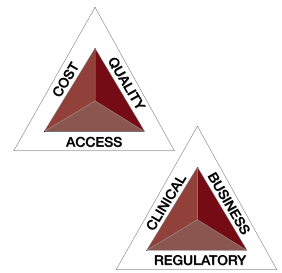


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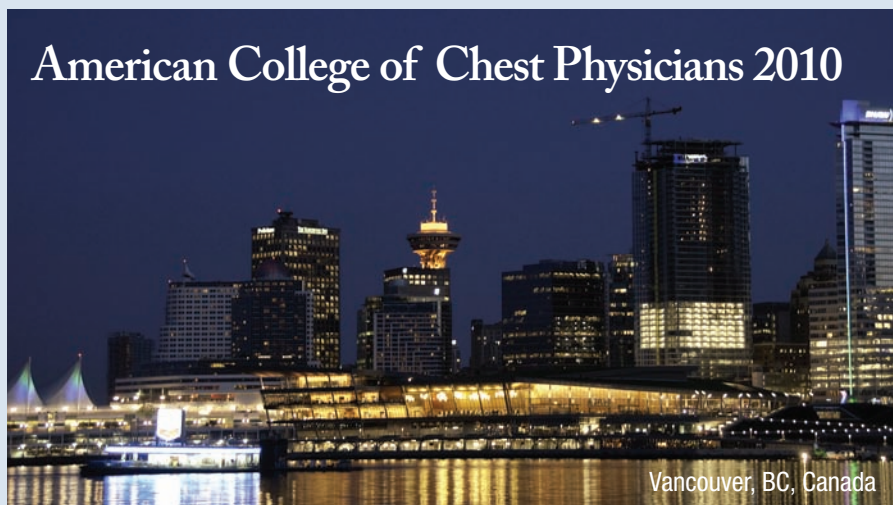
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ACCP 2010: Payers' Perspectives

INTRODUCTION

Chest 2010 Explores State-of-the-Art Management of COPD and Treatments on the Horizon

By Wayne Kuznar



According to the latest report released in December 2010 from the Center for National Health Statistics at the US Centers for Disease Control and Prevention,

chronic lower respiratory diseases, which include chronic obstructive pulmonary disease (COPD), have replaced stroke as the third leading cause of death in the United States.^{1,2}

Continued on page S2

Emerging Drugs for COPD Target Lung Function, Inflammation, Smooth-Muscle Cells in Airways

By Wayne Kuznar

Pharmacologic approaches to the treatment of chronic obstructive pulmonary disease (COPD) are evolving rapidly. Thinking outside of the current comfort zone will be required if treatment of COPD is to be improved, said respiratory experts during a symposium sponsored by Forest Laboratories at Chest 2010.

Current pharmacotherapies do not

change the natural history of COPD, and many patients remain symptomatic despite the available therapies, said Nicola Hanania, MD, MS, Director of the Asthma Clinical Research Center, Baylor College of Medicine, Houston, TX. Furthermore, inadequate adherence to inhaled therapy is a major cause of poor clinical outcomes in the treatment of COPD, he added.

Continued on page S8

Patients with COPD and Their Caregivers Are Satisfied with Nebulizer Therapy

By Wayne Kuznar

Nebulizer therapy for chronic obstructive pulmonary disease (COPD) receives high marks from patients and their caregivers, according to the results of 2 separate surveys presented at Chest 2010.

Inhalation therapy is a cornerstone of the treatment of COPD, because it is a targeted mode of delivery, produces high local concentrations of the active drug, and lessens systemic exposure. Several devices for inhalation therapy are available, including

metered-dose inhalers, dry powder inhalers, and nebulizers.

Caregivers Acknowledge Benefits of Nebulization

In the first survey, 400 caregivers of patients with COPD who are currently using nebulized therapy were interviewed over the telephone. "The majority of caregivers recognized the benefits of nebulization therapy and its positive impact on the quality of life of their friend or family member with

Continued on page S5

Total Annual COPD Costs Top \$4000 per Patient

Disease Severity, Exacerbations Increase Economic Burden

By Wayne Kuznar

The annual cost of maintenance and exacerbation therapy for chronic obstructive pulmonary disease (COPD) exceeds \$4000 per patient in Canada, reported M. Reza Maleki-Yazdi, MD, FRCPC, Division of Respiratory Medicine, Women's College Hospital, University of Toronto, Canada. The cost becomes higher as the number of exacerbations increases and as COPD severity increases.

"There are substantial cost, exacerbation frequency, and impairment in quality of life in all stages of COPD," Dr Maleki-Yazdi said. "The results of this study highlight the importance of early detection of the subjects at risk of COPD exacerbations even in earlier stages of the disease."

This 1-year study included 285 men (59.3%) and women, aged ≥50 years (mean age, 70.4), who had a diagnosis

Continued on page S3

IN THIS ISSUE

HEALTH ECONOMICS

Burden of COPD S3
Treatment complexity affects resource utilization S4

INHALATION SYSTEMS

Selecting inhalation device for COPD S6
Updates on aerosol delivery S7

EMERGING THERAPIES

Investigational anticholinergic .. S9
Novel PDE 4 inhibitor S9
Indacaterol shows promise S10

COPD MANAGEMENT

Systemic effects of COPD and comorbidities S11
Heading off exacerbations is crucial S12
The risk of first acute exacerbation S12

PROVIDERS' PERSPECTIVE

COPD: What's state-of-the-art, what's in the future? S13

PAYERS' PERSPECTIVE

COPD and associated costs ... S14

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Chest 2010 Explores State-of-the-Art Management of COPD... *Continued from cover*

COPD is characterized by progressive airflow limitation that is not fully reversible. Almost 13 million people in the United States were diagnosed with COPD in 2006, but the overall prevalence of COPD in the United States has been estimated at 24 million, indicating substantial underdiagnosis.^{3,4}

As such, better recognition and management of COPD and its exacerbations are required to reduce the clinical and economic burden of this chronic, progressing disease. Current therapies focus almost solely on airway obstruction and consist mainly of bronchodilators.

Despite the efficacy of current pharmacotherapies in controlling symptoms, they do not change the natural history of the disease, and many patients remain symptomatic.

At the 2010 annual meeting of the American College of Chest Physicians (Chest 2010), new and emerging therapies for COPD and state-of-the-art management of the disease were highlighted in more than 20 scientific plenary sessions, symposia, panel discussions, oral abstract sessions, and poster sessions.

Potential future therapies also received special emphasis, given the scope, morbidity, and mortality of COPD.

The State of COPD Therapy

As discussed in this publication, new beta-agonists, anticholinergics, and combination therapies are under development to better address the multifactorial nature of COPD and enhance patient adherence to medication regimens.

New therapies for COPD currently in development and presented in this supplement address other aspects of COPD, such as inflammation, mucociliary dysfunction, and airway scarring and remodeling.

Many of the novel agents being developed are once-daily therapies, an important advance in patient acceptance and adherence.

Delivery Systems Can Affect Treatment Efficacy, Patient Adherence

Several methods of aerosol drug delivery are available, and improvements to their design are improving the efficiency of drug delivery (page S7).

Inefficient delivery of drug to the lungs is a problem with current pressurized metered-dose inhalers (MDIs) and dry powder inhalers, and pressurized MDIs have the added drawback of requiring coordination between their actuation and breath inhalation for optimal efficacy (page S6).

Nebulized therapy (page S7) is making inroads, because nebulizers require no such coordination between actuation and inhalation and can be used effectively in patients with low peak inspiratory flow rates.

The 2 classes in development that may provide unexpected benefits in COPD are phosphodiesterase (PDE) 4 inhibitors and peroxisome proliferator-activated receptor agonists (pages S9-S10).

Importance of COPD Exacerbations

Our understanding of COPD exacerbations is evolving, as new data indicate the serious impact of an acute exacerbation on mortality. More than one third of patients with COPD will die within 4 years of a first acute exacerbation (page S12). In one study reported here, an acute exacerbation was typically preceded by 10 days of worsening symptoms and worsening pulmonary function (page S11).

Preventing exacerbations in COPD is therefore essential for limiting the decline in lung function that can lead to exacerbations (page S12). Long-acting bronchodilators and inhaled corticosteroids have been shown to decrease the rate of exacerbations in COPD.

Theoretically, antibiotics would have a positive impact in this regard, because bacterial infection is an important risk factor in COPD exacer-

bations; preliminary evidence indeed shows that cyclical antibiotics may reduce the risk of exacerbation, as discussed by Dr Hanania (page S13).

A new agent—roflumilast, a PDE 4 inhibitor—is in late-phase development in the United States but is already approved in Europe; in clinical trials, roflumilast reduced the rate of moderate or severe exacerbations of COPD (page S9).

COPD Therapies Must Address an Inflammatory State

Comorbidities are abundant with COPD, and treatments have differential effects on some of the many systemic manifestations of COPD (page S11). The inflammation that characterizes COPD may represent a generalized inflammatory state, and this inflammation may initiate or worsen comorbid conditions.

Some of the diseases that often coexist with COPD are cardiovascular disease (ischemic heart disease, heart failure), skeletal muscle weakness and osteoporosis, depression and anxiety disorders, anemia, and obstructive sleep apnea.

Treatment of COPD inflammation may therefore concomitantly treat systemic inflammation and associated comorbidities. For instance, inhaled corticosteroids appear to decrease the risk of heart attack in patients with COPD. Some therapies that may serve to calm the inflammatory state of COPD are broad-spectrum anti-inflammatory treatments. ■

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Important Resources for COPD

GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines:

www.goldcopd.com

TORCH (Towards a Revolution in COPD Health) study:

www.nejm.org/doi/pdf/10.1056/NEJMoa063070

Total Annual COPD Costs Top \$4000... *Continued from cover*

of COPD for at least 1 year. Mean pack-years of cigarettes smoked was 45.6; mean COPD duration, 8.2 years; and mean postbronchodilator into forced expiratory volume in 1 second (FEV₁), 58% predicted.

The researchers reviewed patient charts and conducted patient surveys to gather information on healthcare resource utilization related to COPD maintenance and exacerbations. In addition, patients completed the EuroQol 5 Dimensions (EQ-5D) questionnaire on enrollment.

The average annual COPD-related cost per patient was \$4147 (Table 1). The annual cost per patient increased with increasing COPD severity—measured by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging criteria—from \$3525 per patient for those with GOLD stage I disease severity to \$6141 per patient for those with GOLD stage IV severity.

The frequency of exacerbations by COPD severity is outlined in Table 2.

A total of 98 patients (34%) had 157 combined exacerbations. “Forty percent of annual COPD-related cost was due to exacerbations, and the percentage of the exacerbation cost contributing to the total cost of COPD increased with disease severity,” the researchers noted.



“There are substantial cost, exacerbation frequency, and impairment in quality of life in all stages of COPD. The results of this study highlight the importance of early detection of the subjects at risk of COPD exacerbations.”

—M. Reza Maleki-Yazdi, MD, FRCPC

The mean cost per exacerbation was \$3035, of which \$2786 was direct costs and \$249 was indirect costs (ie, the cost of patient’s and caregiver’s missed time from work). Treatments for exacerbations included medications and outpatient care, 19 visits to

Table 1 Annual COPD-Related Cost per Patient, by Disease Severity

COPD severity category	Exacerbation-related cost, \$	Maintenance cost, \$	Total cost, \$
GOLD I	698	2041	2739
GOLD II	1354	2171	3525
GOLD III	2414	2984	5398
GOLD IV	2631	3510	6141
All patients	1673	2474	4147

COPD indicates chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 2 Annual Frequency of Exacerbations per Patient, by COPD Severity

Disease severity category	Patients with 1 exacerbation/yr, %	Patients with ≥2 exacerbations/yr, %
GOLD I	11	14
GOLD II	15	14
GOLD III	29	14
GOLD IV	18	46

COPD indicates chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

the emergency department, and 40 hospitalizations.

The mean scores for EQ-5D and the EQ visual analog scale (VAS) were 0.74 and 68.25, respectively. Although the

EQ-5D and EQ VAS scores were associated with COPD-related total costs and maintenance costs, the scores were not correlated with the FEV₁ percent predicted or the exacerbation costs. ■

Burden of COPD on Older Employees Is Substantial

By Wayne Kuznar

Work productivity and quality of life are significantly worse in workers aged ≥65 years with chronic obstructive pulmonary disease (COPD) compared with those without COPD, according to survey data presented at Chest 2010.

Researchers examined the health outcomes of 3358 older employees (aged ≥65 years) using the US 2009 National Health and Wellness Survey, an online cross-sectional survey. Of these employees, 297 self-reported a diagnosis of COPD and 3061 did not.

Outcomes measured included health-related quality of life (QOL), healthcare resource use, and work productivity and activity, measured by absenteeism, presenteeism, overall work loss, and activity impairment.

After adjusting for demographic and health history variables, older workers with COPD had significantly lower scores on the mental component summary measure of health-related QOL

(mean scores: 52.05 for patients with COPD vs 53.37 for those without; range 0-100, with higher scores indicating better health). The physical component score was also lower in patients with COPD (mean: 40.29 for those with COPD vs 47.19 for those without).

Overall work loss and activity impairment were also significantly worse for older workers with COPD than those without the disease (Table).

“These results highlight the substantial burden of COPD in the elderly US workforce, particularly as it

relates to on-the-job productivity, an effect not often documented in the literature,” the researchers observed. The research team was led by Marco daCosta DiBonaventura, PhD, Health

Sciences Practice, Kantar Health, New York City.

Older workers with COPD had higher levels of presenteeism and had more work loss and activity impairment than those without the disease.

Table Impact of COPD on Older Employees (Age ≥65)

Productivity measures (mean)	Employees with COPD, % (N = 297)	Employees without COPD, % (N = 3061)
Presenteeism	12.60	8.71
Work loss	19.26	10.00
Activity impairment	23.93	13.69

COPD indicates chronic obstructive pulmonary disease.

In addition, older workers with COPD had higher levels of presenteeism, defined as the percentage of health-related impairment while at work in the past 7 days.

There were no significant differences in the number of emergency department visits, hospitalizations, or traditional healthcare provider visits between the 2 groups.

“Effective programs and policies may be necessary to better manage COPD in the US workforce, particularly in the elderly population,” the researchers suggested. ■

COPD Treatment Complexity Affects Adherence, Resource Utilization

By Wayne Kuznar

An examination of a large database of employers, health plans, and public organizations revealed that persistence and adherence to therapy are greater and resource utilization and costs are less with the use of single long-acting inhalers compared with multiple long-acting inhalers in the treatment of chronic obstructive pulmonary disease (COPD), according to Andrew P. Yu, PhD, of Analysis Group, a consulting group in Boston, MA.

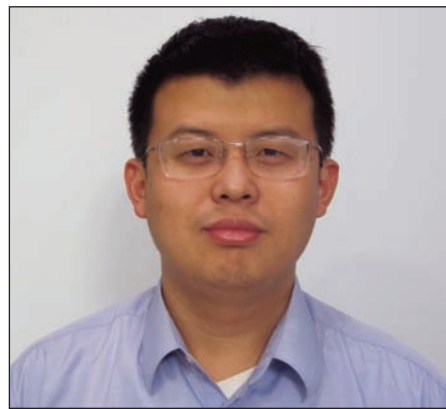
Dr Yu and colleagues examined a commercial medical claims database of 23,494 patients with COPD plus ≥ 2 medical claims. A matched-pair analysis was conducted of patients who used single inhalers versus those who used multiple inhalers. The patients were followed for 12 months.

Treatment discontinuation was defined as an interruption in prescription drug claims that lasted for ≥ 30 days. Adherence to inhaler treatment was estimated based on the proportion of days covered.

Adherence: Multiple versus Single Inhalers

Multiple-inhaler users were less adherent to their medication regimen than users of a single inhaler—79.2% of multiple-inhaler users were not adherent (defined as less than 80% of study medication use) compared with 71.5% of single-inhaler users.

After controlling for potential confounders, the proportion of days covered was 8.6% greater for single-



Andrew P. Yu, PhD

Compared with single-inhaler users, total 12-month costs were \$3319 greater for multiple-inhaler users.

inhaler users, who were 34% more likely to be adherent than the multiple-inhaler users.

Over the 12 months, 86.7% of the multiple-inhaler users discontinued ≥ 1 of their index inhaler medications compared with 78.6% of the single-inhaler users (Table 1). After adjusting for confounders, multiple-inhaler users were 40% more likely to discontinue treatment.

Higher adherence to COPD medication is strongly associated with a lower risk for mortality and hospitalization for COPD exacerbations, Dr Yu noted. The lower adherence to multiple-inhaler use may also be responsible for increased healthcare resource utilization in this group, he said.

Resource Utilization, Cost

Another analysis of the same database showed an increase in the number of healthcare visits for multiple-inhaler users (Table 2), resulting in higher healthcare costs for multiple-inhaler users versus single-inhaler users.

After adjusting for potential confounders, multiple-inhaler users had 64% more inpatient admissions for COPD, 20% more inpatient days, 27% more COPD-related emergency department visits, 10% more urgent care visits, and 6% more outpatient visits compared with single-inhaler users.

Incremental all-cause healthcare costs were higher for the multiple-inhaler users compared with the costs of single-inhaler users. Compared with single-inhaler users, total healthcare costs for the 12 months of the

study were \$3319 greater for multiple-inhaler users; their medical costs were \$1586 higher, and their pharmacy costs were \$1776 higher.

Similarly, incremental costs for COPD-related healthcare costs were higher for multiple-inhaler users. The convenience of a single inhaler could explain the better adherence rate in this group, Dr Yu said.

This study was an observational study; therefore, although the researchers controlled for proxies of disease severity to reduce bias, “multiple-inhaler users may still have had a little more severe disease to begin with, which could have affected exacerbation rates and outcomes,” said Dr Yu. He noted that for now, the most convenient inhaler regimen that controls disease may be the best option. ■

COPD Alliance Aims for Better Recognition and Care of COPD

Launched at Chest 2010, a new COPD Alliance is focusing on a national education campaign to raise the awareness of primary care physicians of chronic obstructive pulmonary disease (COPD) and bring about significant change in the diagnosis and treatment of this progressing, chronic disease.

The COPD Alliance is composed of several national societies—the American College of Chest Physicians, the American Academy of

ed to be \$49.9 billion, which includes \$29.5 billion in direct healthcare expenditures and \$20.4 billion in indirect costs.

The alliance will ask primary care physicians to integrate the routine use of validated screening measures for patients at risk for the development of COPD, to use spirometry to confirm the diagnosis, and to use evidence-based therapy in the management of COPD patients, Dr Carlin said.

The COPD Alliance has launched a website (www.COPD.org) that grants access to free COPD tools; it will serve as an electronic toolkit to support the efforts of healthcare providers, patients, and caregivers. Outreach and promotional strategies will be used to reach members.

In 2011, each society in the alliance will develop and deliver educational strategies specifically tailored to its membership. Clinicians in training will also be targeted, Dr Carlin said, because few training programs offer comprehensive training in COPD management for residents or fellows.

As part of its strategy, the alliance will keep current tools available, such as the COPD Population Screener, the Tobacco Dependence Treatment Toolkit, the GOLD (Global Initiative for Chronic Obstructive Lung Disease) recommendations for diagnosing and treating COPD, and case-based COPD video vignettes.—WK ■

Although only about 50% of the 24 million Americans with COPD have been diagnosed, the total cost of the disease in 2010 is expected to be \$49.9 billion.

Nurse Practitioners, the American Academy of Family Physicians, the American College of Osteopathic Family Physicians, and the American College of Osteopathic Internists (representing about 200,000 primary care and specialty physicians).

The need for the campaign is obvious considering that only about 50% of the 24 million Americans with COPD have been diagnosed. According to Brian W. Carlin, MD, Chair of the COPD Alliance, the total cost of COPD in 2010 is expect-

Treatment discontinuation	Single inhaler, %	Multiple inhalers, %	Adjusted hazard ratio
All patients	78.6	86.7	1.40
Well-controlled patients	76.7	86.1	1.44
Poorly controlled patients	82.1	88.4	1.40

Resource utilization	Single inhaler	Multiple inhalers	Adjusted incidence rate ratio
Inpatient admissions	0.32	0.36	1.15
Inpatient days	2.09	2.43	1.20
Emergency department visits	1.15	1.00	0.93
Urgent care visits	3.24	3.43	1.10
Outpatient visits	43.84	45.57	1.06
Other medical service visits	9.63	10.66	1.12

Expect Widespread Adoption of P4P as Healthcare Spending Increases

By Wayne Kuznar

Although pay-for-performance (P4P) is an intimidating concept for many clinicians, it is rapidly working its way into healthcare delivery, according to speakers at a panel discussion at Chest 2010. P4P relies on the use of evidence-based medicine, which can be defined as “the integration of the best research evidence with clinical expertise and patient values,” said Michael H. Baumann, MD, MS, Chief Quality Officer and Professor of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, University of Mississippi, Jackson.

Performance measures are a hot topic as a result of the projected increase in health expenditures in the United States. Health spending was 16.6% of the gross domestic product (GDP) in 2008, up from 15.3% in 2002, and is projected to be 19.6% of the GDP in 2019. The wide variation between health costs and outcomes has fueled government scrutiny and the adoption of performance measures as a way to improve patient outcomes and quality of care.

The recommendations generated from evidence-based medicine are often turned into performance measures, Dr Baumann said. Performance measures are a tool to evaluate the extent to which the actions of a health-

care provider conform to practice guidelines or standards of quality. It can also be considered a value against which the performance of an individual, group, or hospital can be compared, or benchmarked.

The components of a “good” performance measure, as defined by the National Quality Forum, include scientific acceptability (it produces consistent or credible results when implemented), usability (the intended audience understands the results and can use them for decisions), and feasibility (the data are obtained in normal workflow).

P4P, also known as value-based performance, is based on critical measures by which a physician’s performance is compared with clinical benchmarks. The individual’s performance level then determines his or her reimbursement.

“Pay-for-performance is already out there,” Dr Baumann said. For example, the Centers for Medicare & Medicaid Services (CMS) is running a Premier Hospital Quality Incentive Demonstration (HQID), in which hospitals receive incentive payments based on performance, improvement in performance, and attaining median-level composite quality scores.

Hospitals participating in HQID



“Pay-for-performance is already out there”; it relies on evidence-based medicine, which can be defined as “the integration of the best research evidence with clinical expertise and patient values.”

—Michael H. Baumann, MD, MS

raised their overall quality by an average of 18.3% over 5 years, based on delivery of standardized care measures in 6 clinical areas.

CMS also produces a “Hospital Compare” website—a consumer-oriented website that provides informa-

tion on how well hospitals provided recommended care to patients, Dr Baumann noted.

The challenges for performance measurement include the time lag in adopting data to keep up with new therapies, said Jun Chiong, MD, Director of the Advanced Heart Failure Program and Associate Professor of Medicine, Pharmacology and Outcomes Science, Loma Linda University, CA.

In the case of heart failure and other diseases, correct dosing of an indicated medication is crucial to optimal outcomes, so performance measures should go beyond “just the percentage of patients on a given drug,” Dr Chiong said. He also asked whether hospital stay is a valid performance measure, or if outcomes downstream should be included in a measure.

In ranking hospitals’ performance, being small has an advantage, Dr Chiong said. In a study of performance measures for acute heart attack from more than 3700 US hospitals, large-volume hospitals were found to have better aggregate performance measures (ie, use of beta-blocker treatment) but were less likely to be identified as a top hospital because of the unequal denominators (number of cases). ■

Inhalation Systems

Patients with COPD and Their Caregivers Are Satisfied... *Continued from cover*

COPD,” said lead investigator Amir Sharafkhaneh, MD, PhD, DABSM, Associate Professor of Medicine, Section of Pulmonary, Critical Care, and Sleep Medicine, Baylor College of Medicine, Houston, TX.

Among the caregivers, 92% expressed satisfaction with nebulized treatment, 80% rated a nebulizer as better than using only an inhaler, and 12% reported that using a nebulizer was not different from using an inhaler.

When asked about their views of nebulization therapy, more than 80% of the caregivers agreed that nebulization made it easier to help care for a friend or family member, that the benefits outweigh any difficulties or inconvenience, and that the overall quality of life of their friend or family

member had improved since beginning nebulization.

More than 80% of the patients agreed that the benefits of nebulization outweighed any difficulties or inconvenience. “Clinicians should consider patient-reported benefits and preferences when choosing a system to deliver inhaled medications.”

—Amir Sharafkhaneh, MD, PhD, DABSM

The most positive aspect of nebulization, cited by 65% of the caregivers, was its ability to allow the patient to breathe easier and/or to open up the airways.

Patients Describe Similar Benefits

A similar survey of 400 patients

with COPD who received nebulized therapy yielded nearly identical

results: 80% of them rated nebulized therapy as better than using only an inhaler, and 12% said that they found it no different from an inhaler. The overall patient satisfaction rate with nebulized therapy was 89%.

More than 80% of the patients

agreed that the benefits of nebulization outweighed any difficulties or inconvenience, that nebulization made it easier for their caregivers to help care for them, and that the overall quality of their lives had improved since starting using a nebulizer. Furthermore, 60% of the patients said that they wished they could have started nebulized therapy sooner.

“Overall, these data do not support the current negative perception that nebulization may be too cumbersome for the patient and/or the caregiver,” Dr Sharafkhaneh concluded. “Clinicians should consider patient-reported benefits and preferences when choosing a system to deliver inhaled medications for COPD.” ■

See also pages S6-S7.

Selecting an Inhalation Device for COPD Should Consider Peak Flow Rates, Patient Satisfaction

By Wayne Kuznar

Peak inspiratory flow rate (PIFR) is an important consideration in the selection of an inhalation device in the management of chronic obstructive pulmonary disease (COPD), said Nicola A. Hanania, MD, MS, Director of the Asthma Clinical Research Center, and Associate Professor of Medicine, Section of Pulmonary and Critical Care Medicine, Baylor College of Medicine, Houston, at a symposium sponsored by Sunovion, Inc, held at Chest 2010.

Patients with low PIFR may obtain greater therapeutic benefit from nebulized therapy, because unlike dry powder inhalers, nebulizers have minimal resistance and PIFR requirements for effective use.

“Why should internal resistance and PIFR matter? For the drug to work, it has to be deposited where you want it.”

—Nicola A. Hanania, MD, MS

PIFR is defined as the maximum amount of air that can be inhaled over the course of 1 deep breath, and is measured in L/min. A low PIFR, which is more common in older patients and those with more severe COPD, may result in inadequate drug deposition in the lungs when using dry powder inhalers, thus compromising

drug efficacy, Dr Hanania explained.

“Why should internal resistance and PIFR matter? For the drug to work, it has to be deposited where you want it,” Dr Hanania said.

A low PIFR—defined as <30 L/min—results in greater drug deposition in the mouth and throat than in the lungs. Lung function is another important measure of effective drug delivery, and low PIFR correlates with poorer lung function, he said.

Although metered-dose inhalers (MDIs) also have minimal resistance and PIFR requirements, MDIs require coordination between actuation of the device and the inhalation for effective drug delivery. Patients must inhale with a slow, deep breath and then hold their breath when using an MDI.

“When choosing a delivery system, you want something the patient can accept. You have to choose the right drug and the right delivery system,” Dr Hanania said.

Coordination between device actuation and inspiration is not necessary for a nebulizer, he said, “and a nebulizer is effective with regular tidal breathing; deep breaths are not required.”

As nebulizers have become more portable, they have become more popular with patients. Approximately 25% of patients with COPD use nebulized therapy to manage their disease, according to Dr Hanania.

In a survey of patients with COPD, the advantages of nebulizer therapy

were considered to outweigh any potential disadvantages of nebulizer therapy. The advantages cited were:

- An increased feeling of well-being
- Better symptom control
- Increased confidence
- Greater independence.



“When choosing a delivery system, you want something the patient can

accept. You have to choose the right drug and the right delivery system.”

—Nicola A. Hanania, MD, MS

The GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines recommend intermittent short-acting beta-agonist therapy for patients with mild COPD, stepping up to the addition of ≥ 1 long-acting beta-agonists (LABAs) with moderate or worse disease. The addition of inhaled corticosteroids is recommended for severe or very severe disease.

The 2 LABAs currently available in the nebulized format are arformoterol tartrate (Brovana) and formoterol fumarate (Symbicort).

Formoterol is a racemic mixture of

the (R,R)- and (S,S)-isomers. Arformoterol contains only the (R,R)-isomer and is 1000 times more potent at receptor sites than formoterol, Dr Hanania said.

Arformoterol is approved for the treatment of COPD, to be dosed every 12 hours. In 12-week comparisons with placebo in patients with COPD, the improvement in forced expiratory volume in 1 second (FEV₁) from baseline was significantly greater with arformoterol (15 μ g) compared with placebo at the end of the 12-hour dosing interval. The mean FEV₁ improvement from baseline was also superior with arformoterol versus placebo over the 12-hour dosing interval.

Shortness of breath was also reduced with arformoterol, as measured by the transitional dyspnea index (TDI) score. The mean improvement in TDI was 2.0 units with arformoterol compared with 1.1 units for placebo, Dr Hanania said.

Use of arformoterol was also associated with a reduction in the use of short-acting bronchodilators, he said. Daily rescue albuterol was reduced by 37% from baseline in arformoterol-treated patients compared with a 2% reduction in placebo recipients, and daily use of supplemental ipratropium was also reduced by 37% with arformoterol and by 9% with placebo. The percentage of patients reporting adverse events was similar between arformoterol and placebo. ■

Performance, Preference Vary for COPD Inhalers

In a comparison of 4 inhalers used in the treatment of chronic obstructive pulmonary disease (COPD), patients preferred the Genuair for its perceived ease of use. The Genuair also ranked highest in overall success rate, which was defined as patients' ability to successfully open, prepare, close, and clean the inhaler.

Chris Hass, Usability Consultant, Bentley University Design and Usability Center, Waltham, MA, and colleagues compared the Genuair, Diskus, HandiHaler, and Respimat inhalers in 48 patients (mean age, 63.5 years) who had COPD, chronic bronchitis, or emphysema.

The patients had 1 to 5 years' experience with other inhalers before

being enrolled in the study. Because the study focused on ease of use rather than on efficacy of the medication, no medication was used.

The Genuair inhaler received the highest satisfaction rating by patients in all categories—overall satisfaction, manipulation measures, interface measures, and all measures for inhaler.

During 90-minute sessions, the researchers observed the patients as they assembled and activated the

inhalers. The patients were asked to open the inhaler packaging, prepare a dose, mimic inhalation, close the inhaler, and clean the device. The researchers recorded errors in any of the processes, and between inhaler examinations they interviewed the patients about their inhaler experiences.

Patients also rated individual and overall device attributes on a 1-to-5 scale (worst to best). The ratings focused on key inhaler use steps and satisfaction with the inhalers. Patients then ranked the inhalers in order of overall preference.

The majority of the patients (94%-100%) were able to open all the inhalers. Dose preparation was done successfully by 73% of patients with

HandiHaler, by 69% of patients with Genuair, by 69% of patients with Diskus, and by 23% of patients with Respimat. Successful cleaning was achieved with Genuair, Respimat, and Diskus most of the time (98%-100%) but only 52% of the time with HandiHaler, Mr Hass said.

Success with all inhaler steps was accomplished by 69% of patients with Genuair, by 67% with Diskus, by 35% with HandiHaler, and by 23% with Respimat.

The Genuair inhaler received the highest satisfaction rating in all the categories assessed—overall satisfaction, manipulation measures, interface measures, and all measures for inhaler.—WK ■

New Developments in Aerosol Delivery Aim to Improve Therapeutic Efficacy

By Wayne Kuznar

Almost two thirds of patients and clinicians do not know the proper inhaler technique to get the maximal benefit of drug treatment for chronic obstructive pulmonary disease (COPD). A panel discussion focused on current and future aerosol drug delivery at Chest 2010.

The effectiveness of aerosolized drug delivery depends on the patient, the properties of the propellant and the drug, and the type of inhaler. Inhalers have as many as 17 steps for typical use and some types require synchronization between inspiration of breath and aerosol actuation or a constant breathing pattern, said James Fink, PhD, Adjunct Professor, Georgia State University, Atlanta, and an independent consultant to the biotechnology industry.

Even with perfect inhalation technique, however, deposition of particles can be limited by airway geometry, which is altered by the presence of COPD and other airway diseases.

Inhalers can be classified as pressurized metered-dose inhalers (MDIs), dry powder inhalers, or jet or ultrasonic nebulizers.

The major drawback of conventional pressurized MDIs and dry powder inhalers is inefficient delivery of drug to the lungs; only about 10% to 40% of the drug reaches the lungs.

Several design changes have been made to inhalers to promote more efficient drug delivery, including production of particles within the extra-fine range to target the deep lung, said Myrna B. Dolovich, PEng, Associate Clinical Professor, Division of Respiriology, McMaster University, Canada.

Pressurized Metered-Dose Inhalers

Spacers are now used with many pressurized MDIs to collect large particles that would normally be deposited in the mouth or the back of the throat. Although spacers have little effect on the concentration of drug deposited in the lungs, they reduce the total amount of the drug deposited in the body. (Lung penetration is determined by the size of drug particles in the aerosol; only particles between 1 μm and 5 μm in diameter reach the airway.)

Newer pressurized MDIs have breath-synchronized devices to control inhalation. Actuators have recently been introduced that will improve the efficacy and efficiency of pressurized MDIs by increasing the respirable frac-

tion of drug delivered, which will also serve to reduce side effects.

Ozone-damaging chlorofluorocarbons (CFCs) must be phased out of medical devices per the Montreal Protocol obligations, and are being replaced by hydrofluoroalkaline propellants. The Modulite is a CFC-free MDI with beclomethasone dipropionate as its constituent. Particle size is smaller to achieve greater lung penetration and the aerosol is slower moving compared with CFC pressurized MDIs, to make it easier for patients to coordinate the breath.

The major drawback of conventional pressurized MDIs and dry powder inhalers is inefficient delivery of drug to the lungs; only about 10% to 40% of the drug reaches the lungs.

The Modulite platform was matched to its CFC counterparts on a microgram-for-microgram basis (using salbutamol pressurized MDIs and some corticosteroid pressurized MDIs), so no dosage modification is needed when switching from a CFC to a hydrofluoroalkaline formulation, Professor Dolovich said.

Breath-actuated pressurized MDIs have been developed to overcome the problem of poor coordination between pressurized MDI actuation and inhalation. Higher pulmonary disposition has been achieved with the Maxair Autohaler, a breath-actuated pressurized MDI, in patients who had poor coordination with a conventional CFC pressurized MDI, she said.

In another study, the onset of bronchodilation was similar between formoterol/beclomethasone Modulite and formoterol/budesonide Turbuhaler (another breath-actuated pressurized MDI), and greater than with formoterol alone in patients with COPD, Professor Dolovich stated.

Nebulizers

The use of nebulizer therapy has been increasing. Nebulizers are typically used by patients who have difficulty operating pressurized MDIs or dry powder inhalers, because of poor hand-lung coordination.

Conventional nebulizers continu-

ously release a drug throughout the respiratory cycle, so that as much as two thirds of the drug is wasted during expiration. They allow delivery of individual drug doses over a longer period than can be achieved with pressurized MDIs or dry powder inhalers, but to use a conventional nebulizer most efficiently, patients must be able to adapt to the device and have a regular breathing pattern.

Vibrating mesh nebulizers are a more recent development; they have a higher lung deposition, negligible residual volumes, and a faster rate of nebulization compared with jet nebulizers.

"Position of the nebulizer has been found to influence drug delivery," Professor Dolovich said. In a study of the effect of nebulizer type and position on drug delivery, it was found that placement of the nebulizer before the humidifier increased drug delivery with vibrating mesh nebulizers and jet nebulizers, and that drug delivery with the vibrating mesh nebulizer was more than double that with the jet nebulizer at all positions.

Adaptive aerosol delivery systems have been designed to detect and constantly adapt to a patient's variable breathing patterns. Software-driven monitoring and control systems monitor inspiratory flow and breathing frequency. The technology enables measurement of the volume of drug



"Position of the nebulizer has been found to influence drug delivery."

—Myrna B. Dolovich, PEng

delivered per aerosol pulse, which ensures that the total preprogrammed dose is delivered.

Dry Powder Inhalers

Dry powder inhalers are breath-actuated devices, and therefore do not require patient coordination, which is an advantage over pressurized MDIs. Newer designs for dry powder inhalers incorporate battery-driven impellers and vibrating piezoelectric crystals that reduce the need for patients to generate a high inspiratory flow rate, as with conventional dry powder inhalers.

Drug delivery into the lungs with dry powder inhalers is 10% to 37%; recent improvements in design permit the dose dispensed to be independent of inspiratory flow rate, at 30 L/min to 90 L/min. Variations in the design and performance of dry powder inhalers may make them not readily interchangeable. ■

Dry Powder Inhalers Compared for Correct Use, Ease of Handling: Breezhaler versus HandiHaler

Patients with chronic obstructive pulmonary disease (COPD) prefer the Breezhaler single-dose dry powder inhaler over the HandiHaler for continued daily use. Their preference stems from ease of use and confidence that the medication is taken correctly using the Breezhaler, according to a poster presented by Kenneth R. Chapman, MD, MSc, Director, Asthma & Airway Centre, University Health Network, Toronto Western Hospital, Canada.

"These initial impressions, after a relatively short familiarization peri-

od, may be important to continued successful use, since a patient may be more adherent when using an inhaler that they like and find easy to use," Dr Chapman and colleagues observed.

They studied 82 patients (aged ≥ 40 years) with mild-to-severe COPD and a smoking history of at least 10 pack-years who required treatment with inhaled medication.

Patients were randomized to either the Breezhaler or the HandiHaler with placebo capsules once daily for 7 days in addition to usual treatment,

Continued on page S8

Emerging Drugs for COPD Target Lung Function... *Continued from cover*

“COPD is a systemic disease and a multicomponent disease,” Dr Hanania said. Novel targets of therapy would reduce local and systemic inflammation, and potentially regenerate the lung.

Ultra-Long-Acting Bronchodilators

Bronchodilators remain the cornerstone of treatment and act to control symptoms; long-acting bronchodilators represent an advance over short-acting bronchodilators in improving lung function (as measured by forced expiratory volume in 1 second [FEV₁]), said Mario Cazzola, MD, Professor of Respiratory Medicine, University of Rome Tor Vergata, Italy.

“Since it has been difficult to discover novel classes of bronchodilator drugs, the logical approach has been to improve the existing bronchodilators,” Dr Cazzola said.

A once-daily bronchodilator would further improve compliance over the current long-acting agents. Other criteria for a new bronchodilator would include a fast onset of action and drug delivery through an efficient and convenient device (ie, a breath-actuated device with effective feedback to indicate successful inhalation), Dr Cazzola said. Several ultra-long-



“Since it has been difficult to discover novel classes of bronchodilator drugs, the logical approach has been to improve the existing bronchodilators.”

—Mario Cazzola, MD

acting beta-agonists (LABAs) are currently under development for COPD.

Indacaterol is one candidate as an ultra-LABA. In preclinical models, indacaterol demonstrated a rapid onset of action that correlated with

high intrinsic efficacy and a 24-hour duration of action.

Its 24-hour duration of bronchodilation may be a result of its retention in the raft domain of the lipid membrane, Dr Cazzola explained. Lipid rafts are areas of cell membranes where beta₂-receptors are held together in close contact with signaling molecules and effectors.

In clinical trials of adult patients with COPD, 12 weeks of therapy with indacaterol proved to be superior to tiotropium, formoterol, and to salmeterol in trough FEV₁ levels compared with placebo.

Indacaterol was also superior to its comparators on measures of health-related quality of life, symptoms of breathlessness, and percentage of days without the use of rescue medication, and it was associated with an increase in the time to a first exacerbation during 1 year compared with placebo.

Carmoterol is another ultra-LABA under investigation. After 14 days of treatment, a 4-μg dose of carmoterol increased peak FEV₁ by a mean of approximately 110 mL (placebo-adjusted), compared with an increase of 80 mL with salmeterol.

Yet another investigational agent in this class, *vilanterol trifenate*, produced dose-dependent increases in trough FEV₁ as high as 160 mL compared with placebo.

Olodaterol is not as advanced in its development; in preclinical studies, it demonstrated a fast onset of and a long duration of action, Dr Cazzola said.

Attacking Inflammation

Ideal future options for COPD should address the multiple components of the disease, which include, among others, mucous hypersecretion, mucosal damage, inflammation, and loss of alveolar attachments, according to Dr Hanania. Ideally, new therapies would blunt proinflammatory cells, modify disease progression, be compatible with other therapies, and be simple to administer.

In addition to improved treatment, “we should not forget the delivery system,” Dr Hanania said. More effective anti-inflammatory therapy is needed, he said. Phosphodiesterase (PDE) 4 inhibitors have anti-inflammatory action in COPD, and there is strong scientific rationale for their use in COPD, said Dr Hanania.

Most PDE 4 inhibitors in development are administered systemically, but some inhaled formulations are in the works, he said.

Roflumilast is the oral PDE 4 inhibitor that is furthest along in develop-

ment; it inhibits PDE 4 activity in proinflammatory cells and is approved for use in the European Union but not yet in North America.

Roflumilast has been shown to reduce the rate of moderate-to-severe COPD exacerbations before or during the use of bronchodilator agents. When used in combination with a long-acting bronchodilator or long-acting muscarinic antagonist in patients with moderate-to-severe COPD, it has also demonstrated an improvement in lung function.

Some *inhaled macrolide antibiotics* are currently being investigated for the treatment of COPD, according to Dr Hanania. The macrolide antibiotic *erythromycin* may also act as an anti-inflammatory agent to reduce the number of exacerbations in COPD, and studies with macrolides are ongoing, he said.

Relaxing Smooth Muscles

Long-acting antimuscarinic agents also are in development, some in combination with ultra-long-acting bronchodilators, and combinations of inhaled corticosteroids and ultra-long-acting bronchodilators are being tested clinically, Dr Cazzola said.

Aclidinium bromide is a new muscarinic antagonist in development. A twice-daily inhaled agent delivered via a dry powder inhaler, it is being investigated for maintenance treatment of COPD.

In placebo-controlled studies it provided long-lasting bronchodilation and was associated with improvements in FEV₁ and other measures of lung function. It has a faster rate of onset of the smooth-muscle-relaxing activity than tiotropium bromide, the current muscarinic antagonist on the market.

Targeting Oxidative Stress

Because oxidative stress is known to occur in COPD, agents that target reactive oxygen species—the *superoxide dismutase inhibitors*—hold promise in the treatment of COPD, said Irfan Rahman, MSc, PhD, Associate Professor of Environmental Medicine, Lung Biology and Disease Program, University of Rochester Medical Center, NY.

Antioxidant therapy may affect important outcomes in COPD, such as helping to overcome steroid resistance, mucous hypersecretion, and inflammation. Antioxidants may have a role in combination with anti-inflammatory agents, bronchodilators, and other COPD treatments, Dr Rahman said. ■

Dry Powder Inhalers... *Continued from page S7*

and then were switched to the opposite inhaler.

On day 1, patients read written instructions for use of the inhaler and had 30 minutes to practice. Patients' ability to perform each of the 21 steps required for correct use of the

In this study, the Breezhaler was preferred for ease of opening and closing the cap and mouthpiece, closing the mouthpiece after inserting the capsule, and holding the inhaler during use.

Breezhaler, as well as the 19 steps required for the HandiHaler, were recorded by 2 trained assessors. For each device, 2 steps were deemed essential for correct use. Patients then received training and a demonstration of correct device use. They were assessed again on day 7. After the end of the second treatment

period, they completed a preference questionnaire.

Most patients completed each handling step for both inhalers correctly after 7 days (78%-100% for Breezhaler; 81%-100% for HandiHaler). For most steps, the proportion of patients correctly performing the step improved from day 1 to day 7.

Patient training had a greater effect on use of the HandiHaler than on use of the Breezhaler, Dr Chapman said. For the critical step of fully releasing the button before inhalation, the Breezhaler score was similarly high on both days (93% and 96%, respectively), whereas the HandiHaler score changed 11 points, from 88% on day 1 to 99% on day 7.

Overall, patients preferred the Breezhaler (61%) over the HandiHaler (31%). The Breezhaler was preferred for ease of opening and closing the cap and mouthpiece, closing the mouthpiece after inserting the capsule, and holding the inhaler during use. It was also preferred for simplicity of use and for confidence in successful intake of the medication.—WK ■

Investigational Anticholinergic Achieves Early Bronchodilation

Cholinergic Tone the Main Reversible Factor in Airflow Obstruction

By Wayne Kuznar

Twice-daily treatment with aclidinium, an investigational long-acting muscarinic antagonist in phase 3 development, results in sustained bronchodilation and improvement in lung function in patients with chronic obstructive pulmonary disease (COPD), according to the results of 2 randomized, controlled clinical trials presented at Chest 2010.

Aclidinium Improves COPD Outcomes

The first was a placebo-controlled, double-blind, 12-week study of 561 patients with moderate-to-severe, stable COPD who were randomized to aclidinium, 200 µg or 400 µg twice daily, or placebo. Patients could continue using salbutamol and inhaled, oral, or parenteral corticosteroids (up to 10 mg/day or 20 mg every other day) as needed. A total of 467 patients completed the study.

According to the investigators, led by Edward Kerwin, MD, at the Clinical Research Institute in Medford, OR, “Cholinergic tone is the major

reversible component of airflow obstruction; thus, therapy with anticholinergics can be effective in the treatment of COPD.”

The change from baseline in trough forced expiratory volume in 1 second (FEV₁) at week 12 was 86 mL greater in the patients randomized to aclidinium 200 µg and 124 mL greater in those randomized to aclidinium 400 µg compared with placebo.

The change in peak FEV₁ from baseline to week 12 was 146 mL greater in the aclidinium 200-µg group compared with placebo, and 192 mL greater in the aclidinium 400-µg group compared with placebo.

Both doses of aclidinium were associated with significantly better improvement compared with placebo in scores on the St. George’s Respiratory Questionnaire (a standardized, self-completed questionnaire for measuring impaired health and perceived well-being in airways disease) and in the transitional dyspnea index.

Both doses of aclidinium were well-tolerated. The incidence of treatment-

emergent serious adverse events was 2.2% in the placebo group, 4.3% in the aclidinium 200-µg group, and 3.2% in the aclidinium 400-µg group.

Both doses of aclidinium—200 µg and 400 µg twice daily—were associated with significantly greater improvement compared with placebo. Adverse events were fewer with the higher dose.

Aclidinium Safe and Effective for COPD

In the second randomized, double-blind study, German investigators compared the safety and efficacy of aclidinium 400 µg twice daily with placebo and with tiotropium 18 µg once daily in 30 patients with moderate-to-severe COPD. Patients were treated for 15 days with their assigned

therapy and then crossed over to another therapy, until they completed 15 days in each of the 3 arms, with a washout period of 9 to 15 days between treatments.

The normalized FEV₁ area under the curve for 12 hours immediately after morning dose administration on day 15 was increased significantly with aclidinium or tiotropium compared with placebo. The researchers reported that optimal bronchodilation was achieved as early as the first day of treatment.

The bronchodilatory effect of aclidinium and tiotropium versus placebo was sustained over 24 hours on day 15.

The average use of rescue medications declined significantly from baseline in the aclidinium (−1.48 puffs) and tiotropium (−0.79 puffs) groups compared with those receiving a placebo (−0.53 puffs).

In addition, aclidinium—but not tiotropium—significantly reduced the scores for breathlessness, cough, and nighttime symptoms compared with placebo. ■

Novel PDE 4 Inhibitor Cuts COPD Exacerbations

Anti-Inflammatory Effects Are Crucial in This Disease

Roflumilast, an oral selective phosphodiesterase (PDE) 4 inhibitor reduced the rate of moderate or severe exacerbations compared with placebo in patients with chronic obstructive pulmonary disease (COPD), said Nicola A. Hanania, MD, MS, Director of the Asthma Clinical Research Center, Baylor College of Medicine, Houston, TX.

The effects of roflumilast were more pronounced in patients who had a history of frequent exacerbations and in those with more severe disease, based on a pooled analysis of 2 year-long studies presented at Chest 2010.

“Reduction of the rate of COPD exacerbations may improve overall patient outcomes and result in a reduction of the healthcare burden,” Dr Hanania said.

Because exacerbations are inflammatory events, and PDE 4 may affect multiple inflammatory cells in the lung, a PDE 4 inhibitor could be expected to reduce the number and severity of COPD exacerbations, he said. “Roflumilast targets key proinflammatory

mediators underlying the pathogenesis of COPD and associated exacerbations,” Dr Hanania said. Frequent exacerbations (≥2 annually) occur in up to 50% of patients with COPD, depending on their disease severity.

“Reduction of the rate of COPD exacerbations may improve overall patient outcomes and result in a reduction of the healthcare burden.”

—Nicola A. Hanania, MD, MS

Dr Hanania and colleagues looked at the exacerbation rate and time to exacerbations in 1538 patients with severe COPD and a history of exacerbations who were enrolled in 1 of 2 multicenter, placebo-controlled trials in which they were randomized to roflumilast or placebo for 52 weeks. An exacerbation was defined as new

or worsening COPD symptoms that required oral or parenteral glucocorticoids or hospitalization. The results of these trials showed that:

- The rate of moderate or severe exacerbations was reduced by 17% with roflumilast compared with placebo
- The time to a first or second moderate or severe exacerbation was extended in roflumilast recipients by 11% and 21%, respectively
- The rate of moderate or severe exacerbations in the roflumilast groups declined by 18.7% in patients with severe COPD and by 19.7% in those with very severe COPD
- Among patients with 2 or more exacerbations before enrollment in the study, roflumilast reduced the exacerbation rate by 22% compared with placebo, and in those with fewer than 2 exacerbations before study entry, it reduced the exacerbation rate by 16%
- Some 27.7% of placebo patients experienced ≥2 moderate or severe exacerbations during the study compared with 21.4% of the roflumilast

groups. The benefit of roflumilast on this end point was observed regardless of disease severity, although the effects were more pronounced in patients with a history of frequent exacerbations and in those with more severe disease.

“Roflumilast has minimal bronchodilatory effects; it’s not a bronchodilator,” Dr Hanania said. “We’re not going to see improvements in FEV₁ [forced expiratory volume in 1 second] of 100 mL with roflumilast.” Instead, its benefits can be attributed to its anti-inflammatory activity. As such, he envisions that roflumilast will be used as add-on therapy to long-acting bronchodilators, but it remains to be seen whether it will be used before or after initiation of inhaled corticosteroids as add-on therapy.

Side effects of roflumilast include nausea and other gastrointestinal side effects, as well as weight loss, but none of these have caused withdrawals from clinical studies. The mechanism behind weight loss is still being explored.—WK ■

Roflumilast Improves Lung Function Independent of Inhaled Corticosteroids

Respiratory Experts Embrace Potential New PDE 4 Inhibitor

By Wayne Kuznar

When used concomitantly with inhaled corticosteroids, roflumilast—the phosphodiesterase (PDE) 4 inhibitor currently under review by the US Food and Drug Administration—further improves lung function, reduces the rate of exacerbations, and has an additive therapeutic effect in patients with chronic obstructive pulmonary disease (COPD), said Stephen I. Rennard, MD, Professor of Internal Medicine, Division of Pulmonary, Critical Care, Sleep & Allergy, University of Nebraska, Omaha. He and his colleagues assessed data from 2 trials in the roflumilast development program that allowed for concurrent inhaled corticosteroid use.

Roflumilast Reduces Exacerbations

Of the 2686 patients enrolled in the 2 studies, roflumilast was used with inhaled corticosteroids in 1622 patients. Prebronchodilator forced expiratory volume in 1 second (FEV₁)

was reduced by 19% with roflumilast compared with placebo with concomitant inhaled corticosteroid use, and by 8% without inhaled corticosteroids.

Dr Rennard said that concurrent treatment with inhaled corticosteroids identified patients who had more exacerbations and worse lung function at study entry. These patients also were more responsive to roflumilast, which suggests potential synergy of the 2 medication classes.

Useful Addition to COPD Armamentarium

A separate pooled analysis of 2 placebo-controlled clinical trials of roflumilast in 3091 patients with COPD demonstrated that roflumilast improved lung function in patients with or without use of an inhaled corticosteroid pretreatment, reported Andrew McIvor, MD, MSc, Firestone Institute for Respiratory Health at McMaster University, Canada.

“This analysis looked at patients who



“Our study showed that roflumilast acted as an anti-inflammatory agent, perhaps with a different mode of action.”

—Andrew McIvor, MD, MSc

were pretreated with inhaled steroids,” he said. “Sometimes, when inhaled steroids are withdrawn, you see an increase in the exacerbation rate.”

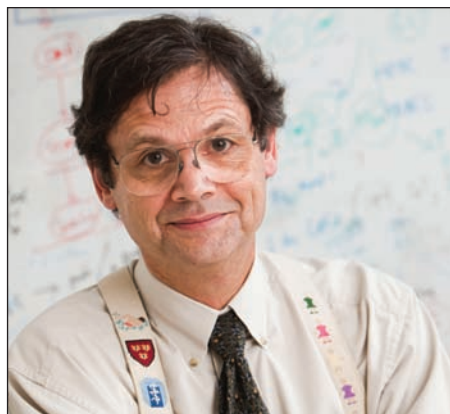
Among the patients randomized to roflumilast who were pretreated with inhaled corticosteroids, prebroncho-

dilator FEV₁ increased by 37 mL over 52 weeks compared with a decline of 10 mL in the placebo groups.

Similar benefits with roflumilast treatment compared with placebo were observed in patients who were not treated with inhaled corticosteroids.

“I certainly feel that it [roflumilast] will be a very useful addition to the armamentarium of our patients. It’s very effective, and over 90% of patients have no problem with it. With PDE 4 inhibitors, some patients will get gastrointestinal intolerance, but there’s no need to monitor blood levels and there are no drug–drug interactions,” Dr McIvor said.

“Our study showed that roflumilast acted as an anti-inflammatory agent, perhaps with a different mode of action,” he continued. “I’m not saying that we’re going to stop Advair [fluticasone/salmeterol] in our patients, but we might be able to reduce the dose from Advair 500/50 to Advair 100/50, and use roflumilast, because it’s tackling a different aspect. Patients are still having exacerbations with triple therapy, so roflumilast perhaps meets an unmet need.” ■



Stephen I. Rennard, MD

Concurrent treatment with inhaled corticosteroids identified patients who had more exacerbations and worse lung function at study entry, according to Dr Rennard.

levels improved by 53 mL compared with placebo in the group receiving roflumilast plus inhaled corticosteroids, and by 49 mL compared with placebo in those not using inhaled corticosteroids.

Roflumilast was better at reducing exacerbations in patients who were also taking inhaled corticosteroids. The mean rate of COPD exacerbations

Ultra-LABA Indacaterol Shows Promise: Fast Onset, 24-Hour Bronchodilation, Favorable Safety

The ultra-long-acting beta-agonist (LABA) indacaterol holds promise for the treatment of chronic obstructive pulmonary disease (COPD), said Mario Cazzola, MD, Professor of Respiratory Medicine, University of Rome Tor Vergata, Italy. In preclinical and early clinical studies, indacaterol demonstrated a fast onset of action and 24-hour bronchodilation.

Indacaterol has already been approved in the European Union, but the US Food and Drug Administration has requested additional data before again considering it for the treatment of COPD.

The high intrinsic activity of indacaterol may allow for faster activation of beta-receptor, permitting fast onset of action. In a study of 89 patients with COPD, single doses of indacaterol (150 µg and 300 µg) had an onset of action that was similar to that of salbutamol and faster than that of salmeterol-fluticasone (Balint B, et al. *Int J Chron Obstruct Pulmon Dis*. 2010; 5:311-318).

Indacaterol’s interaction with lipid rafts may explain its 24-hour bron-

chodilation, Dr Cazzola said. In one study (Lombardi D, et al. *Eur J Pharm Sci*. 2009;38:533-547), indacaterol had equivalent interaction with lipids to salmeterol but had a 2-fold higher affinity for raft microdomains.

Single doses of indacaterol had an onset of action that was similar to that of salbutamol and faster than that of salmeterol-fluticasone.

In the INERGIZE COPD phase 3 clinical trials released by Novartis in 2009, indacaterol proved superior to current comparators (ie, tiotropium, formoterol, salmeterol) in improvements over placebo in trough forced expiratory volume in 1 second at 12 weeks of treatment, Dr Cazzola said. Its effect on quality of life and breathlessness was also superior to these same comparators. Indacaterol also increased the percentage of days

without rescue medication more than these other agents.

In a 1-year comparison of once-daily indacaterol with twice-daily formoterol and placebo (Dahl R, et al. *Thorax*. 2010;65:473-479), indacaterol improved the BODE (body mass index, obstruction, dyspnea, exercise) index at week 12 and week 52 compared with placebo. The BODE index correlates with the risk of exacerbations.

In this same study, indacaterol increased the time to first exacerbation over 52 weeks compared with placebo. Indacaterol has a favorable cardiovascular safety profile, with minimal changes in the corrected QT interval observed over 52 weeks, he said.

Cough is a frequent adverse event with indacaterol; 17% to 20% of patients in this study experienced a sporadic, short-lasting cough within 15 seconds after inhalation of indacaterol. In other clinical trials, only 6.8% of patients reported cough as an adverse event, and no patients discontinued the study because of cough, Dr Cazzola noted. ■

Systemic Effects of COPD Linked to Many Comorbidities, Affect Treatment Decisions, Increase Costs

By Wayne Kuznar

See also page S12.

Chronic obstructive pulmonary disease (COPD) is often accompanied by other conditions that can potentiate its morbidity, leading to hospitalizations and increased healthcare costs. The systemic effects of COPD were examined at a Meet the Professor session at Chest 2010.

Systemic Manifestations Guide Treatment Decisions

“Airflow obstruction has profound effects on cardiac function and gas exchange, with systemic consequences,” said Paolo Palange, MD, Associate Professor of Internal Medicine, University of Rome, Italy.

COPD inflammation may initiate or worsen comorbid conditions, including ischemic heart disease, heart failure, osteoporosis, depression, and diabetes.

The systemic manifestations of COPD have been explained by 2 hypotheses:

1. There is systemic spillover of the inflammatory and respiratory events occurring in the lungs of patients with COPD
2. COPD is the expression of a systemic inflammatory state, with multiple organ compromise.

These hypotheses have important implications on treatment pathways, Dr Palange said. If one subscribes to the first hypothesis, therapy should be centered in the lungs. If the second hypothesis is more accurate, however,

therapy should shift toward the systemic inflammatory state.

“Treatment of COPD inflammation may concomitantly treat systemic inflammation and associated comorbidities,” Dr Palange said. Broad-spectrum anti-inflammatory treatments—phosphodiesterase inhibitors, peroxisome proliferator-activated receptor agonists—may therefore provide unexpected benefits in patients with COPD.

“Treatment of COPD inflammation may concomitantly treat systemic inflammation and associated comorbidities.”

—Paolo Palange, MD

Cardiovascular disease (CVD) is common in patients with COPD, and evidence suggests that anti-inflammatory treatments for COPD can also reduce CVD risk. Patients with COPD have a 2- to 3-fold higher risk for CVD mortality compared with those without COPD.

Low-dose inhaled corticosteroids have been shown to decrease the risk of acute heart attack in patients with COPD. Dr Palange speculated that acute reductions in the inflammatory marker C-reactive protein (CRP) with inhaled corticosteroids may partially explain reductions in CVD risk with

these agents when used in patients with COPD.

In contrast, beta-agonists may have deleterious effects in patients with heart failure and COPD. This excess risk, however, appears to be confined to short-acting beta-agonists, whereas the long-acting beta-agonists (LABAs) appear to have an acceptable safety profile; however, LABAs also should be used with caution in patients who also have CVD.

In an observational study, patients with COPD who were being treated with statins had a near halving of mortality compared with those not treated with statins, and statin therapy in combination with inhaled corticosteroids was associated with a lower rate of mortality than either therapy alone.

Skeletal muscle weakness is one of the main systemic effects of COPD. It leads to reduced exercise capacity independent of disease severity, worsening health status, increased mortality, and higher healthcare resource utilization.

Pulmonary rehabilitation improves the skeletal muscle dysfunction of patients with COPD, improves exercise capacity, and accelerates the speed of reoxygenation of skeletal muscle, Dr Palange noted.

Osteoporosis is another serious comorbidity in patients with COPD. Although therapy with inhaled corticosteroids had been thought to be a

factor in the development of osteoporosis in patients with COPD, there were no significant changes in the rates of osteoporosis or osteopenia in men or women with COPD after treatment with inhaled corticosteroids in the TORCH (Towards a Revolution in COPD Health) study.

Anxiety disorders and depression in patients with COPD appear more frequently in women than in men. Women also have greater psychological distress and worse perceived control of COPD symptoms.

Anemia and obstructive sleep apnea syndrome are 2 other diseases that appear frequently in patients with COPD. Anemia with COPD is related to dyspnea, worse exercise capacity, and worse 3-year survival.

Evolving COPD Biomarkers

The search for systemic biomarkers to predict COPD worsening continues. CRP “may be the best biomarker,” Dr Palange said.

Other biomarkers with promise include an imbalance of leptin/adiponectin, surfactant protein D, and plasma proadrenomedullin.

The coexistence of metabolic syndrome in patients with COPD is one obstacle in the search for biomarkers to predict COPD exacerbation, because the metabolic syndrome itself is a proinflammatory state associated with the release of many inflammatory proteins and molecules. ■

Worsening Symptoms, Lung Function Precede COPD Exacerbations

Impending chronic obstructive pulmonary disease (COPD) exacerbations are heralded by 10 days of worsening COPD symptoms, worsening pulmonary function, and increased daytime rescue medication use, said Donald P. Tashkin, MD, Director, Pulmonary Function Laboratory, University of California at Los Angeles.

Dr Tashkin evaluated the changes in symptoms and pulmonary function during the 10 days preceding an initial COPD exacerbation in 1964 patients with moderate-to-very-severe COPD. To be eligible, patients could not have had an exacerbation within 1 month of their pre-enrollment screening. COPD exacerbations

were defined as those requiring oral corticosteroids or hospitalization.

Patients were being treated with twice-daily budesonide/formoterol pressurized metered-dose inhaler (MDI) 320/9 µg, budesonide/formoterol pressurized MDI 160/9 µg, formoterol dry powder inhaler 9 µg, or placebo.

Patients recorded dyspnea, cough, and sputum scores; peak expiratory flow; and nighttime rescue medication use (inhalations/night) in a diary. Mean changes from baseline in those variables were assessed during the 10 days preceding the patient’s first exacerbation. A total of 669 had ≥1 exacerbations. Patients with exacerbations had more severe disease and worse

lung function at baseline.

“There were slight increases in sputum, dyspnea, and cough starting 10 days prior to exacerbations,” Dr Tashkin said.

“There were slight increases in sputum, dyspnea, and cough starting 10 days prior to exacerbations.”

—Donald P. Tashkin, MD

The mean change in dyspnea score overall during the 10 days was approximately 0.40 units, which exceeded the predefined criteria for

a minimal important difference (0.2-unit difference).

No matter which treatment the patient received, the mean changes in scores indicating dyspnea, cough, and sputum accelerated at day 5 before the exacerbation.

“There was a small change in peak flow in the run off to exacerbation,” he said. “The trajectories were similar with all drugs.” Morning peak expiratory flow (all treatment groups combined) dropped by 9.4 L/min starting 10 days before the exacerbation.

An increase in the use of rescue medications occurred, especially in the 5 days closest to the exacerbation, with a similar pattern of increase across all treatment groups.—WK ■

Heading Off Exacerbations in COPD Is Crucial

By Wayne Kuznar

See also Emerging Therapies, pages S8-S10.

Preventing exacerbations in chronic obstructive pulmonary disease (COPD) is crucial to limit the decline in lung function that can lead to hospitalizations and poor outcomes. Methods to prevent exacerbations, with an emphasis on newer therapies, were the focus of a symposium presented by Nicola A. Hanania, MD, MS, and Mario Cazzola, MD.

Patients with COPD who have exacerbations experience faster declines in lung function and worsening lung inflammation compared with those without exacerbations, said Dr Hanania, Director of the Asthma Clinical Research Center, and Associate Professor of Medicine, Section of Pulmonary and Critical Care Medicine, Baylor College of Medicine, Houston, TX.

Exacerbations are also associated with poorer quality of life and an increased risk of mortality in the years after a hospitalization. According to Dr Hanania, patients at high risk for exacerbation include those with:

- A more severe airway obstruction
- Chronic bronchial mucous hypersecretion
- A longer duration of COPD
- Productive cough and wheeze
- Bacterial colonization.

A reliable predictor of future exacerbation is a history of exacerbation.

Influenza vaccination is a simple way to prevent exacerbations. Influenza vaccination has been shown in a randomized clinical trial to reduce exacerbations, "due to a reduction in exacerbations ≥ 3 weeks after vaccination and due to influenza," Dr Hanania said.

Nonpharmaceutical strategies include pulmonary rehabilitation, which is underutilized in the United States, and education to self-manage COPD, which has been shown to reduce the incidence of short- and long-term hospitalization and reduce healthcare utilization.

A 12-week, home-based program of pulmonary rehabilitation was effective in improving exercise tolerance, dyspnea, and quality of life in housebound patients with COPD. At 6 months, patients undergoing pulmonary rehabilitation had a significantly shorter average length of stay at readmission to the hospital with exacerbations.

Long-acting bronchodilators decrease the rate of exacerbations, as evidenced by findings from the UPLIFT (Understanding Potential Long-Term Impacts on Function with Tiotropium) study, in which the addition of tiotropium to a baseline COPD treatment regimen reduced exacerbations (median

delay to first exacerbation of 16.7 months vs 12.5 months for placebo).

Inhaled corticosteroids have also been proved to reduce exacerbation risk. Fluticasone demonstrated clear efficacy in this regard, Dr Hanania said, and in the TORCH (Towards a Revolution in COPD Health) trial, the combination of a long-acting beta-agonist and an inhaled corticosteroid decreased the number of exacerbations. In patients with severe COPD, triple therapy with tiotropium, fluticasone, and salmeterol may reduce hospitalization risk, as observed in the Canadian Optimal Therapy of COPD trial.

The risks for COPD exacerbation include having a more severe airway obstruction, chronic bronchial mucous hypersecretion, a longer duration of COPD, productive cough and wheeze, and bacterial colonization.

The data behind mucolytics with respect to exacerbation risk are mixed. In the PEACE study, oral carbocysteine decreased exacerbation risk by about one third compared with placebo, but results from the BRONCUS (Bronchitis Randomized on NAC Cost-Utility Study) showed no beneficial effect of acetylcysteine on exacerbations. The



Mario Cazzola Nicola A. Hanania

conflicting data may possibly be explained by the different patient populations enrolled in the studies and the different pharmacologic properties of the 2 mucolytics, said Dr Cazzola, Professor of Respiratory Medicine, University of Rome Tor Vergata, Italy.

"The BRONCUS study recruited less severe patients, with a forced expiratory volume in 1 second [FEV₁] predicted of 57% in BRONCUS patients compared with 43% in the PEACE study," Dr Cazzola said.

Furthermore, more patients in BRONCUS than in the PEACE study were being treated with inhaled corticosteroids (70% vs 17%), which might have diluted the findings in BRONCUS. In addition, the PEACE study was conducted in Chinese patients, whereas BRONCUS enrolled white patients, and there may be pharmacogenetic differences between these 2 ethnic groups, Dr Cazzola said.

With respect to the 2 mucolytics studied, the action of carbocysteine is unique and may, in part, depend on inhibition of viral adherence to the airway.

Because bacterial infection is one of the most important risk factors in COPD exacerbations, it has been pro-

posed that antibiotics could reduce risk. Cyclical moxifloxacin (5 days every 8 weeks) was shown to decrease exacerbations compared with placebo.

A polyvalent mechanical bacterial lysate (the first 10 days of 3 consecutive months) added to regular treatment with salmeterol/fluticasone reduced the total number of exacerbations, the rate of exacerbations per patient per year, the number of exacerbations that required treatment with oral corticosteroids, and the total rate of hospitalizations in a study of 63 patients with COPD, Dr Cazzola said.

While waiting for new families of antibiotics to be developed, current antimicrobial strategy may need to be changed, he said. This may include administration of inhaled or nebulized antibiotics, which would require a motivated patient and is expensive. Another option is to use antibiotics with different mechanisms of action in combination to reduce the possible development of resistance, but "this approach will increase costs and possible side effects."

Emerging therapies with some success at preventing exacerbations are indacaterol, which increased the median time to a first exacerbation over 52 weeks compared with placebo; aclidinium, which improved the time to a first moderate-to-severe exacerbation in 2 clinical studies; and roflumilast, which was effective in reducing exacerbations with 1 year of treatment in patients with severe COPD. ■

First Acute COPD Exacerbation a Significant Risk for Death within 4 Years

More than one third of patients with a first acute exacerbation of chronic obstructive pulmonary disease (COPD) died within 4 years in a recent small study presented by Kamil Klenha, MD, and colleagues from the Regional Hospital Tabor in the Czech Republic.

The study included 80 patients with a first acute COPD exacerbation who met the GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria for hospitalization. The patients were treated in a nonintensive care unit ward; the cause of exacerbation was infectious in 57.5% of the patients and noninfectious in 42.5%.

Patients were treated according to current recommendations and were monitored every 3 to 6 months in the hospital's outpatient clinic. By year 4

of follow-up, 35% of the group had died—7 patients during the first year, 8 during the second year, 7 during the third year, and 6 during the fourth year.

Significant predictors of mortality were older age, worsening lung function, frequent acute exacerbations, and a history of smoking.

The mortality in this case series was not as high as in other series, some of which are as high as 59%; this likely reflects the absence of patients with the most severe disease, because no

patients required treatment in an intensive care unit ward, according to the researchers. Significant predictors of mortality were:

- Older age
- Worsening lung function as determined by a lower forced expiratory volume in 1 second
- Frequent acute exacerbations
- A history of smoking.

Current smokers, as well as those who quit <10 years earlier, had 3.8 times the risk for death compared with lifelong nonsmokers or those who quit ≥ 10 years earlier.

Hypoxemia and/or hypercapnia were associated with a more than doubling of the risk for mortality.

The researchers concluded that their data confirm the seriousness of an acute exacerbation.—WK ■

COPD: What's State-of-the-Art, What's in the Future?

An interview with Nicola A. Hanania, MD, MS

Director of the Asthma Clinical Research Center, and Associate Professor of Medicine, Section of Pulmonary and Critical Care Medicine, Baylor College of Medicine, Houston.

At the 2010 meeting of the American College of Chest Physicians, *American Health & Drug Benefits* asked Dr Hanania to weigh in on the current and emerging therapies for chronic obstructive pulmonary disease (COPD).

What is the current state of COPD therapy, and why are newer options needed?

We have therapy for COPD that can improve symptoms, exercise tolerance, and quality of life (QOL). The concern is that despite available therapy, many patients with COPD continue to have symptoms and exacerbations that require emergency department visits and even hospitalization.

Current therapy does not modify the cause of the disease, and this has been shown in 2 large trials—UPLIFT (Understanding Potential Long-Term Impacts on Function with Tiotropium) and TORCH (Towards a Revolution in COPD Health), which showed that although the current therapies—including long-acting bronchodilators and the long-acting bronchodilator/inhaled corticosteroid combination—can improve frequency of exacerbations and improve QOL, they have a limited effect on the declining lung function that occurs over time with COPD, which is a major problem.

Also, available therapies have a minimal effect on mortality. COPD is now the third (up from fourth until recently) leading cause of death in the United States.^{1,2} In addition, some COPD medications have dose-dependent side effects.

Finally, cost is also an issue for current therapies. Many patients cannot afford using them, because they are expensive.

Has there been any breakthrough in COPD treatment in the past few years?

The biggest breakthrough is that guidelines written for COPD consider it a treatable disease. For many years we approached COPD as a disease that happens in smokers, and that we could not do much for them. We had a nihilistic attitude about treatment; we did not believe that treatment could improve outcome.

Since the past few years, with the release of the landmark trials (UPLIFT and TORCH), we know that treatment does improve outcomes, but there is still a way to go. There is still the need for more intervention.



The biggest breakthrough is that guidelines written for COPD consider it a treatable disease. We know that treatment does improve outcomes, but there is still a way to go.

Where do we stand with delivery systems?

Some patients, especially elderly patients, have problems with certain delivery systems. Currently, most COPD medications are delivered through the inhaled route. The inhaler devices are not all the same. Some are easier to use than others. We have metered-dose inhalers, dry powder inhalers, and nebulizers. In some patient populations, one delivery system may be better than the other. In addition to what drug we give the patient, it is important to keep in mind that the choice of delivery system plays a major role in the acceptance of the medication, as well as adherence.

Can you discuss some of the newer agents in development?

There are 4 areas of new drugs or new interventions. One is the development of drugs similar to what we have now, except in a simpler platform, such as once-daily drugs and combination therapies. Many companies are developing once-daily long-acting bronchodilators, including once-daily long-acting beta-agonists (LABAs), once-daily long-acting anticholinergic (antimuscarinic) agents (LAMAs), and a combination of these 2—what we call a LABA/LAMA combination.

Some manufacturers are looking at a combination of a once-daily LABA/inhaled corticosteroid. The agents we have now are twice daily. The emerging drugs will be much of the same agents we have today, but with once-daily inhaled delivery system.

Many of them are in phase 3 trials.

The most advanced is indacaterol, which is a once-daily LABA. It is approved in Europe and in some countries in South America, but not in the United States. Others are in phase 2 or starting phase 3 trials, including vilanterol, olodaterol, and carmoterol.

The others are LAMAs. Probably the most advanced is aclidinium. It can be once daily or twice daily. The problem with aclidinium is that it may not be as long-acting as tiotropium, but there are other options.

The second avenue is to look at novel therapeutic targets. COPD is an inflammatory disease, and multiple pathways of inflammation can be targeted. The most advanced group of drugs in this field is the phosphodiesterase (PDE) 4 inhibitors. Roflumilast is approved in the European Union but not yet in the United States. It is still under review by the Food and Drug Administration (FDA) and may be approved early in 2011. It is an oral agent with once-daily dosing, which is an advantage.

Roflumilast has anti-inflammatory activity, but it is not a bronchodilator. It has decreased exacerbations in most of the clinical studies as a stand-alone therapy, but it is more impressive when added to long-acting bronchodilators. It will have to be studied as stand-alone therapy to get FDA approval, but in my mind, it will be used as an add-on therapy. The effect is very significant when added to long-acting bronchodilators.

Several drugs that target mediators of inflammation are being studied. Many of these studies so far have

been disappointingly negative. For example, anti-interleukin-8 has been looked at, as well as leukotriene B₄ inhibitors and anti-tumor necrosis factor-alpha inhibitors.

Several mitogen-activated protein (MAP) kinase inhibitors are in phase 2 trials; MAP kinase may play a role in chronic inflammation. The problem with these agents is potential toxicity. They are given systemically (by mouth), so inhaled versions will probably need to be developed to reduce systemic exposure.

Drugs such as antioxidants and synthetic protease inhibitors are potentially beneficial, but it is too early to tell how effective they will be. Some of them are targeting thiol (an extra- and intracellular antioxidant in the lungs) and inflammation of the alveoli. Retinoids are also being tested right now, but they are very early in development.

The third group of interest includes drugs that we use for other comorbidities, which may have an effect on COPD. There is some interest in statins in COPD; they may reduce exacerbations. They have anti-inflammatory effects and were shown in observational studies to decrease exacerbations and even mortality. STATCOPE (Prospective Randomized Placebo-Controlled Trial of Simvastatin in the Prevention of COPD Exacerbations) is a large multicenter study that will investigate simvastatin in COPD.

Another group is prophylactic antibiotics. Inhaled antibiotics are in early development in COPD to prevent exacerbations. Inhaled levofloxacin and ciprofloxacin are 2 such antibiotics in the fluoroquinolone class.

By which mechanism would antibiotics be acting in COPD?

These are antibacterial agents—bronchial bacterial colonization is a problem in COPD that could contribute to progression of airway disease and decline in lung function, but bacterial colonization is also associated with airway inflammation, and antibiotics may also have anti-inflammatory effects.

Macrolides are another group of antibiotics being investigated in COPD; erythromycin has been shown to decrease exacerbations. A large macrolide study (with erythromycin over 1 year) has just been completed, but the data will only be presented at the 2011 meeting of the American Thoracic Society.

Continued on page S15

COPD and Its Associated Costs

Gary M. Owens, MD

President, Gary Owens Associates, Philadelphia, PA

Although not discussed as often as diabetes, heart disease, or even oncology, chronic obstructive pulmonary disease (COPD) is a significant, challenging disease state for managed care organizations in 2011. According to a study presented at the American Thoracic Society's 2006 annual meeting, the US medical costs related to COPD are expected to total approximately \$832.9 billion between 2006 and 2026.¹

Approximately 12 million Americans have COPD, which is second only to heart disease as a disability forcing employees to quit working.² As recently reported by the Centers for Disease Control and Prevention, COPD is now the third most common cause of mortality in the United States,^{3,4} accounting for more than 120,000 annual deaths.¹ The mortality rate from COPD has increased more than 60% over the past 20 years, with more than 95% of all COPD-related deaths being those aged >55 years.² COPD affects more women than men, but the mortality rates are approximately the same for both sexes.²

The mortality rates for COPD are greater in whites than nonwhites and also greater in blue-collar workers than white-collar workers.² These are sobering statistics about a serious and disabling illness that is often underdiagnosed and undertreated. In 2006 it was estimated that close to 13 million Americans had been diagnosed with COPD, but 24 million people had the disease, indicating substantial underdiagnosis.^{5,6}

This report highlights data related to COPD presented at the 2010 annual meeting of the American College of Chest Physicians (ACCP 2010), with a focus on new and emerging therapies, as well as data presented at ACCP 2010 that show that the cost of care for COPD escalates based on GOLD (Global Initiative for Chronic Obstructive Lung Disease) severity criteria.

According to the study by M. Reza Maleki-Yazdi, MD, FRCPC, FCCP, and colleagues discussed in this publication, almost half of the cost of care for COPD is related to exacerbations of the disease. This study shows that the average annual COPD-related cost per patient is \$4147 in Canada, and that the cost rises to \$6141 for those with GOLD stage 4 COPD. Of that \$6141, \$2631 results from exacerbations of the illness, and \$3510 is maintenance cost, according to this study.

A study presented at ACCP 2010 by Andrew P. Yu, PhD, and discussed in



According to a 2006 study, the US medical costs related to COPD are estimated to amount to \$832.9 billion between 2006 and 2026.

this supplement, is based on real-world information that is derived from a robust claims database with nearly 23,500 patients with COPD. From this study we learn that increased patient adherence to COPD therapies is strongly associated with reduced mortality and hospitalization risks for patients with COPD.

We also learn that the use of a more complex routine of multiple inhalers compared with single inhalers results in lower adherence to medication, and this lower adherence is associated with a total healthcare cost increase of \$3319 for these patients.

Clearly these are negative cost implications related to the severity of disease and medication nonadherence. One can certainly hypothesize that the combination of severe disease, which is likely to need more complex care, and the associated nonadherence seen with more complex care, may have a negative cost impact on the healthcare system.

This publication also presents information about new therapies in the pipeline for the treatment of COPD. The cornerstones of therapy for this condition remain bronchodilation and reduction of inflammation. To that end, ultra-long-acting beta-agonists, such as indacaterol, carmoterol, vilanterol, or olodaterol, may soon offer clinicians and payers alternatives to currently available bronchodilators. Roflumilast (Daxas), an oral phosphodiesterase 4 inhibitor, shows promise in reducing inflammation in patients with COPD. However, it remains to be determined if any of these newer

agents will offer clinical advantages over existing therapies.

So where do we go from here? We know that health plans and physicians must work together to help improve outcomes and control the cost of this progressive and debilitating disease. New medications and new guidelines alone are not enough to change clinical outcomes and "bend the cost curve." A systemwide approach involving all stakeholders is necessary to improve outcomes in this patient population.

Successful health plans may therefore need to consider the following approaches to managing COPD:

- Improving diagnosis
 - Does the health plan have processes in place to ensure that members with COPD are properly diagnosed?
 - The plan must also be able to demonstrate to their employers that diagnosing patients with previously undiagnosed COPD will have a major impact on future costs
- Improving treatment
 - Does the health plan have processes in place to ensure that its members are receiving recommended treatments according to guidelines? As we have learned in this supplement, optimal care for those already diagnosed can result in substantial improvements in symptoms and quality of life, as well as reductions in medical expenses
- Improving outcomes
 - Plans with disease management programs for COPD must be able to demonstrate that the education and adherence support provided to patients with COPD ultimately results in decreases in hospitalizations, emergency department visits, admissions to the intensive care unit, unscheduled office visits, and acute exacerbations; if this cannot be shown, the programs need to be assessed and redesigned to achieve these end points
- Working with employers
 - *Prevention at the worksite:* smoke-free work environments and careful adherence to occupational safety procedures can reduce exposure to environmental pollutants that increase the risk of COPD or worsen symptoms for those with the disease
 - *Education:* campaigns to increase employee awareness of the symptoms of COPD (eg, shortness of breath is not a normal part of getting older and should be brought to the attention of a physician) and the impact of smoking, which can improve early detection of COPD

- *COPD screening:* programs to encourage lung function testing for those at high risk for COPD will improve early detection
- *Patient programs:* smoking cessation programs can help reduce the incidence of COPD. Once an employee has been diagnosed with COPD, one-on-one case management programs can be effective.

Several important conclusions are relevant to the health plan perspective concerning the management of COPD. First, the number of patients with COPD is still growing as a result of the aging of the population and the significant time it takes to see the effect of reduced rates of smoking on the prevalence of COPD. Second, the cost of caring for individuals with COPD is likely to increase as this patient group increases. Therefore, it is imperative to manage guidelines and use the most effective treatments available. Third, it is important that we have new treatment options in the quest to better manage patients with COPD.

And yet, pharmaceutical innovation alone will not result in better management of COPD. In addition to new treatment options, we must better understand how to help patients improve their medication adherence. Finally, helping physicians to manage these patients according to well-established guidelines will continue to be a major challenge.

To adequately manage patients with COPD and to control the clinical and economic consequences of this disease, an equal amount of effort needs to be invested in finding new treatments, managing patients to established guidelines, educating physicians, working with employers, and better understanding how to motivate patients to comply with care routines. Only by involving all stakeholders in this process will we be able to improve clinical outcomes and control cost-effectively in patients with COPD. ■

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Providers' Perspective

What's State-of-the-Art... *Continued from page S13*

Some studies suggest that cyclic oral antibiotics may be effective. One study showed that giving moxifloxacin for 5 days every 8 weeks on a cyclic basis decreases exacerbations compared with placebo, but we are not ready to prescribe antibiotics to everybody with COPD.

Beta-blockers also look like they may have an effect on COPD, but it is too early to know. In one recent study, beta-blockers were associated with reductions in mortality and risk of exacerbations in COPD.

What is the fourth intervention being investigated?

The fourth area is nonpharmacologic interventions, such as bronchoscopic avenues for patients with emphysema. One trial involved putting valves in the upper lobes of patients with emphysema. Lung volume reduction surgery is also being performed for patients with end-stage disease (severe emphysema in the upper lobes).

What do you envision 3 or 4 years from now?

This is a very slow-moving field, which is a bit frustrating. New drugs are expensive to research, and the US Food and Drug Administration has put in many safety issues, which is important but slows approval.

A few years from now, we will likely have 1 or 2 of the LABAs available. The PDE 4 inhibitor roflumilast will probably come on board in 2011, but I do not think we will move far forward. Five years down the road we will likely see more of the novel agents on the market.

The key question is, how will long-acting bronchodilators compete with the drugs we have now? Many of the current agents will go off patent and will be cheap. They may have to be given twice daily, but if they are cheaper, they may still be preferred, because patients may not be able to afford the long-acting medications. That is a concern now. This is a competitive field, and the long-acting bronchodilators will have to differentiate themselves. People will also have to look at an easier way of delivery.

Nebulized delivery is emerging—in the United States at least—so there may be more combination therapies in a nebulized platform. ■

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Emerging Therapies

See also pages S8-S10.

Novel Selective Beta-Agonist Improves Lung Function in COPD: Preliminary Analysis

By Wayne Kuznar

A new, highly selective intravenous (IV) beta-agonist in development—MN-221 (bedoradrine sulfate)—improves lung function in patients with stable, moderate-to-severe chronic obstructive pulmonary disease (COPD), according to a dose-ranging study presented at the meeting.

In development for the treatment of acute exacerbations of asthma and COPD, MN-221 has higher selectivity for the beta₂-receptors than the currently used beta-agonists (ie, albuterol, levalbuterol, terbutaline), which suggests that the cardiac-stimulating action on beta₁-receptors may be reduced with this investigational agent. Therefore, MN-221 may reduce bronchospasm, while minimizing cardiovascular complications.

James Pearle, MD, and colleagues at California Research Medical Group in Fullerton, examined 3 dose levels of MN-221 (300 µg, 600 µg, and 1200 µg IV) in 16 patients with stable, moderate-to-severe COPD. The patients were randomized to receive either MN-221 or placebo in a 3:1 ratio—half of the

dose was given over 15 minutes, followed by the remaining dose over 45 minutes, for a total 1-hour infusion.

Lung function improved with all 3 doses; the improvement was significant compared with placebo at the 600-µg and 1200-µg doses. The forced

Lung function improved with all 3 doses; the improvement was significant compared with placebo at the 600-µg and 1200-µg doses.

expiratory volume in 1 second (FEV₁) increases from baseline were 9.2% with the 300-µg dose (not a significant difference), 16.2% with the 600-µg dose ($P = .02$), and 21.5% with the 1200-µg dose ($P = .025$). In comparison, FEV₁ declined by 4% in patients receiving placebo infusion.

The researchers noted that MN-221 at doses of 600 µg and 1200 µg improved lung function for at least 6 hours compared with placebo. ■

Coming in April

ACAAI 2010: Payers' Perspectives

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