New Paradigms in Asthma Pharmacotherapy

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Thanks to the development of highly effective asthma medications, most patients now have the ability to achieve and maintain well-controlled asthma. Nevertheless, for many patients, asthma control actually achieved is less than ideal, due to factors such as compliance, failure to eliminate exposure to triggers, and underlying disease severity. For other patients who remain well-controlled, concerns often arise regarding the necessity and consequences of using controller medications indefinitely. This article reviews three novel strategies for asthma management designed to address these issues.

ANTI IGE THERAPY FOR SEVERE ASTHMA

Illustrative case

A 25 year old man continues to have poorly controlled asthma despite taking a long-acting beta-agonist in combination with high doses of an inhaled steroid. He has multiple environmental allergies documented by skin testing and a serum IgE level of 250 IU/ml (600 ng/ml). He insists he has done everything possible to control allergens in his home and complies faithfully and effectively with his inhalers. He asks whether any new treatments are available that could help his asthma.

Evidence and outcomes

IgE is a key mediator of allergic inflammation, which is central to asthma pathophysiology. Biological therapeutic agents have been developed that reduce allergic inflammation by binding to the high-affinity IgE receptor and preventing its participation in inflammatory responses. Omalizumab (Xolair®) is the only anti-IgE drug currently available for clinical use in Canada. It is administered as a subcutaneous injection every 2 to 4 weeks with doses calculated based on the patient’s weight and serum IgE level (Table 1).

Evidence regarding anti-IgE therapy for chronic asthma has been summarized in five meta-analyses, of which the most recent in 2006 included 14 randomized trials with follow-up as long as 60 weeks. In these studies, omalizumab significantly reduced asthma exacerbations, allowed tapering or discontinuation of inhaled steroids, and improved patient self-assessment of asthma control. Statistically significant but clinically minor benefits were demonstrated for asthma-specific quality of life, symptom scores, and rescue medication use. Omalizumab was well-tolerated with few adverse effects, the most common being local injection site reactions in 10% of patients.

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EDITORIAL

Asthma Therapy: Not Seeing the Forest for the Trees

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Asthma prevalence continues to rise in industrialized societies, including Canada. The reasons for this are poorly understood and appear to be due to more than better diagnosis. I am encouraged by a personal observation that admissions to hospital for asthma have become very rare events and admissions to intensive care units for this problem are virtually unheard of. Despite better therapies that have likely contributed to the decline in the severe consequences of asthma, recent studies have highlighted the continued high level of poorly controlled asthma in Canada and the unacceptable compromises that our patients are willing to make in their daily lives as a consequence of having asthma.1,2

In this issue, Dr. Stanbrook describes both a new therapy for asthma as well as novel ways to use existing therapies. He discusses the newest “designer” drug, omalizumab, that targets a specific antibody known to play a key role in the inflammatory cascade going on in asthmatic airways. The near future will bring with it numerous other specific mediator and cytokine antagonists.3 Aside from the greatly increased expense of these products is the dilemma of not being able to predict which drug will work best for a specific patient. Perhaps pharmacogenetics will be the solution, allowing us to target therapy appropriately in the future4 but, for the moment, this still represents an elusive dream. In addition, more readily available markers of airway inflammation such as exhaled nitric oxide may allow us to better determine which patients require intermittent versus persistent inhaled steroid therapy and may allow easier dose titration.5

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RESPIROLOGY JOB FAIR AT BETTER BREATHING 2008

Please plan to attend the 5th annual Respirology Job Fair to be held on Friday, February 1, 2008 at Better Breathing 2008. You will have an opportunity to present information about positions available in your centre (academic or community) to all residents in the Respirology and combined Respirology/Critical Care Programs in Ontario. The Respirology Program Directors will be present if you wish to discuss the future needs of your centre. Informal mingling allows for plenty of opportunity to meet the upcoming graduates of the Ontario Respirology Programs.

Hope to see you there!

When you can't breathe, nothing else matters.

ONTARIO THORACIC REVIEWS Fall 2007
am pleased to give you a preview of Better Breathing 2008, the annual conference of the Ontario Lung Association and the Annual General Meeting of the Ontario Thoracic Society. The Planning Committee is very excited about the topics and speakers chosen for Better Breathing 2008. Plan now to attend the OTS Program, which offers an exciting series of lectures, lunch sessions and debates.

The focus of the Friday morning Plenary Session is “Lifestyle and the Lungs”. The objective is to explore and discuss the role of the health professional in delivering care in diseases impacted by lifestyle choices. We are very fortunate to have two highly regarded plenary speakers. Dr. Andrew Pipe, the Director of the Minto Prevention & Rehabilitation Centre, University of Ottawa Health Institute, will review Smoking Cessation: What Every Health Professional Must Know. Dr. Robert Butcher, Bioethicist, Health Information and Privacy, London Health Sciences will talk about Duty to Care: Limits and Responsibilities.

The mid-morning OTS/ORCS Joint Session, “What’s New in Lung Health” will feature two members of the Ontario Thoracic Society and one member of the Ontario Respiratory Care Society. Dr. Anna Day (Women’s College Hospital, Toronto) will discuss Smoking and Screening: are we still in the 20th century? Jennifer Olajos-Clow, a member of the Ontario Respiratory Care Society, will update us on Asthma Management in the Emergency Department. Dr. Ian MacLuskey (Children’s Hospital of Eastern Ontario, Ottawa) will complete the session with Longterm Sequelae of Bronchopulmonary Dysplasia.

During lunch-time on Friday, attend the General Lunch with the exhibitors or select one of three “Lunch with a Professor Series”. One lunch session is Difficult Asthma Patients with an adult and a pediatric focus (Dr. Parameswaran Nair, Firestone Institute for Respiratory Health and Dr. Sharon Dell, the Hospital for Sick Children). A second lunch session, So You Think You Can Read a Chest X-ray? (Dr. Colm Boylan, St. Joseph’s Hospital, Hamilton) looks at tough radiology cases. The third session is the André Peloquin Case Presentations from Community Respiriologists and is dedicated to the memory of Dr. André Peloquin. The case presentations are facilitated by Dr. John Bertley (St. Catharines) and this year’s case presenters are Dr. Robert Chernish (Windsor), Dr. Stephen Chao (London) and Dr. Frank Ritacca (Mississauga). Please book early for the lunch-time clinical sessions as seating is limited.

The Friday afternoon program, “State of the Art in Respiratory Medicine”, will feature presentations on Rare Lung Diseases (Dr. Gregory Downey, Executive Vice-President for Academic Affairs, University of Colorado) and Surgical Management of Chronic Thromboembolic Pulmonary Hypertentions (Dr. Fraser Rubens, Cardiac Surgeon, Ottawa Heart Institute). The popular and entertaining Resident Case Presentations, facilitated by Dr. David McCormack (University of Western Ontario, London), will follow the Friday afternoon talks. The afternoon session concludes with the OTS Annual General Meeting.

On Saturday morning, return to the OTS Sessions for the ever-popular and provocative debates: “Controversies in Pulmonary Medicine”, chaired by Dr. Gerard Cox. This year’s speakers will debate controversial statements including: CT Angio should be done in every patient suspected of Pulmonary Embolism (Dr. Carole Dennie, Ottawa and Dr. Mark Crowther, Hamilton); Bronchoscopy is essential for diagnosis and management of Ventilator Associated Pneumonia (Dr. William Cameron, Ottawa and Dr. John Muscedere, Kingston); The pathologist is extinct in the diagnosis of Interstitial Lung Disease (Dr. Jean Seeley, Ottawa and Dr. Brendan Mullen, Toronto); and Asthma Never Goes Away (Dr. Diane Lougheed, Kingston and Dr. Nigel Patterson, London). You will not want to miss your chance to vote for the winners of these debates.

I want to thank all the members of the OTS BBC 2008 Planning Committee (Dr. John Bertley, Dr. Hedy Ginzberg, Dr. Sheri Katz, Dr. Chris Licskai, Dr. Peter Macleod, Dr. Param Nair, Dr. Mitra Niroumand, Dr. Chris Parker, Dr. Mark Soth) for their hard work in organizing this exciting roster of speakers and interesting topics.

Exhibitors will display their products and services and draw prizes will be awarded throughout the conference.

Watch for the program brochure. Mark February 1-2, 2008, on your calendar and register early!
The major disadvantage of anti-IgE therapy is cost. Omalizumab is extremely expensive relative to most other asthma medications (over $1000 per dose for most patients).

**Alternative strategies**

Patients with severe asthma usually require maintenance therapy with high-dose inhaled steroids and a long-acting beta-agonist, plus additional medication(s), to achieve or at least optimize asthma control. Among these additional medications, choices include leukotriene receptor antagonists (montelukast (Singulair®) or zafirlukast (Accolate®)), theophylline, or oral prednisone. Leukotriene receptor antagonists are expensive and the degree of benefit varies among patients. Prednisone is inexpensive and is the most effective asthma medication available, but long-term systemic steroid therapy causes significant adverse effects and therefore is usually a last resort. Theophylline is also inexpensive but has a narrow therapeutic index and interacts with many other common medications.

**Guidelines**

The 2006 update of the Global Initiative for Asthma (GINA) guidelines recommends anti-IgE therapy as one possible option for first-line therapy in severe persistent asthma with an allergic component, to be given in conjunction with high-dose inhaled steroids and a long-acting beta-agonist. Alternative recommended options include sustained-release theophylline, a leukotriene modifier, a long-acting oral beta-agonist, or oral steroids. The most recent update of the Canadian asthma consensus guidelines in 2003 predated the availability of omalizumab in Canada, therefore the Canadian guidelines do not discuss the role of this therapy.

**Evidence and outcomes**

The combination of an inhaled corticosteroid (ICS) and a long-acting beta-agonist (LABA) is a highly effective therapy for maintaining control in patients with moderate asthma. How doses of these medications should be adjusted once asthma control has been achieved is controversial. Traditionally, ICS/LABA therapy has been prescribed as a fixed regimen with health care providers determining dose reductions for patients who appear to demonstrate long-term stability at follow-up assessments.

An alternative strategy of allowing patients to adjust their ICS/LABA dose themselves from day to day based on their symptoms has recently undergone extensive study. While the adjustable maintenance dosing strategy can in theory be implemented with either of the two ICS/LABA combinations currently licensed in Canada (budesonide/formoterol (Symbicort®) and fluticasone/salmeterol (Advair®)), studies to date have evaluated this strategy only with the budesonide/formoterol combination.

More than a dozen randomized controlled trials to date have evaluated adjustable maintenance dosing, but only three of these studies have been double-blind, placebo-controlled comparisons of the adjustable strategy against fixed-dose ICS/LABA therapy. Two of these studies have demonstrated significantly greater benefits with the adjustable strategy, yet one study observed the opposite. O’Byrne and colleagues found that a low dose of budesonide/formoterol 100/6 µg twice daily with extra doses of budesonide/formoterol as needed, compared against budesonide/formoterol 100/6 µg twice daily with the short-acting beta-agonist terbutaline (Bricanyl®) as needed, reduced severe exacerbations by 45%. Similarly, Rabe and colleagues found that a higher dose of budesonide/formoterol 200/6 µg twice daily plus extra doses of budesonide/formoterol as needed, compared against budesonide/formoterol 200/6 µg twice daily plus either terbutaline or formoterol as needed, reduced severe exacerbations by 48% and 33% respectively. In both of these studies, nocturnal awakenings and days with poor asthma control were decreased with
adjustable dosing and medication use in the adjustable arm amounted to approximately 200 µg per day of budesonide. In contrast, the CONCEPT trial found that patients assigned a regimen of budesonide/formoterol, adjusted according to a specified protocol that permitted variations from high to very low doses (averaging approximately 500 µg of the budesonide component daily over time), had nearly twice as many exacerbations and 11% fewer symptom-free days as patients assigned to a fixed regimen of a moderate to high dose of fluticasone/salmeterol 250/50 µg twice daily.

Differences among individual study characteristics may account for these discordant results. One possibility is that fluticasone/salmeterol is a more effective asthma therapy than budesonide/formoterol at the doses evaluated. However, in an open-label study, adjustable budesonide/formoterol was found to reduce exacerbations by 25% compared to fixed fluticasone/salmeterol at equivalent doses, arguing against an inherent difference in drug efficacy. A second possibility is that maintenance doses of budesonide/formoterol used in some study groups were too low to maintain asthma control. For example, the study of Rabe et al. included only patients who failed initially to demonstrate control on the fixed maintenance regimen, making it unsurprising that those who received extra budesonide/formoterol did better. In contrast, the CONCEPT trial included in its continuation phase only patients who had achieved initial control on their maintenance ICS/LABA dose, but in the adjustable arm allowed dose reductions to as low as one inhalation once daily, which may have permitted patients to fall below a protective threshold. A third possibility is that the type of reliever medication affects adherence to the adjustable regimen. In the CONCEPT trial, patients in both arms used open-label salbutamol for as-needed relief and thus may have relied excessively on this rescue inhaler instead of increasing the dose of their maintenance inhaler when indicated. Supporting this explanation, compliance was found to be substantially lower with the adjustable-dose inhaler than with the fixed-dose inhaler in both groups. In contrast, in the studies observing greater benefit with adjustable dosing, patients were allowed only budesonide/formoterol as a reliever, ensuring that extra maintenance medication was received simultaneously with reliever medication.

Alternative strategies
A fixed-dose regimen of ICS/LABA, titrated up to a level that maintains adequate control, is a highly effective therapy in moderate asthma. In the GOAL study, dose escalation of fluticasone/salmeterol within the recommended therapeutic range achieved well-controlled asthma in 63% of patients and total asthma control in 41% after one year. Proponents of fixed dosing emphasize the value of suppressing airway inflammation continually, rather than reacting to inflammation only after it has produced symptoms. However, in patients who are already on sufficient anti-inflammatory therapy to keep asthma symptoms under control, whether failing to extinguish any residual inflammation has clinically important long-term consequences has not been established. Critics of fixed dosing emphasize concerns about possible long-term adverse effects of high-dose inhaled steroids such as accelerated osteoporosis and cataract formation, since adjustable dosing offers the potential to maintain control with lower cumulative medication doses.

Guidelines
Both the Canadian guidelines and the GINA guidelines recommend an ICS/LABA combination as first-line therapy for moderate to severe asthma. The GINA guidelines list adjustable maintenance dosing with budesonide/formoterol among acceptable treatment strategies.

Recommendations
Adjustable maintenance dosing is an acceptable strategy for patients who require combined ICS/LABA therapy for asthma control. Benefits of adjustable dosing have been demonstrated most clearly when a minimum dose equivalent to no less than budesonide/formoterol 100/6 µg twice daily is used and when budesonide/formoterol is used as the reliever as well as the maintenance inhaler. In more severe asthma patients who fail to achieve control on submaximal doses of ICS/LABA, a fixed high-dose ICS/LABA regimen is likely more appropriate.
screening protocol with a run-in period that identified and excluded patients whose asthma was either not persistent or more severe. Such accuracy in classification of asthma severity is unlikely to occur in usual practice.

**Alternative strategies**

A leukotriene receptor antagonist may be used as an alternative to inhaled steroids in selected patients who manifest a good response to them. However, the IMPACT study discussed above found that outcomes with zafirlukast did not differ on average from placebo. Theophylline, which appears to have anti-inflammatory as well as bronchodilator properties, can be used as a controller medication in mild asthma, but it is not known whether theophylline can produce acceptable outcomes in comparison to inhaled steroids. The mast cell stabilizer nedocromil (Tilade®), which is less effective than inhaled steroids, was recently taken off the market in Canada due to low levels of use.

**Guidelines**

The Canadian guidelines recommend inhaled steroids as initial maintenance therapy for all patients with persistent symptomatic asthma, including mild disease. For patients who cannot or will not use inhaled steroids, leukotriene receptor antagonists are recommended as a less effective alternative. Similarly, the GINA guidelines recommend low-dose inhaled steroids as preferred maintenance therapy for all patients with mild persistent asthma.

**Recommendations**

Regular daily inhaled steroids remain the treatment of choice in mild persistent asthma, because they produce objectively better outcomes that many patients would consider important. For patients who are unwilling or unable to adhere to inhaled steroids regularly, intermittent use during periods of increased symptoms appears to be safe over the short term, although asthma symptoms may be more frequent. Asthma education and an explicit written action plan are particularly important components of care for such patients. Whether intermittent inhaled steroid users are at increased risk of long-term complications of ongoing inflammation, such as airway remodeling and fixed obstruction, remains unknown.

**REFERENCES**

Towards a COPD Strategy for Ontarians

Cindy Shcherban, Vice-President, Provincial Programs

The Ontario Lung Association (OLA), in conjunction with its two medical societies, the Ontario Thoracic Society (OTS) and the Ontario Respiratory Care Society (ORCS) has recently provided the government with a proposal for a comprehensive COPD strategy for Ontario. In late 2006, the OLA convened a COPD Advisory Panel1 comprised of thought leaders, clinical leaders from across the healthcare continuum, and other experts at both provincial and national levels. The Panel provided direction to the content of the submission and it is envisioned will continue to guide the implementation of the proposed COPD Strategy.

While there are existing approaches that can be applied to the prevention, detection and management of COPD, they are not well coordinated and are not well integrated across the province’s health system. Among the public, the awareness of COPD prevention, detection and treatment is low and, in the absence of a coordinated, system-wide approach, patients and families must navigate what is currently a fragmented array of services which are variably available across settings in the Province.

The proposed COPD Strategy represents a step-wise introduction of activities within and across the continuum (Figure 1), to improve health care processes and results. Key priorities to be enacted are:

### Health Promotion and Prevention
- Integrate COPD Strategy activities with Smoke-Free Ontario initiatives of the Ministry of Health Promotion which target prevention, cessation, protection and public policy
- Integrate Smoke-Free Ontario programming into clinical practice by exploring the feasibility of developing smoking cessation programs into existing continuing medical education (CME) programs for primary care physicians and for nursing and respiratory therapy staff throughout the system

### Diagnosis
- Build on the results of the COPD Demonstration Site Project in order to increase primary care providers’ use of spirometry for COPD screening and diagnosis
- Ensure processes for linking primary care providers and specialists once patients have been diagnosed (i.e., shared care approach).
- Institute quality control procedures to ensure standardization amongst those performing spirometry
- Build on the platform of the Government’s Asthma Plan of Action by expanding the role of Asthma Educators to include COPD, and become Respiratory Health Educators

### Management
- Increase the supply of and support for COPD Respiratory Educators in varied settings in Ontario
- Enact shared care models and approaches which involve interdisciplinary providers
- Ensure improved access to pulmonary rehabilitation and improved rehabilitation capacity
- Identify designated centres that can evaluate the patient’s need for oxygen

### Palliative Care
- Provide healthcare providers with education about end-of-life care for COPD
- Ensure healthcare providers have access to tools and resources to facilitate patients’ end-of-life decision making and needs for palliation

### Provider Education
- Build on the platform of the government’s Asthma Plan of Action and the COPD Demonstration Site Project by implementing continuing medical education (CME) accredited workshops province-wide, focused on improved identification, diagnosis, and management of COPD in accordance with Canadian Thoracic Society Guidelines

### Surveillance and Evaluation
- Establish linkages among the Ontario Lung Association/COPD Advisory Panel and Institute for Clinical Evaluative Science (ICES) and other key partners, as appropriate, for the purposes of COPD surveillance and evaluation of all initiatives undertaken within a COPD Strategy

### Communications
- Raise public awareness of COPD by implementing a campaign and education initiatives about risks, symptoms and treatments

In summary, a COPD Strategy is an initiative that can benefit many in Ontario. It is time to act.

For a copy of the Proposal for a Comprehensive COPD Strategy for Ontario go to www.on.lung.ca. If you have views you would like to share with the Advisory Panel, please email me at cshcherban@on.lung.ca.

1. Members of the COPD Advisory Panel are: Chair: Dr. Roger Goldstein; Dr. Pauline Bragaglia; Ainsley Chapman; Dr. Anthony D’Urzo; Nancy Garvey; Dr. Andrea Gershon; Rosario Holmes; Lawrence D. Jackson; Carole Madeley; Louise McRae; Dilshad Moosa; Dr. Dennis O’Donnell; Lorelei Samis; Cindy Shcherban; Dr. Teresa To; Dr. Ross Upshur; Pam Wilton

World COPD Day is November 14, 2007.

New President and CEO, Ontario Lung Association

We would like to welcome Mr. George Habib, the new President & CEO of the Ontario Lung Association effective October 1, 2007.
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