21</sup> These studies support the concept that early treatment intervention with allergen immunotherapy in patients with allergic rhinitis or mild allergic asthma will down-modulate inflammatory responses and lessen the severity of future disease.<sup>21, 22</sup> Recent investigations also found that early intervention by an allergy subspecialist (including immunotherapy) in the management of allergic rhinitis and asthma is more effective in improving clinical outcomes while reducing overall resource utilization and net costs to treat these diseases, compared with care provided by a general internist.<sup>7, 48</sup> Expert care encompasses specialized clinical, pharmaceutical, and immunologic skills including allergen immunotherapy. Although the optimal time to implement immunotherapy remains an unsettled question, logically it should be administered early on in the course of disease if the same rationale for early introduction of inhaled anti-inflammatory agents for the treatment of asthma to reduce disease severity and improve clinical outcomes is applied.<sup>5, 26</sup>

In summary, allergen immunotherapy has been demonstrated to be effective in the treatment of allergic rhinitis and mild asthma. The critical decision for management of patients with allergic rhinitis and allergic asthma is whether to rely on avoidance measures and medications for suppression of disease related symptoms or to combine them with allergen immunotherapy in an attempt to gradually reduce the need for chronic medication by attenuating the inflammatory events responsible for clinical disease. If the clinical situation suggests the necessity for long-term treatment and the patient is a candidate for allergen immunotherapy, treatment should be initiated early on in the course of disease to prevent disease progression and severity. Further outcome studies are necessary to determine more precisely the cost-effectiveness of allergen immunotherapy compared with medication and avoidance measures, taking into account indirect costs, such as quality of life. In the past, such studies have been difficult to implement because allergic rhinitis and allergic asthma have variable courses for each individual. Cost-effectiveness analysis studies using "construction and analysis of references case" methods may prove useful for demonstrating the beneficial pharmacoeconomic impact of allergen immunotherapy in the treatment of allergic diseases.<sup>40, 42, 49</sup>

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