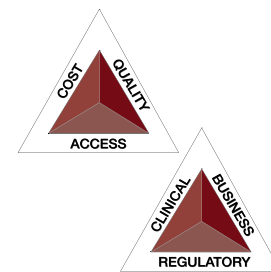


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ACAAI 2010: Payers' Perspectives

Introduction

The Current State of Management of the Patient with Allergic Rhinitis/Asthma: ACAAI 2010

By Richard Hyer



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The 68th Annual Scientific Meeting of the American College of Allergy, Asthma & Immunology (ACAAI), held in Phoenix, AZ, November 11-16, 2010, featured more than 300 ab-

stracts, plenary sessions, and symposia related to allergic conditions, including allergic rhinitis and asthma. According to allergic rhinitis expert William E. Berger, MD, this condition

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Investigational Ciclesonide HFA Safe and Effective for Seasonal Allergic Rhinitis

By Richard Hyer

Nasal congestion, sneezing, itching, and rhinorrhea are all characteristic of allergic rhinitis (AR). Results of 2 current studies with a total of 1260 patients with seasonal AR showed that the investigational nasal aerosol ciclesonide hydrofluoroalkane (CIC-HFA)—delivered via metered dose inhaler—is safe and

very effective for treating these symptoms.

Both were randomized, phase 3, placebo-controlled, double-blind, parallel-group, multicenter studies of the drug in 2 doses—80 µg and 160 µg. One study compared CIC-HFA's efficacy and safety versus placebo; the other study evaluated the drug's spe-

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Focus on What's Best for the Patient with Allergic Rhinitis

Allergies among 5 Top Chronic Conditions in the United States

By Richard Hyer

From the patient's viewpoint, most nasal allergy medications do not work quickly enough or long enough, according to William E. Berger, MD, Clinical Professor of Medicine at the University of California, Irvine. Dr Berger spoke at a symposium that examined the challenges in the care of patients with allergic rhinitis (AR).

Healthcare providers often overestimate the patient's satisfaction with therapy, and patient dissatisfaction results in frequent medication changes

or outright nonadherence, Dr Berger stressed. The willingness of patients to try new medications is also influenced by their insurance coverage.

The epidemiology of AR is almost startling, according to Dr Berger. Allergic disease affects more than 50 million people in the United States, he said, and is among the country's top 5 chronic medical conditions.

AR is "probably one of the most common diseases," Dr Berger said. And yet, the disease burden is considerable.

Continued on page S68

Inpatient Treatment of Asthma Is Costly

\$5000 per Hospitalization Calls for Proper Office Management

By Richard Hyer

The cost of a visit to the emergency department or hospitalization for a patient with asthma can range from \$400 to a staggering \$28,000, making a forceful argument for a continuum of care aimed at appropriate asthma management, according to Richard H. Stanford, PharmD, MS, a researcher with GlaxoSmithKline. He presented the results of a study on resource utilization for asthma events requiring

emergency department visits and/or hospitalizations.

"We were trying to determine the cost of severe asthma exacerbations," said Dr Stanford, that is, "patients who go to the emergency room or hospital for their asthma."

This cross-sectional, retrospective, observational study reviewed patients admitted to the emergency department or hospital for asthma between

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Introduction**The Current State of Management of the Patient with Allergic Rhinitis...** *Continued from cover*

is among the 5 most common illnesses in the United States, and yet its full impact on the patient is often underappreciated.

This supplement to *American Health & Drug Benefits* focuses on the management of patients with allergic rhinitis and asthma, highlighting current and emerging therapies for these conditions and the role of immunodeficiency.

The Economic Burden of Allergic Rhinitis and Asthma

In his reevaluation of allergic rhinitis, Dr Berger suggested that the estimated cost of this disease to the US economy is \$14.2 billion; this includes \$6.3 billion in direct costs and \$7.9 billion in indirect costs. In addition, lost productivity contributes another \$3 billion to this burden, according to Dr Berger (**page S68**). These estimates are based on 2003 data, suggesting that the current total medical costs for this chronic condition are likely to be considerably higher in 2011.

The economic implication of the overprescription of inhaled corticosteroids combined with long-acting beta-agonists was investigated in a pharmacoeconomic analysis presented by R. Thomas Manley, BSPHarm, who suggested that primary care physicians, not allergists, were the most likely clinicians to prescribe this combination therapy, often unnecessarily, when other therapies can be more effective (**page S67**).

Furthermore, treating asthma in the emergency department rather than in the office setting has a considerable economic impact that can reach as much as \$28,000 annually, according to Richard H. Stanford, PharmD, making a persuasive argument for a continuum of care aimed at appropriate asthma management in the office or clinic rather than in the costly emergency setting (**page S67**).

The Clinical Burden of Allergic Rhinitis

Dr Berger focused on the symptoms associated with allergic rhinitis, a

chronic, often seasonal, disease characterized by ocular and nasal symptoms, such as itchy eyes and blocked nose, leading to patient irritability and disrupted sleep that seriously compromise the patient's quality of life.

In addition, comorbid conditions are quite common in patients with allergic rhinitis; this disease occurs in almost 60% of patients with asthma. Nevertheless, this disease is often trivialized by health professionals and the public. The patient's first visit is most often to a general practitioner rather than an allergist, which experts suggest results in patient lack of satisfaction with treatment (**page S68**).

Emerging Therapies for Allergic Rhinitis

Several studies presented at the meeting highlighted the benefits of the investigational product ciclesonide hydrofluoroalkane (CIC-HFA), an alternative system wherein CIC-HFA is delivered via a metered-dose inhaler and is targeting the symptoms of allergic rhinitis, including nasal congestion, sneezing, itching, and rhinorrhea. Several trials showed that this approach is safe and effective for the treatment of patients with allergic rhinitis (**page S69**).

In 2 other analyses, Eli O. Meltzer, MD, and colleagues uncovered new performance markers for ciclesonide aqueous nasal spray (**page S70**).

Many presentations at the meeting focused on sublingual immunotherapy (SLIT) for patients with allergic rhinitis or asthma. Although there have been only a few small clinical trials related to SLIT in the United States, this approach accounts for almost 6% of prescriptions in this country and for more than 50% of prescriptions in Europe.

A number of speakers suggested that approval of SLIT by the US Food and Drug Administration (FDA) was inevitable, addressing what allergy experts should do to prepare for that anticipated FDA approval. Although the pharmacoeconomics of SLIT are not yet clear, the available evidence

mainly from trials outside of the United States suggests that this therapy is effective and has the potential to have a disease-modifying effect that could last 1 year or more after treatment discontinuation, which will have promising implications for patients and for payers.

Ira Finegold, MD, suggested that children are an ideal population for SLIT, with their inherent shyness around needles. He noted that despite the absence of FDA approval, 5.9% of US allergists now prescribe SLIT for their patients (**page S72**). The task of the allergy community is to begin preparing for regulatory approval of SLIT, he said.

The Forefront of Science on Allergies

Harold S. Nelson, MD, highlighted a number of the year's most significant studies in the area of allergies and allergic rhinitis. Among other things that stood out as a theme was the persistence of the positive effect with grass allergy immunotherapy tablets. The first study's results showed reductions in allergic symptoms and medication scores of 22% and 26%, respectively, after SLIT with ragweed extract.

A second study highlighted the benefit of timothy pollen tablets, which can significantly reduce symptom and medication scores by 18% and 26%, respectively. A third study concluded that combination treatment with SLIT and timothy pollen extract was effective. Dr Nelson also cited a study that suggested that pretreatment with omalizumab may lower the overall cost of therapy (**page S72**).

Thomas Casale, MD, discussed the leading edge of research in immunomodulation, including the use of toll-like receptor 4, 6, 8, and 9 agonists; depigoids; and recombinant peptides. Peptide research alone may result in a safer product applicable to a broad range of allergies, Dr Casale said (**page S73**). SLIT is by no means the final frontier of asthma and allergy therapy. ■

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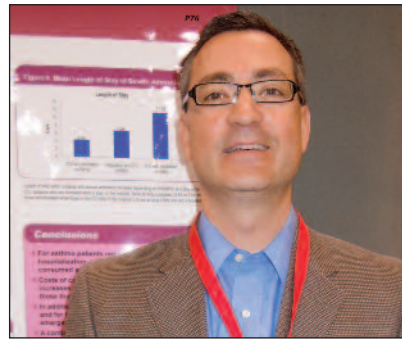
Inpatient Treatment of Asthma... Continued from cover

January 1, 2008, and December 31, 2008. It included eligible patients with a discharge diagnosis of asthma from 411 hospitals from Premier's Perspective Comparative Database.

Costs and length of stay were calculated for 3 cohorts: patients treated and discharged from the emergency department only; patients seen in the emergency department and subsequently admitted to the hospital; and patients evaluated in a non-emergency department setting and subsequently admitted as inpatients.

"We have a very large data set of inpatient hospitalizations and emergency room [visits], and over a year's time, we looked at every emergency room and hospital event that occurred in over 400 hospitals," Dr Stanford said.

A total of 149,319 patients with events were identified, with 108,569 for emergency department only, 30,829



"The standard inpatient visit costs health systems about \$5000 per hospitalization for patients who get hospitalized for asthma, while ED visits are about \$400 per patient."

—Richard H. Stanford, PharmD, MS

for emergency department plus inpatient, and 9921 for inpatient only.

For patients who visited the emergency department only, the average cost was \$391.56; for emergency department patients subsequently admitted to the hospital, the average length of stay was 3.76 days, with a cost of \$5911.34. Inpatient-only patients had a length of stay of 3.56 days, and a cost of \$5039.97. Nursing

care was the primary source of hospital costs for asthma, followed by medications and respiratory therapy.

"Overall cost of care is higher if they move from the emergency department into the inpatient setting," Dr Stanford said. "That's because emergency department costs are rolled into that. The standard inpatient visit costs health systems about \$5000 per hospitalization for

patients who get hospitalized for asthma, while emergency department visits are about \$400 per patient."

Costs increase substantially with the severity of the inpatient visit. "A patient who ultimately goes to the intensive care unit without intubation is about \$9000; a patient who goes to the intensive care unit with intubation is about \$28,000. A lot of that is based on the intensity of care as well as length of stay, because length of stay goes up as the severity levels go up. So, standard inpatient stay is about 3.5 days. But a patient who goes to the intensive care unit with intubation, they're in the hospital about 12 days," Dr Stanford said.

Considering the high costs of hospitalization associated with asthma, a continuum of care aimed at appropriate asthma management could result in substantial cost-savings by reducing the need for hospital utilization. ■

Overprescription of Inhaled Corticosteroid/LABA Combination Therapy Increases Costs, No Clear Clinical Benefit

By Richard Hyer

A new pharmaco-economic analysis presented at ACAAI 2010 showed that inhaled corticosteroid/long-acting beta-agonist (LABA) combination therapy is widely used in patients with mild asthma, despite guidelines to the contrary. This practice increases asthma-related pharmacy costs and total asthma-related healthcare costs, without apparent clinical benefits.

Inhaled corticosteroid monotherapy is the preferred treatment for mild persistent asthma, and inhaled corticosteroid/LABA combination therapy should be reserved for moderate-to-severe persistent asthma that is not controlled with inhaled corticosteroids alone.

Commenting on the results of the study, lead investigator R. Thomas Manley, BSPHarm, of Medco, Spokane, WA, said, "Clinical outcomes were the same, but folks who were on inhaled corticosteroid monotherapy had lower pharmacy costs, and, mostly attributed to that, lower total healthcare costs, than the patients that were on inhaled corticosteroid/LABA combination therapy."

The study also showed that family practice and primary care physicians were the most likely to prescribe inhaled corticosteroid/LABA combination products in patients with mild asthma; pediatricians were the least likely to do so.

Using data from the Medco Health Solutions database, a large pharmacy benefit manager (PBM) population, medical and pharmacy claims for the period from July 1, 2008, to December 31, 2008, were analyzed for patients with mild asthma who received single-entity inhaled corticosteroids or inhaled corticosteroid/LABA combination therapy. The investigators calculated the cost and adjusted it for age, sex, and baseline clinical characteristics. Clinical outcomes were assessed during 1 year of follow-up.

"We looked at asthma patients with an ICD-9 [International Classification of Diseases, Ninth Revision] code of asthma, without an ICD-9 code for COPD [chronic obstructive pulmonary disease], or those who were also not on tiotropium," to define patients with mild asthma, Mr Manley said.

A patient with mild asthma was defined in 3 ways:

- No hospitalization or emergency department visit in the previous 12 months
- Use of 3 or fewer short-acting beta-agonist canisters in the preceding 12 months
- Fewer than 2 claims of oral steroids in the past 12 months.

"We looked at patients who were prescribed an inhaled corticosteroid as monotherapy versus patients that were prescribed an inhaled corticosteroid/



"There was no difference in medical costs between the 2 therapies, but the overall cost, the total adjusted healthcare cost, was significantly higher in the...combination group."

—R. Thomas Manley, BSPHarm

LABA combination product. We followed them 12 months forward from the index date, and we looked at clinical outcomes and cost," Mr Manley said.

Of 8424 patients treated for mild asthma, 5523 were prescribed inhaled

corticosteroid/LABA and 2901 were prescribed inhaled corticosteroid monotherapy. The rate of inhaled corticosteroid/LABA combination therapy use was highest (75.1%) in patients aged 18 to 49 years.

Treatment with the combination therapy was associated with significantly higher asthma-related drug costs than inhaled corticosteroid monotherapy (\$1137.70 vs \$922.95; $P < .01$); adjusted asthma-related costs, number of oral steroid claims per patient, and number of short-acting beta-agonist canisters remained similar between treatment groups. The total adjusted asthma-related healthcare costs were also higher in the combination group (\$1529.35 vs \$1265.51; $P < .01$).

"The inhaled corticosteroid alone adjusted pharmacy cost was \$923 compared with \$1138 for the inhaled corticosteroid/LABA combination," Mr Manley said. "There was no difference in medical costs between the 2 therapies, but the overall cost, the total adjusted healthcare cost, was significantly higher in the inhaled corticosteroid/LABA combination group."

Mr Manley reiterated that this was a retrospective observational study of claims data from a large PBM population. "You can't actually tell the symptoms of the patients when they go into the offices," he said. ■

Focus on What's Best for the Patient... *Continued from cover*

He listed as problems its high and increasing prevalence and cost, comorbidities, and the impaired quality of life and work productivity. Compounding the problem, the disease is often trivialized as less serious than other conditions.

AR accounts for 3 million lost work days among adults, and affects up to 40% of children, resulting in 2 million lost school days.

"So if you're in pediatric practice, almost half of the patients coming in have allergic rhinitis," Dr Berger said.

Economic Impact

The enormous economic impact is, therefore, not surprising. Direct medical costs of AR are estimated to be \$6.3 billion annually, based on 2003 data, and indirect costs are estimated to be \$7.9 billion, for a total of \$14.2 billion annually, according to Dr Berger.

The lost productivity associated with AR is estimated at more than \$3 billion annually, and approximately 14 million office visits to healthcare providers were attributed in 2002 to issues related to AR.

Quality of Life

The distress of patients with AR is not only financial, he said. Quality-of-life issues are just as important. One study used the AR Medical Outcomes Study 36-Item Short-Form Health Survey to compare patients with



"Allergic rhinitis is underappreciated, and is not yet viewed as a serious disease."

—William E. Berger, MD

nasal and ocular symptoms with healthy controls.¹ It showed that the symptomatic patient had lower overall health scores and worse emotional and mental health than those without this condition.

Considering the symptoms of AR, this is not surprising. Dr Berger noted that in the landmark Allergies in America study, results from patients with AR showed that²:

- 99% of patients reported itchy eyes
- 98% reported stuffy/blocked nose
- 92% reported irritability
- 87% said they could not get a good night's sleep.

Overall, Dr Berger said, in terms of a patient's quality of life, "The number one complaint is nasal congestion." In

fact, in that landmark Allergies in America study, 38% of persons with allergies said that they could not tolerate a nasal allergy attack.²

The problem is not limited to medical measures. Dr Berger presented another study that reported a decrease in bank customer service worker productivity related to increases in ragweed pollen levels.³ Yet another study showed a relationship between allergy severity and worker functionality at a trucking company, showing a decline in productivity.⁴

Comorbid Airway Diseases

A number of related diseases may accompany AR. For example, AR is found in up to 58% of patients with asthma, and treatment of AR reduces the incidence and severity of asthma.

Ocular allergies often accompany AR, as well as maxillofacial problems. Otitis media with effusion is often associated with nasal allergy in children, further contributing to sleep disorders in this patient population.

Despite all this, "allergic rhinitis is underappreciated, and is not yet viewed as a serious disease," Dr Berger said. A total of 72% of patients who suffer from AR report that persons without the condition are unsympathetic to them.

In addition, many patients with AR consult physicians only when they have severe symptoms, and 90% of

patients with moderate-to-severe AR symptoms first consult a primary care physician. They also consult pharmacists, internal medicine specialists, and herbalists before ever getting to an allergy specialist.

Why Specialists Are Needed for AR

Many patients are dissatisfied with their therapy, according to Dr Berger; in fact, 78% claim that they are not knowledgeable about seasonal allergies. Almost 50% report feeling that the physician does not spend enough time talking to them about their allergies, and 40% say that they believe that the physician only prescribes the medications with which he/she is familiar. "We tend to think the patients know about allergy, but in fact, they still need to be educated," Dr Berger said.

"Allergy is one of those diseases where patients don't know that there is a need very much for someone who is a specialist."

—William E. Berger, MD

Almost 50% of patients with AR report feeling a strong need for better education about nasal allergies from their healthcare providers. "When you actually ask patients when doctors aren't in the room, their perception of what is going on is very different from what the doctor perceives," Dr Berger said.

Physicians must improve patient adherence, Dr Berger said, and more patients should see a specialist. "Allergy is one of those diseases where patients don't know that there is a need very much for someone who is a specialist," Dr Berger said. He suggested improving patient communication and education.

According to a Gallup survey, patients overall want medications that specifically target individual symptoms, have a fast onset of action, have few adverse effects, and contain no steroids.

"Remember, this is America," Dr Berger said. "We do not believe in delayed gratification." ■

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New Questionnaire Assesses Patients' and Caregivers' Satisfaction with Allergic Rhinitis Therapy

By Richard Hyer

One effective way to measure a child's response to therapy for allergic rhinitis (AR) is to first assess the caregiver's degree of satisfaction with that treatment. Medication side effects can affect the patient's quality of life and often lead to lack of medication adherence. Assessing caregiver satisfaction with treatment can provide insights regarding patients' and providers' attitudes toward treatment, especially when efficacy is similar among treatments.

A new 12-question instrument developed by 2 scientists from Alcon Research, Fort Worth, TX, and by Eli O. Meltzer, MD, of the Allergy & Asthma Medical Group and Research Center, San Diego, CA, provides a reliable way of measuring patients' and caregivers' response to AR therapy.

"The question we were asking is, what makes a difference to the parents?" said lead investigator Carol J.

Fairchild, PhD, of Alcon Research. "And, to ask that question, to develop a questionnaire, you go first to the parents and say, 'What is it that bothers you about your child's illness?' And then after they've had a little bit of treatment, 'What is it that was satisfying about that?'"

Although many effective treatments exist for AR in children, some have a negative impact on the child's overall quality of life and ability to function, the investigators said. Dissatisfaction affects adherence, leading to inadequate disease control (and presumably, increased cost). Because the caregiver's satisfaction with treatment (or lack of it) is an outcome in clinical trials, it was considered a valid target for study.

"After in-depth interviews of 21 parents and their children who received nasal therapy for allergic rhinitis, we started with a gamut of

114 questions," Dr Fairchild said. "By applying psychometric methodology, we reduced and revised the questions and came out with a final questionnaire that is now just 12 items. We've shown that it's valid and reliable."

These 12 items cover 4 domains—efficacy, function, family disruption, and overall satisfaction. In the course of refining the questionnaire, other widely accepted tests were also administered to collect additional data; these were the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire, total nasal symptom score, and the caregiver treatment satisfaction visual analog scale (VAS).

The researchers found this Caregiver Treatment Satisfaction Questionnaire for Allergic Rhinitis to be very reliable; it correlated particularly well with the caregiver treatment satisfaction VAS. ■

Investigational Ciclesonide HFA... *Continued from cover*

cific effect on rhinoconjunctivitis-related quality of life.

"This is an alternative delivery system for allergic rhinitis," said Shailesh Desai, PhD, a researcher with Sunovion Pharmaceuticals. "This is a drier, alcohol-based formulation. Contrary to the old CFCs [chlorofluorocarbons] that were there in the market, we have very low incidences of nasal serious adverse events and low incidences of epistaxis [with HFA]."

Safety and Efficacy

The first study consisted of a 14-day treatment period in 707 patients (aged ≥ 12 years) with a history of seasonal allergies to mountain cedar pollen. Eligibility criteria were a minimum cumulative patient-assessed reflective total nasal symptom score (rTNSS) of 47 (maximum 84) and reflective score for runny nose or nasal congestion of at least 10 (maximum 21).

Patients were randomized to CIC-HFA 80 μg , CIC-HFA 160 μg , or to placebo. The primary end point was change from baseline in patient-reported morning and afternoon rTNSS. Secondary end points were morning and afternoon instantaneous TNSS (iTNSS) and individual morning and afternoon reflective and instantaneous nasal symptom scores of nasal congestion, runny nose, sneezing, and nasal itching.

Demographic and baseline characteristics were similar across the treatment groups, as were mean baseline rTNSSs (range, 9.10-9.46). Baseline iTNSS ranged from 8.61 to 8.94.

Improvements in Total Nasal Symptom Scores

Both CIC-HFA treatment groups demonstrated significant improvements ($P < .001$) in total reflective and instantaneous nasal scores from baseline compared with placebo, averaged over the 2-week period.

The daily improvement in rTNSS and iTNSS was consistent over the 2-week double-blind treatment period.

Both treatment groups demonstrated improvements in individual reflective and instantaneous nasal symptom scores of runny nose, itchy nose, sneezing, and nasal congestion.

The overall incidence of treatment-emergent adverse events was low, with 58 events (24.7%) in the placebo group compared with 51 (21.5%) in the 80- μg treatment group and 44 (18.7%) in the 160- μg treatment group. The investigators characterized these as mostly mild or moderate. All events of epistaxis were resolved without intervention, and no nasal septal perforations were reported.

Effect on Rhinoconjunctivitis-Related Quality of Life

The second trial measured the ability of CIC-HFA to improve the rhinoconjunctivitis-related quality of life associated with seasonal AR, as evaluated by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) with standardized activities in patients aged ≥ 12 years. Lead investigator, Dale Mohar, MD, of Kerrville Research Associates, TX, presented this study.

The study design and treatment period matched those of the first study. Patients were eligible if they had a history of seasonal AR to mountain cedar pollen for ≥ 2 years immediately preceding the study. The 2 treatment groups were similar to those in the first study and were compared with placebo.

"You don't often see patients citing improvements that are almost triple or more than triple placebo." —Dale Mohar, MD

The primary and key secondary efficacy end points were change from baseline in patient-reported morning and afternoon rTNSS, iTNSS, and reflective total ocular symptom score. (See also article on ocular symptoms, this page.) Rhinoconjunctivitis-related quality of life measured by RQLQ with standardized activities was evaluated as one of the secondary end points. "With the HFA, we are showing that it does relieve ocular symptoms as well," Dr Desai commented on the results of this study.

Change in overall RQLQ with standardized activities scores was calculated for the intent-to-treat population, as well as for patients with baseline RQLQ with standardized activities scores ≥ 3 as defined a priori in the statistical analysis protocol. The RQLQ with standardized activities was self-administered by patients at baseline and at the end of the study medication period.

In patients with baseline RQLQ ≥ 3 , the 80- μg ($n = 187$) and 160- μg ($n = 183$) treatment groups demonstrated improvement, as seen in the **Table**.

The overall RQLQ for the 80- μg group was -1.05 versus -0.42 for placebo ($n = 183$), a significant difference (95% confidence interval [CI], 0.36-0.89; $P < .001$). For the 160- μg group, the overall RQLQ was -1.07 , a significant difference (95% CI, 0.37-0.91; $P < .0001$) versus placebo.

Commenting on these results, Dr Mohar said, "You don't often see

Table Change in Overall RQLQ Scores in Patients with Baseline RQLQ ≥ 3 and Individual RQLQ Domains, Averaged Over 2 Weeks

Symptom	CIC-HFA 80 μg (N = 187)	CIC-HFA 160 μg (N = 183)	Placebo (N = 183)
Overall RQLQ score	-1.05 (0.10)	-1.07 (0.10)	-0.42 (0.10)
Individual scores			
Activities	-1.00 (0.10)	-0.96 (0.10)	-0.28 (0.10)
Sleep	-1.01 (0.11)	-1.12 (0.11)	-0.41 (0.11)
Non-nose/eye symptoms	-1.01 (0.10)	-0.91 (0.10)	-0.39 (0.10)
Practical problems	-1.16 (0.11)	-1.26 (0.11)	-0.54 (0.11)
Nasal symptoms	-1.15 (0.10)	-1.24 (0.11)	-0.46 (0.11)
Eye symptoms	-0.94 (0.11)	-0.99 (0.11)	-0.52 (0.11)
Emotions	-1.04 (0.11)	-0.95 (0.11)	-0.43 (0.11)

CIC-HFA indicates ciclesonide hydrofluoroalkane; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire with standardized activities.

Source: Presented at the American College of Allergy, Asthma & Immunology Annual Scientific Meeting; Phoenix, AZ; November 11-16, 2010. Abstract 332.

patients citing improvements that are almost triple or more than triple placebo." He cited the individual RQLQ domain of "activities," where the change from baseline was -0.96 over placebo's -0.28 —a significant difference (95% CI, 0.40-0.97; $P < .001$), cred-

iting the aerosol formulation of ciclesonide for this improvement.

Patients in both groups demonstrated improvements in individual domains, including activities, sleep, practical problems, nasal and eye symptoms, and emotions. ■

Ocular Symptoms of Seasonal Allergic Rhinitis Relieved by Ciclesonide

By Richard Hyer

Itching, tearing, red eyes are symptoms of allergic rhinitis (AR), a heterogeneous disorder also characterized by nasal congestion, sneezing, and rhinorrhea. Ciclesonide with a hydrofluoroalkane propellant (CIC-HFA), a nasal aerosol currently in clinical development, was found to improve reflective total ocular symptom score (rTOSS), instantaneous TOSS (iTROSS), and individual ocular symptoms compared with placebo in patients with seasonal AR.

"With this once-daily treatment, things that are important to patients improved measurably," said study investigator Frederick Bode, MD, of Marlborough, MA.

This phase 3 randomized, placebo-controlled, double-blind, parallel-group, multicenter study consisted of a 14-day treatment period for patients aged ≥ 12 years with a diagnosis of seasonal AR to mountain cedar pollen for ≥ 2 years.

Patients assessed themselves. Those who had a minimum cumulative patient-assessed reflective total nasal symptom score of 47 (of a possible 84) and a minimum cumulative reflective score for runny nose or nasal conges-



"With this once-daily treatment, things that are important to patients

improved measurably."

—Frederick Bode, MD

tion ≥ 10 (of a possible 21) over any 3 of the past 4 days of the 7-day period were randomized to receive CIC-HFA 80 μg , 160 μg , or placebo, once daily in the morning for 2 weeks.

Change from baseline in individual ocular symptom scores of tearing or itching eyes, and redness of eyes over a 2-week treatment period were evaluated.

An important secondary end point was change from baseline in morning and afternoon rTOSS averaged over the 2-week treatment period in patients with baseline rTOSS ≥ 5.0 .

Changes in total ocular symptoms were recorded and calculated for the intent-to-treat population and for patients with baseline rTOSS ≥ 5 and

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New Performance Markers of Ciclesonide Aqueous Nasal Spray for Seasonal Allergic Rhinitis

By Richard Hyer

Two post-hoc analyses of data on patients with allergic rhinitis (AR) have uncovered new performance markers for ciclesonide aqueous nasal spray (CIC-AQ), said lead investigator Eli O. Meltzer, MD, of the Allergy and Asthma Medical Group and Research Center, San Diego, at ACAAI 2010.

Both analyses were based on data from a double-blind, placebo-controlled, multicenter efficacy and safety study of 327 patients aged ≥ 12 years with seasonal AR (Ratner PH, et al. *J Allergy Clin Immunol.* 2006;118:1142-1148). The patients received 200 μg of CIC-AQ (n = 164) or placebo (n = 163) once daily in the morning for 28 days.

Correlation between Nasal Symptoms and Quality of Life

The first analysis evaluated the correlation between improvement in reflective total nasal symptom score (rTNSS) and instantaneous TNSS (iTNS) and rhinoconjunctivitis-related quality of life as measured by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Patients with seasonal AR were treated with CIC-AQ 200 μg once daily or with placebo.

“The correlation analysis showed improvement in the reflective total nasal symptom scores and in the instantaneous total nasal symptom scores, so it [CIC-AQ] had a long duration of action,” Dr Meltzer said. “These 2 related very well—0.9%—a correlation coefficient which is really quite high.”

Two post-hoc correlation analyses were performed. The first was in patients with baseline rTNSS (ie, moderate severity) or iTNS ≥ 6 ; patients were divided to CIC-AQ (n = 137) or to placebo (n = 132). The other analysis



“As the patients improved in their symptoms, they improved in these other aspects, like feeling thirsty, feeling tired, eye symptoms, their ability to participate in activities, their emotions.”—Eli O. Meltzer, MD

was in patients with baseline rTNSS ≥ 6 and RQLQ ≥ 3 (also moderate severity); patients were randomized to CIC-AQ (n = 119) or to placebo (n = 110).

Patients with baseline rTNSS and iTNS ≥ 6 were divided into 2 groups—CIC-AQ 200 μg once daily versus placebo. Patients with baseline rTNSS ≥ 6 and RQLQ ≥ 3 were also divided into similar treatment groups.

Improvement in rTNSS was highly correlated with improvement in iTNS, regardless of treatment group. However, improvement in rTNSS was more correlated with improvement in RQLQ in the CIC-AQ group than in the placebo group.

Dr Meltzer said that the correlation between rTNSS and RQLQ was especially important to him as a clinician. “So as patients improved in their symptoms, they also improved in these other aspects, like feeling thirsty, feeling tired, eye symptoms, their ability to participate in activities, their emotions—those were improved as well,” he said. “So there was a good correlation: symptom improvement with quality-of-life improvement.”

Dr Meltzer added, “Clearly the studies showed the people on ciclesonide did better than the placebo group....And although there’s some improvement in the placebo-treated group, because placebo does amazing things, clearly there’s a

much greater improvement in the ciclesonide-treated group; both from the symptom standpoint (both reflective and instantaneous) and the quality of life.”

Improvements in Nasal Congestion with CIC-AQ versus Placebo

The second analysis measured

changes at 14 days in the 44 patients with baseline nasal congestion scores of < 2 (CIC-AQ, n = 21; placebo, n = 23), and in the 280 patients with scores ≥ 2 (CIC-AQ, n = 141; placebo, n = 139) with CIC-AQ versus placebo. Both groups showed improvements with CIC-AQ 200 μg once daily compared with placebo, but the improvements were greater in those with scores ≥ 2 in the baseline nasal congestion group.

The improvements (mean change from baseline) in the < 2 congestion group were CIC-AQ = -0.48 versus placebo = -0.19 ($P = .052$). Greater improvements were seen in the ≥ 2 congestion group: CIC-AQ = -0.59 ; placebo = -0.35 ($P < .001$) after 14 days of treatment. ■

Systemic Bioavailability of Beclomethasone Dipropionate HFA for Allergic Rhinitis

A new dry spray using the corticosteroid beclomethasone dipropionate (BDP) in combination with hydrofluoroalkane (HFA) is currently in clinical development. Two studies presented at ACAAI 2010 demonstrated the safety, efficacy, and systemic bioavailability of the BDP-HFA formulation.

A randomized, double-blind, placebo-controlled, parallel-group, 2-week multicenter study in patients with seasonal allergic rhinitis triggered by Texas mountain cedar pollen demonstrated the drug’s safety and efficacy. Mountain cedar pollinates in midwinter and causes significant allergies.

Patients were randomized to receive either BDP-HFA nasal aerosol 320 μg daily or placebo nasal aerosol. Medication was administered once daily in the morning, and nasal symptoms were assessed in the morning and in the evening. The efficacy outcome was change in morning and evening patient-reported reflective total nasal symptom score (rTNSS) over the 2-week treatment period.

Investigators reported 4 positive efficacy outcomes.

Patients treated with BDP-HFA 320 μg /day demonstrated significant improvements in morning and evening patient-reported rTNSS compared with placebo (-1.96 vs -1.05 ; $P < .001$; values represent least square mean [\pm structural equation modeling]; least square mean treatment difference from placebo, -0.91 [95% confidence inter-

val; -1.3 vs -0.5]). The improvements in average morning and evening patient-reported rTNSS were reported as early as day 2, and were maintained throughout the 2-week treatment period ($P < .05$).

“There is a clear separation between the patients that received the active medication...versus the ones on placebo. The effectiveness...could be seen at 2 days of treatment, and persisted for the whole 2-week treatment period,” said study investigator Julius Van Bavel, MD, of Isis Clinical Research, Austin, TX, and an allergist in private practice.

Patients treated with BDP-HFA 320 μg /day had significantly greater improvements in average morning and evening patient-reported rTNSS compared with placebo ($P < .001$).

Finally, significantly greater improvements were seen in each of the 4 individual nasal symptoms (sneezing, rhinorrhea, nasal itching, and nasal congestion) for patients treated with BDP-HFA 320 μg /day compared with placebo ($P < .001$).

Overall, the treatment was well tolerated, with an adverse event profile similar to placebo.

Second Study Compares Doses, Methods of Administration

A second study noted that BDP is a prodrug with weak glucocorticosteroid receptor-binding affinity, and that it is hydrolyzed via esterase enzymes to an active metabolite, beclomethasone 17-monopropionate

Ocular Symptoms... *Continued from page S69*

iTOSS ≥ 5 as defined a priori in the statistical analysis protocol. P values for iTOSS and individual reflective and instantaneous ocular symptom scores were not adjusted for multiplicity.

Patients in the rTOSS group were divided into 3 groups—CIC-HFA 80 μg (n = 164), CIC-HFA 160 μg (n = 160), and placebo (n = 148). Patients in the iTOS group were also divided into 3 groups—CIC-HFA 80 μg (n = 149), CIC-HFA 160 μg (n = 150), and placebo (n = 134).

Over the 2-week study, significant changes from baseline were reported in both types of ocular symptoms in patients with baseline TOSS ≥ 5 in both

treatment groups, CIC-HFA 80 μg and CIC-HFA 160 μg .

For example, the iTOS was -1.0 in the 80- μg group and -0.12 in the placebo group ($P = .008$). In the 160- μg group, the iTOS was -1.07 ($P = .002$) versus placebo. In the intent-to-treat population, change from baseline in both scores averaged over the 2-week treatment period was also significant.

The rTOSS was -0.78 in the 80- μg treatment group (n = 237) and -0.23 in the placebo group (n = 235; $P = .0002$). In the 160- μg treatment group (n = 235), the rTOSS was -0.75 , a difference of 0.52 ($P = .0004$) versus placebo.—RH ■

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Mometasone Furoate Nasal Spray Provides Sustained Symptom Relief in Allergic Rhinitis

By Richard Hyer

A pooled analysis of 1812 patients with seasonal allergic rhinitis (AR) showed that 15 days of therapy with once-daily mometasone furoate nasal spray provided 24-hour symptom relief of nasal congestion/stuffiness, said Mark Dykewicz, MD, of Wake Forest University School of Medicine, Winston-Salem, NC, who presented the results in a poster session.

Although AR is characterized by congestion, rhinorrhea, sneezing, and itching, patients tend to single out congestion as the most bothersome symptom. Almost 50% of patients say that they experience the most severe symptoms in the day; almost 66% want medicine that lasts 24 hours.

Mometasone furoate nasal spray has already demonstrated symptom relief in this patient population. This study focused on the 24-hour nasal symptoms relief through morning awakening.

Data were pooled from 5 randomized, placebo-controlled, parallel-group, multicenter 15-day trials (N = 1812) of mometasone furoate nasal spray 200 µg once daily in patients with symptomatic seasonal AR. Four trials were double-blind phase 3, and 1 was sin-

rated the previous 12 hours, as well as the present moment (referred to as "NOW"). Changes from baseline in the morning NOW nasal congestion/stuffiness score and morning NOW TNSS were used as indicators of 24-hour efficacy after dosing.

day 2, the decrease in morning NOW nasal congestion/stuffiness score was already significantly greater with mometasone furoate nasal spray 200 µg once daily than with placebo and continued to be greater on each day thereafter ($P < .001$).

The decrease from baseline in morning NOW TNSS averaged over days 2 through 15 was also significantly greater with the active drug than with placebo nasal spray ($P < .001$).

Mometasone furoate nasal spray was well tolerated, with similar rates of adverse events in the treatment and placebo spray groups. The investigators concluded that mometasone furoate nasal spray 200 µg administered once daily was superior to placebo in improving the severity of nasal congestion/stuffiness and of TNSS, and was still effective 24 hours after dosing in patients with moderate-to-severe seasonal AR. ■



Almost half of patients with AR say that they experience the most severe symptoms during the day. —Mark Dykewicz, MD

gle-blind phase 2. Each of the 5 trials followed a similar protocol, patient characteristics, and comparable nasal congestion and overall total nasal symptom scores (TNSSs).

All patients scored nasal symptom severity once in the morning and 12 hours later. At each evaluation, they

Impact on Nasal Congestion, Stuffiness

The decrease from baseline in morning NOW nasal congestion/stuffiness score averaged over days 2 through 15 was significantly greater with mometasone furoate nasal spray 200 µg once daily than with placebo ($P < .001$). On

Immunotherapy

Significant Advances in the Treatment of Seasonal Allergies

Annual Literature Review

Some of the year's most significant scientific research was reviewed by Harold S. Nelson, MD, Professor of Medicine at National Jewish Health, Denver, CO. The studies showed considerable advances in subcutaneous immunotherapy, allergen extract application by patch, and the mechanisms of subcutaneous and sublingual immunotherapy (SLIT), to name a few.

Good Safety Profile for Subcutaneous Immunotherapy

Year-1 outcomes of the ACAAI/American Academy of Allergy, Asthma & Immunology collaborative study examining systemic reactions to subcutaneous immunotherapy were generally positive.¹

Physician members of the 2 organizations were asked to complete a web-based survey reporting the number of injections administered in their practices, the number of injections or skin tests associated with fatal reactions, and all severe but nonfatal systemic reactions. They were also asked to record fatal reactions in their clinical practices in the preceding 12 months.

Of 1922 prescribers of immunotherapy, 806 physicians responded. "So

there was about 50% reporting," Dr Nelson said. No fatal reactions were reported with this therapy; 6 previously unreported fatalities from 2001 to 2007 were reported, but none had occurred during the preceding 12



Of the 8052 systemic reactions [to subcutaneous immunotherapy] reported..., only 265 were severe or life-threatening reactions. "This represented an incidence of only 3 for every 100,000 injections."

—Harold S. Nelson, MD

months. Of the 8052 systemic reactions reported (0.1% of visits), only 265 were severe or life-threatening reactions. "This represented an incidence of only 3 for every 100,000 injections," he said.

Grass Allergy Immunotherapy Tablet Shows Cost-Effective Persistent Improvement

A study of the long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with a standardized grass allergy immunotherapy

tablet suggests a cost-effective persistence of effect after 3 years.²

A group of 257 grass-sensitive adults received daily treatment with sublingual grass pollen tablets for 3 years. After completing treatment, they were

followed through a grass pollen season. In the year after treatment was discontinued, sustained reduction was seen in symptom scores (26%), medication scores (29%), Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ; 23%), and percentage of symptom- and medication-free days (27%). The researchers noted that there was persisting improvement in symptom and medication scores, RQLQ, and symptom-free and medication-free days for the first year without treatment after 3 years of high-dose SLIT.

Sublingual Immunotherapy Efficacy

David Skoner and colleagues reported on a study in which they randomized 115 subjects with ragweed rhinoconjunctivitis to a 1-day updosing and daily maintenance SLIT with placebo, medium-dose, or high-dose ragweed extract.³ The researchers concluded that SLIT employing US-standardized short ragweed extracts at cumulative doses 10 and 100 times those given subcutaneously can reduce symptom/medication scores in patients with ragweed rhinoconjunctivitis.

Epicutaneous Allergen Administration

A double-blind study of epicutaneous (patch) allergen administration as a novel method of allergen-specific immunotherapy was conducted in 37 grass-sensitive adults in Zurich, Switzerland.⁴ Before and during the 2006 grass pollen season, patients had 13 weekly patches applied to tape-stripped sites (2 in clinic and 11 by patient). The patches remained on the patients' skin for 48 hours, and clinical response was assessed for the grass pollen seasons of 2006 and 2007, without further treatment.

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Is SLIT Coming Soon to the United States?

Some US Allergists Use It Off-Label for Allergic Rhinitis, Most Await FDA Approval

By Richard Hyer

Will sublingual immunotherapy (SLIT) ever come to the United States? Very probably, said Ira Finegold, MD, Chief of Allergy, St Luke's-Roosevelt Hospital Center, and Clinical Professor of Medicine at Columbia University, NY.

"Since we are really on the cusp of a sublingual tablet being approved by the FDA [US Food and Drug Administration]...we have to start thinking about the issues for the practice of sublingual therapy," Dr Finegold said.

Dr Finegold reminded the audience that immunotherapy is not new; the first paper on it was published in 1911. Nor is it alien to the United States. "To some extent, it's already here," he said. Low-dose immunotherapy has been around since the 1930s, but there are still no good studies showing efficacy.

According to a recent study (Amar SM, et al. *J Allergy Clin Immunol.* 2009; 124:150-156), 5.9% of US allergists are using SLIT but almost 62% said that they were holding off till FDA approval; commercially available extracts are used off-label 80% of the time, and 66% charge the patient directly. A 2010 poll conducted by the Joint Council of Allergy, Asthma and Immunology echoed these findings, showing very similar percentages.

Another barrier is lack of insurance reimbursement, and "cost-effectiveness cannot be assessed until you know what the effective dose is," Dr Finegold said.

Risk factors for SLIT have not been established either. Based on ongoing studies, certain trends with SLIT are emerging that can be applied to clinical practice, such as:

- SLIT can be used in children with allergic rhinoconjunctivitis and seasonal asthma, especially if they are monosensitive, for a duration of no less than 3 years
- The earlier the treatment, the better the outcome
- Long-term (ie, 3 years of treatment) use appears to result in clinical improvement and accompanying sustained immunologic changes 1 year posttreatment
- SLIT can have a disease-modifying effect.

Based on the evidence, Dr Finegold said, "after 3 years' treatment, the improvement is there for at least 1 year."

Practical Implications

A minority of studies have not demonstrated efficacy for SLIT, and SLIT's safety record is not perfect. "There is no doubt that SLIT is safer than SCIT [subcutaneous immunotherapy]," Dr Finegold said. "There have been no reported fatalities with SLIT, nor in the last 2 years with SCIT, although severe systemic reactions can occur."

Therefore, "It would seem prudent to initiate therapy in a physician's office," he said, but the prescribing physician must be knowledgeable in the prevention and treatment of anaphylaxis, and patients should carry an epinephrine self-injector.

"Although I can't speak for the FDA, and further, the FDA approves a drug based on efficacy and safety, they do not tell us how to practice medicine. So at this point, we have to start thinking about the issues for the practice of sublingual therapy," Dr Finegold said.

"There are unanswered questions, and actually, I think the role of allergy



"We are really on the cusp of a sublingual tablet being approved by the FDA."

—Ira Finegold, MD

societies is to start now, and start formulating what, if the FDA approves a tablet, are going to be our recommendations, so that our members can safely and adequately treat their patients," he said. "In the United States, 5.9% of allergists are doing it now....With an approval of the product, this will greatly increase. In Europe, 45% are doing it."

US-Based Evidence Lacking

In another session on SLIT, Harold S. Nelson, MD, said that SLIT is effective in pollen-induced seasonal allergic rhinitis using American extracts, although efficacy and dosing must be determined separately for each allergen. More studies are needed, he said, to determine the efficacy of simultaneous administration of multiple allergens. "There's almost no evidence that has been generated in the United

States," he said. "In fact, there are 3 articles" using American extracts.

The first study (led by David Skoner; see page S71), showed reductions in symptom and medication scores in 22% and 26% of patients, respectively, although neither reached significance. "This study suggests that sublingual immunotherapy employing US standardized short ragweed extract as an oral drop preparation at cumulative doses 10 and 100 times those given subcutaneously can reduce symptom/medication scores in patients with ragweed rhinoconjunctivitis," Dr Nelson said.

The second study, led by Dr Nelson, involved 1-year use of grass allergen immunotherapy tablets versus placebo, and 16 weeks of SLIT. The mean reduction was "18% for symptoms, 26% for medication," he said, adding that the 2 studies demonstrate "sublingual immunotherapy employing a timothy pollen tablet...can significantly reduce symptom/medication scores in adults and children with grass-induced rhinoconjunctivitis by 20% and 26%."

The third study compared SLIT with grass pollen extract in monotherapy versus combination therapy with a multiallergen extract (Amar SM, et al. *J Allergy Clin Immunol.* 2009;124:150-156). "Most of the people in the United States are sensitized clinically to multiple aero allergies. So this study was designed to address the question, do multiple allergens work?" he said.

Because of the study's small size (N = 56), no significant differences were seen between the 2 active treatment groups—SLIT with timothy pollen extract alone and SLIT with timothy pollen extract plus 9 other pollen extracts. ■

Significant Advances in the Treatment of... *Continued from page S71*

The application of the patches significantly increased allergen tolerance on nasal provocation after the 2006 and 2007 grass pollen seasons. The application also resulted in significantly improved symptoms of allergic rhinitis, compared with placebo, for both seasons.

Patches in a Pediatric Population

A study of grass transcutaneous immunotherapy in children with seasonal rhinoconjunctivitis also had a positive outcome. In this study, 15 children received grass transcutaneous immunotherapy, as well as placebo patches, from February to April.⁵ The patches contained grass pollen extract with

11.25 µg of major allergen, 50% petroleum jelly, and <3% salicylic acid. They were applied once weekly for 12 weeks and were removed after 24 hours.

The patches were well tolerated and reduced symptoms and medication use during the grass pollen season.

Initial High Cost May Lower Overall Cost of Therapy

Pretreatment with omalizumab affected the tolerability of specific immunotherapy in allergic asthma in a study of 248 patients reported by Massanari and colleagues.⁶ These findings would seem to indicate that increasing initial cost yields a clinically meaningful outcome.

The group of 248 patients with at least moderate persistent, allergic asthma were randomized to omalizumab or to placebo for 3 months, followed by cluster immunotherapy with cat, dog, or mite extracts (8 visits over 4 weeks). Maintenance therapy was continued for 2 months without further omalizumab.

Patients who were pretreated with omalizumab had significantly reduced systemic allergic reactions from immunotherapy, resulting in a clinically meaningful shift in the severity of systemic allergic reactions from immunotherapy. A significantly higher proportion of omalizumab patients were able to reach the target maintenance dose of

immunotherapy, and overall, omalizumab was well tolerated.—RH ■

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Novel Approaches to Immunotherapy: Immunomodulation

SLIT Is Not the End of Pharmacotherapy for Allergies

By Richard Hyer

For anyone who fears that sublingual immunotherapy (SLIT) will be the final frontier of immunotherapy, Thomas Casale, MD, Chief of Allergy, Creighton University, Omaha, NE, says, think again. A number of other exciting novel agents are in development.

"Yes, SLIT will be in the US," Dr Casale said during a symposium at ACAAI 2010. "But some of these molecules will change what we all do in immunotherapy, and it will be important for us to keep up with the immunology of allergic response, so we can understand and be the experts in using these and managing adverse events."

The 4 broad categories of the novel immunotherapy approaches include adding omalizumab, toll-like receptor (TLR) agonists, and chemical and molecular modifications.

The goal of immunomodulation is to reduce or stop the pathologic immune response rather than return the patient to the immunologically naïve or unresponsive state, he said. "The only immunomodulator that we currently have is immunotherapy," he said, "which has been shown to meet these criteria." Subcutaneous immunotherapy (SCIT) has come under fire, because of its serious potential for adverse events.

Adding Omalizumab

A number of studies show that pretreatment with omalizumab adds efficacy and safety to SCIT and allows more patients to reach maintenance. However, questions remain, including the length of time needed to treat, and whether omalizumab can be safely stopped after reaching maintenance immunotherapy.

TLR-4 Agonists

There are probably a total of 13 TLR ligands in humans, 11 of which have already been identified, he said. The monophosphoryl lipid (MPL) A TLR-4 agonist has been around since the 1970s, and is used in Europe in an ultrashort-course vaccine for seasonal allergic rhinitis (AR), grass, tree, or ragweed, although "at the time, nobody knew that MPL was actually a TLR-4 receptor agonist," Dr Casale said.

A number of studies have shown that 4 preseasonal injections of this will reduce symptoms and medication use, elevate antigen-specific immunoglobulin (Ig)G, and blunt the seasonal elevation of IgE.

In a 2010 study by Pfaar and colleagues, after 10-week SLIT and MPL A



"Ultimately, what we want to do is provide better therapeutic options with decreased symptoms, improved quality of life, and immunomodulation, where you could prevent or alter the disease course."

—Thomas Casale, MD

TLR-4 agonist treatment, patients who received the highest doses of MPL had more than a 2-fold better inhibition of nasal allergen challenge responses. "So, we'll have to see if even using SLIT with MPL or a toll-4 receptor agonist might be a way to go in the future," Dr Casale said.

CpG Molecules: TLR-9 Agonists

CpG molecules, the TLR-9 agonists, were also celebrated in the past. One in particular (Tolamba) seemed promising, but a clinical studies problem led to its discontinuation. Cytos Pharmaceuticals has recently tried a new paradigm.

"Cytos took a CpG molecule and put it in a virus-like particle. This is injected and transported to the lymph node, where the protein shell is degraded, and the CpG molecule is released, with activation of toll-9 receptors," Dr Casale said.

A 2010 study showed that the combination of this molecule with the house dust mite led to "a nice improvement," Dr Casale said. "But the interesting thing to me is that after stopping treatment at 10 weeks, you had a sustained effect for 48 weeks."

Just using the CpG molecule and the virus-like particle in patients with asthma brought a 50% reduction in symptoms after 4 weeks. There was also a continuous improvement in symptom scores, even though the patients were no longer taking corticosteroids. After the corticosteroids were halved and

then cut, patients using this molecule maintained their forced expiratory volume in 1 second.

This molecule improved objective and patient-reported outcomes in AR and asthma, he said. It may also have steroid-sparing and anti-inflammatory effects, and two thirds of patients had well-controlled asthma even after steroid discontinuation. This agent acts through an allergen-independent mechanism and not through an adjuvant effect. Treatment was safe and well tolerated.

TLR-8 Agonists

"If you want to inhibit allergic responses, what you want to do is to generate a cytokine profile that will do that more efficiently," Dr Casale said. "And that really occurs with TLR-8 agonists."

A first-in-man study of 4 administrations of TLR-8 receptor agonists, given once weekly, used intranasal active treatment, after which patients were placed in a grass allergen chamber for 6 hours. Total nasal symptom scores were significantly improved; total ocular symptom scores improved almost significantly; and rhinometry trended toward improvement, as well. "So, another approach is using weekly intranasal TLR-8 agonists," Dr Casale said.

Depigoids

Dr Casale then discussed ways to use allergen immunotherapy by changing the molecule slightly to make either recombinant allergens or peptide allergens. One example is depigoids, a depigmentation and polymerization of allergen into a pure allergoid or polymerized allergen. The 2010 Depigoid birch study measured the effect of Depigoid treatment in patients allergic to birch pollen immunotherapy. As the

pollen count went up, the increase was blunted in patients treated with Depigoid.

"So, a different way of doing the immunotherapy, a little less onerous," Dr Casale said.

Recombinant Peptides

Several recombinant peptides are in development, said Dr Casale. Because there are no B-cell epitopes in the peptides, there is no need to dose-escalate. This should result in a safer product that is broadly applicable across a range of allergies.

A recent study compared the cat antigen ToleroMune single injection with house dust mite weekly injection, birch whole allergen, or grass sublingual. At the end of 4 days of challenge to cat allergen in an environmental exposure chamber, patients had a marked reduction in rhinitis symptoms, suggesting that with increasing antigen load, they had improved efficacy.

"It appears that peptides manufactured synthetically allow for better dose standardization," Dr Casale said. "You don't need dose escalation; you have a room-temperature stable formulation. The safety profile looks good. A short course of immunotherapy over 3 months is what they would recommend; and they've shown you actually have clinical efficacy with 4 administrations," he said.

"Ultimately, what we want to do is provide better therapeutic options with decreased symptoms, improved quality of life, and immunomodulation, where you could prevent or alter the disease course. And of course you want to do this where it's cost-effective, and that's been a problem with monoclonal antibodies."

He concluded, "I think the future is getting closer and closer." ■

Systemic Bioavailability... *Continued from page S70*

(17-BMP). This study was therefore designed to investigate the systemic bioavailability of 17-BMP after intranasal administration of BDP compared with that of orally inhaled BDP.

"We are comparing an already safe product, QVAR, with this new product," said study investigator Sudeesh K. Tantry, PhD, of Teva Branded Pharmaceutical Products R&D, Horsham, PA. "One [QVAR] is taken through the oral route, the other is taken through the nasal route."

In this single-center, randomized,

open-label, 3-period crossover study, 30 persons were randomized to receive single doses of intranasally administered BDP-HFA (80 µg and 320 µg) and orally administered BDP-HFA (320 µg) in a 3-way crossover design according to the randomization sequence.

Results of the analysis support the hypothesis that systemic exposure of intranasally administered BDP is markedly lower than that of orally inhaled BDP, according to the researchers. ■

The Scope of Seasonal Allergic Rhinitis in the United States

An Underappreciated, Common Condition with Serious Implications

An interview with Eli O. Meltzer, MD

Clinical Professor of Pediatrics, University of California, San Diego; Co-Director, Allergy & Asthma Medical Group and Research Center, San Diego

Dr Meltzer is a founder of the Allergy/Immunology Fellowship Training Program at the University of California, San Diego, and for nearly 25 years has also been part of the faculty for allergy/immunology fellows at the Scripps Clinic and Research Foundation in San Diego. He is also past Chief of the Division of Allergy and Immunology at Children's Hospital, San Diego. In an interview with *American Health & Drug Benefits*, Dr Meltzer discussed the place of intranasal corticosteroids in the treatment of allergic rhinitis (AR) and the state of research, as well as new information on this condition, presented last November at ACAAI 2010.



The true US prevalence is probably around 20%, which means that 50 million to 60 million people in the United States have rhinitis. It is a very common and underappreciated condition....We need to recognize that this is an illness. We need to identify all patients and offer appropriate intervention.

What is the true prevalence of seasonal allergic rhinitis in the United States?

The true prevalence of seasonal AR was brought into sharp focus by the publication of the Allergies in America study in 2006 and the subsequent publication of Pediatric Allergies in America in 2007. These studies documented that 14% of the US population has AR—an enormous number, which nevertheless likely underestimates the scope of the problem.

We believe that this condition is underreported, because many people self-diagnose or self-treat AR. So the true US prevalence is probably around 20%, which means that 50 million to 60 million people in the United States have rhinitis. It is a very common and underappreciated condition.

What are the common symptoms and how serious are they?

The standard 4 symptoms are familiar—nasal itch, sneezing, rhinorrhea (ie, nasal discharge either forward or backward), and nasal congestion. These 4 symptoms vary in each patient, but the most common is nasal congestion. And according to the 2006 Allergies in America survey, congestion is also the most bothersome symptom.

Not only is nasal congestion burdensome by itself, it also leads to comorbidities, including:

- It provokes and predisposes to middle-ear problems, because of congestion in the back of the Eustachian tube
- It leads to sinus problems, because of congestion of the openings of the sinus drainage areas
- It leads to more asthma cases; approx-

imately 33% to 40% of people who have nasal allergies have asthma.

Overall, if a patient's nose is not functioning well, that person mouth-breathes and ends up breathing more irritant and allergies into the lower airways. The inflammation from nasal allergies causes a reflex problem in the lower airways, and inflammation in the nasal passages becomes systemic. That is, allergies are not a local problem but a systemic condition, affecting other parts of the body. The nose affects the eyes and the chest, hence the typical comorbidities associated with this illness.

AR is not just an acute cold or toothache; it is something that goes on for weeks and months, and often years. It can affect people at work; it can affect kids' school learning and patients' social relationships. So this is an underserved population that is either underrecognized or inadequately cared for.

This sounds like a cascade of problems, which may make it difficult to quantify?

In addition to having problems with the symptoms, and in addition to the comorbidities, there is a clear impact on what we call quality of life. There

are now very good measures of quality of life. One is the Rhinoconjunctivitis Quality of Life Questionnaire, which has 28 questions in 7 domains, including sleep, which serves as an instrument to quantify physical, social, emotional, and mental disabilities.

From allergy surveys we know that at least 40% of the people with nasal allergies have sleep issues compared with about 4% to 7% of the general population—trouble falling asleep, staying asleep, or waking up refreshed are common in AR, because patients do not breathe comfortably.

This results in excessive fatigue, which also affects work productivity, contributing to absenteeism and presenteeism; these have been found more common in this patient population. Patients with AR are generally compromised in their attention, cognitive skills, or the ability to be productive. It also can inhibit social relationships and physical activities, so quality of life is truly compromised.

You paint an alarming picture. Has the medical community underestimated this problem?

I believe the underestimated issue is the disease we call allergic rhinitis. I like the word disease, which stands for dis-ease. Patients with rhinitis are not in the hospital, their life is not at risk usually, but they are certainly not feeling very well. We've all had a cold or a toothache, and we know that such things can truly interfere with our well-being on all those domains mentioned before—physical, social, emotional, and mental.

And having AR affects all these aspects of well-being on a persistent basis. It is not just an acute cold or toothache; it is something that goes on for weeks and months, and often years. It can affect people at work; it can affect kids' school learning and patients' social relationships. So this is an underserved population that is either underrecognized or inadequately cared for.

Has the therapeutic landscape changed during your medical practice?

Yes, medications have become a lot better than years ago. I have been in medical care now for 40 years, and the changes that have occurred in therapies over this period are impressive.

There are now 8 intranasal corticosteroids available to treat seasonal AR:

- Beclomethasone is one of the oldest, and we do not use it very much today, because it is associated with growth problems in children
- Flunisolide is associated with burning, because of the excipients
- Fluticasone propionate (formerly Flonase) is now available in generic formulations
- Budesonide (Rhinocort)
- Triamcinolone (Nasacort)
- Mometasone (Nasonex)
- Fluticasone furoate (Veramyst)
- Ciclesonide (Omnaris) is the most recently developed therapy.

None of these 8 medications existed when I started practicing medicine, and that is only one class of drugs now available for patients with rhinitis.

What advice do you have for providers and for payers?

We need to recognize that this is an illness. We need to identify all patients and offer appropriate intervention. Medications for AR have improved considerably and more are still in development. As providers, we need to monitor the patients to make sure each patient is adequately managed and the condition is improving. And we know there is individual variability; certain treatment modalities and certain medications are more appropriate for some patients than for others, and vice versa. We need to have a treatment plan for the individual patient, and this should be properly managed by the provider and the health insurance company. ■

Allergic Rhinitis and Asthma: Major Cost and Clinical Burdens for Health Plans

By Gary M. Owens, MD

President, Gary Owens Associates, a healthcare consulting company

Allergic rhinitis (AR) and asthma represent significant issues for all health plans. According to the American Academy of Allergy, Asthma & Immunology, the statistics for asthma are astounding¹:

- Approximately 34.1 million Americans have been diagnosed with asthma during their lifetimes
- Between 1980 and 1994, the prevalence of asthma increased by 75%, according to the Centers for Disease Control and Prevention (CDC)
- The latest data from the CDC indicate that the prevalence rate of asthma in the United States is 8.4%
- Asthma rates in children younger than age 5 years have increased by more than 160% from 1980 to 1994
- Asthma accounts for 217,000 emergency department visits and 10.5 million physician office visits annually
- Asthma results in approximately 500,000 hospitalizations annually
- The annual cost of asthma to US healthcare is \$19.7 billion, with direct costs comprising \$14.7 billion of that total, and indirect costs, such as lost productivity, comprising \$5 billion
- Prescription drug spending, at more than \$6 billion, represents the largest single direct medical expenditure related to asthma.

The cost of treating AR almost doubled between 2000 and 2005—from \$6.1 billion to \$11.2 billion. These are numbers that no health plan manager can afford to ignore.

However, compared with asthma, the number of patients with AR and the associated costs of this condition are even more staggering²:

- AR affects between 10% and 30% of all US adults, and up to 40% of children
- AR is estimated to affect approximately 60 million persons in the United States, and its prevalence continues to increase
- AR was the cause of more than 12 million physician office visits in 2006

- The cost of treating AR almost doubled between 2000 and 2005—from \$6.1 billion to \$11.2 billion (in 2005 dollars). More than half of that amount was spent on prescription medications.

Simply stated, these are numbers that no health plan manager can afford to ignore. During the past decade, plans have attempted to improve the clinical outcomes of AR and asthma and manage the costs associated with these conditions by improving a variety of approaches, including population health management, compliance management, prescription drug step therapy, and case management, to name a few.

The Clinical and Economic Challenges

In this supplement, which highlights findings from the 2010 American College of Allergy, Asthma & Immunology annual meeting, we learn that clinicians are equally challenged by the magnitude of the clinical burden of AR and asthma, and their associated costs. Richard Stanford, PharmD, reported the results of a retrospective observational study of patients admitted to the hospital or emergency department. In that study, we learn that the average cost for a patient with asthma who visits the emergency department is \$400 and that the cost of an admission is nearly \$6000.

Even more alarming is that for patients with asthma who get admitted to the intensive care unit for intubation, the cost soars to \$28,000. Couple this with the findings of the Asthma Insight and Management (AIM) survey discussed in this supplement, which show that 8% of the general adult population meets criteria for current asthma, and that 71% of the patients in the AIM survey met National Asthma Education and Prevention Program criteria for being not well controlled, and the implications for health plans become obvious.

According to William E. Berger, MD, allergic disease affects more than 50 million Americans, and 40% of US children suffer from AR, resulting in 2 million lost school days. Dr Berger further notes the enormous economic impact of AR, which is estimated at \$6.3 billion annually in



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direct medical cost and \$7.9 billion in indirect costs annually.

New Directions

Dr Berger cites the lost productivity associated with AR to be approximately \$3 billion annually. He focuses on what is best for the allergic patient, highlighting the considerable clinical burden of AR, which is often underestimated and even trivialized by providers and health plans, although the impact on quality of life can be severe, based on his experience with patients with AR.

However, we also learn that there are new treatments and new directions for the management of allergic diseases. Such treatments as sublingual immunotherapy, patch allergen immunotherapy, and even oral immunotherapy may offer improvements in treatment for selected individuals.

In addition, pharmacotherapy of

allergic diseases is advancing, with the investigation of the use of toll-like receptor (TLR)-4 agonists, TLR-9 agonists, and depigoids (recombinant peptide allergen), to name a few. Any of these agents may have the potential to improve AR and asthma outcomes, but at a cost that is yet to be determined.

Payers' Challenges

In the meantime, health plans will continue to be challenged to find more effective ways to manage these populations. One area on which to focus appears to be medication adherence. According to data from the AIM survey, only 48% of asthma patients reported that they are adherent. With more than half of the population reporting that they are nonadherent, clinicians and health plans have an ongoing challenge to find ways to better engage these patients. Even though the advances in science are likely to make strides in controlling allergies and asthma, they will not be effective on a population basis unless we find better methods of patient engagement. The conclusion reached by Michael S. Blaiss, MD, when speaking about the AIM survey is most alarming: "So the bottom line is, over the last 10 years there's been no improvement in asthma control in the United States."

With the cost of healthcare continuing to rise, and access and affordability issues still looming for many Americans, all healthcare stakeholders involved in the management of AR and asthma need to find better solutions to the many problems associated with chronic allergies.

New technology and scientific advances in the absence of improved strategies to engage these populations in improved adherence and self-management of their conditions will not be enough to change the outcomes. We simply cannot afford another decade of no improvement in allergy-related disease control. ■

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