“The Management of Severe Asthma”

Program

Chairs:
G. Walter Canonica, University of Genova DIMI
Genova, Italy
Constance H. Katelaris, Westmead Medical Centre
Westmead, Australia

1. Welcome to the World Allergy Forum Symposium and Introduction to “The Management of Severe Asthma”
G. Walter Canonica, University of Genova DIMI
Genova, Italy
Constance H. Katelaris, Westmead Medical Centre
Westmead, Australia

2. The Natural History of Severe Asthma
Michael Kaliner, Institute for Asthma and Allergy
Chevy Chase and Wheaton, Maryland

3. Treatment Options for Severe Asthma
Carlos E. Baena-Cagnani, Catholic University of Cordoba
Cordoba, Argentina

4. Economic Analysis of the Cost of Treatments for Severe Asthma
Michael S. Blaiss, University of Tennessee Health Science Center
Memphis, Tennessee

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About the World Allergy Organization

World Allergy Organization (WAO)
The World Allergy Organization (WAO) is an international umbrella organization of almost 80 regional and national allergy and clinical immunology societies. By collaborating with member societies, WAO provides direct educational outreach programs, symposia and lectureships to WAO individual members around the globe.

The World Allergy Organization Mission
The World Allergy Organization (WAO) exists to build a global alliance of allergy societies to advance excellence in clinical care, research, education and training.

Programs of the World Allergy Organization

GLORIA Global Resources in Allergy™
The GLORIA program promotes good practice in the management of allergic diseases through programs developed by panels of world experts. GLORIA educates medical professionals worldwide through regional and national presentations and local training initiatives. GLORIA educational modules promote the World Allergy Organization’s (WAO) mission – to optimize allergy care worldwide.

GLORIA Modules
Module 1: Allergic Rhinitis and Allergic Conjunctivitis
Module 2: Allergic Conjunctivitis (Expanded Version)
Module 3: Allergic Emergencies
Module 4: Immunotherapy
Module 5: Symptoms and Treatment of Asthma
Module 6: Food Allergy

World Allergy Forum (WAF) symposia are held at major international allergy meetings. Developed by international expert advisory panels, the symposia provide up-to-the-minute presentations on scientific and clinical developments in the field of allergic disease.

PAAA: Prevention of Allergy and Allergic Asthma
Prevention of Allergy and Allergic Asthma (PAAA) is a collaborative project with the World Health Organization providing guidelines and recommendations for prevention of the allergen-specific immunological sensitization necessary for disease.

Emerging Societies Meetings
WAO offers advice on initiating and developing allergy societies throughout the world. This proactive initiative aims to expand and improve the specialty of allergy by supporting colleagues working in the field of allergy worldwide. Through sharing practical experiences and alerting new societies to the criteria required for WAO membership, ESM creates relationships with future World Allergy Organization member societies, and educates WAO’s leadership about the challenges and opportunities faced by colleagues in developing countries.

WAO Journals
ACI-International – Journal of the World Allergy Organization (ACII - JWAO) and International Archives of Allergy and Immunology
Read the latest in global allergy and asthma news and research through subscriptions to WAO’s journal partners: ACI International - Journal of the World Allergy Organization (ACII - JWAO) and International Archives of Allergy and Immunology.
National Member Societies*

Albanian Society of Allergology and Clinical Immunology
American Academy of Allergy, Asthma and Immunology
American College of Allergy, Asthma and Immunology
Argentine Association of Allergy and Immunology
Argentine Society of Allergy and Immunopathology
Australasian Society of Clinical Immunology and Allergy
Austrian Society of Allergology and Immunology
Azerbaijan Society for Asthma, Allergy and Clinical Immunology
Bangladesh Society of Allergy and Immunology
Belgian Society of Allergology and Immunology
Brazilian Society of Allergy and Immunopathology
British Society for Allergy and Clinical Immunology
Bulgarian National Society of Allergology
Canadian Society of Allergy and Clinical Immunology
Chilean Society of Allergy and Immunology
China Allergology Society and Chinese Allergists
(Chinese) Hong Kong Institute of Allergy
Colombian Allergy, Asthma and Immunology Association
Croatian Society of Allergology and Clinical Immunology
Cuban Society of Allergology
Danish Society of Allergology
Ecuadorian Society of Allergy and Immunology
Egyptian Society of Allergy and Clinical Immunology
Finnish Society of Allergology and Clinical Immunology
French Society of Allergology and Clinical Immunology
German Society for Allergy and Clinical Immunology
Georgian Association of Allergology and Clinical Immunology
Hungarian Society of Allergology and Clinical Immunology
Icelandic Society of Allergy and Clinical Immunology
Indian College of Allergy, Asthma and Applied Immunology
Indonesian Society for Allergy and Immunology
Israel Society of Allergy and Clinical Immunology
Italian Society for Allergology and Clinical Immunology
Japanese Society of Allergology
Korean Society of Allergology
Lebanese Society of Allergy and Immunology
Malaysian Society of Allergy and Immunology
Mexican College of Pediatricians Specialized in Allergy and Clinical Immunology
Mexican College of Allergy, Asthma and Clinical Immunology
Mongolian Society of Allergology
Netherlands Society of Allergology
Norwegian Society of Allergology and Immunopathology
Paraguayan Society of Immunology and Allergy
Peruvian Society of Allergy and Immunology
Philippine Society of Allergy, Asthma and Immunology
Polish Society of Allergology
Portuguese Society of Allergology and Clinical Immunology
Romanian Society of Allergology and Clinical Immunology
Russian Association of Allergology and Clinical Immunology
Allergy Society of South Africa
Singapore Society of Immunology, Allergy & Rheumatology
Spanish Society of Allergology and Clinical Immunology
Swedish Association for Allergology
Swiss Society for Allergology and Immunology
Allergy and Immunology Society of Thailand
Turkish National Society of Allergy and Clinical Immunology
Ukrainian Association of Allergologists and Immunology
Uruguayan Society of Allergology
Venezuelan Society of Allergy and Immunology
Vietnam Association of Allergy, Asthma and Clinical Immunology
Zimbabwe Allergy Society

Regional Organizations

The Asian Pacific Association of Allergology and Clinical Immunology
CIS Society of Immunology and Allergology
European Academy of Allergology and Clinical Immunology
Latin American Society of Allergy and Immunology

Affiliate Organizations

International Association of Asthmology

Associate Member Societies

Czech Society of Allergology and Clinical Immunology
Ecuadorian Society of Allergology and Affiliated Sciences
Egyptian Society of Pediatric Allergy and Immunology
Italian Association of Territorial and Hospital Allergists

Latvian Association of Allergists
Panamanian Association of Allergology and Clinical Immunology
Association of Allergy and Clinical Immunology of Serbia and Montenegro

*As of September 2005

For WAO membership information please contact the Secretariat
World Allergy Organization (WAO)
555 East Wells Street, Suite 1100 • Milwaukee, WI 53202-3823 USA
Tel: +1 414 276 1791 • Fax: +1 414 276 3349
e-mail: info@worldallergy.org
Web site: www.worldallergy.org
Dear Colleagues and Friends,

It is my pleasure to welcome you to the American College of Allergy, Asthma and Immunology Annual Scientific Meeting, and to the 27th World Allergy Forum symposium, “The Management of Severe Asthma”. The World Allergy Forum is the longest-running educational program of World Allergy Organization (WAO), and we are proud to bring you an excellent international faculty for today’s symposium. WAO sincerely recognizes the unrestricted educational grant, provided by Novartis and Genentech, which supports the World Allergy Forum program.

WAO is an alliance of allergy and clinical immunology societies, and currently represents almost 80 Allergy and Clinical Immunology Societies around the world. Partnership with our member organizations is essential for the success of WAO and the worldwide development of Allergy as a specialty. I would like to warmly thank Dr. Mike Zitt and ACAAI for hosting today’s World Allergy Forum presentation.

In 2005, as an addition to World Allergy Forum and the well-established Global Resources in Allergy - GLORIA™ program, WAO launched the Seminars & Conferences Program. This new program offers member societies the opportunity to apply for WAO Lectureships at member society meetings, to provide an international speaker to lecture on a topic of the society’s choice. WAO is very proud of the outstanding educational programs it offers, and in collaboration with the ACAAI, WAO is now working to bring GLORIA™ to regional and local allergy meetings in the United States. This project is currently under development, but we urge you to regularly visit the WAO Web site: www.worldallergy.org for updates about the program.

To automatically receive updates on WAO activities and membership benefits, register for WAO News and Notes, our monthly e-letter. Each e-letter offers a review of the latest allergy papers published in the major journals, news from our member societies, information about WAO happenings, and other items, such as new allergy book reviews and educational synopses on all aspects of allergic disease. To subscribe to our e-letter, please visit www.worldallergy.org.

Thank you for attending this World Allergy Forum symposium today and for your valuable contribution to the specialty of allergy.

With my best regards,

Prof. G. Walter Canonica

World Allergy Organization Secretary General
Dear Colleagues,

In this era of economic rationalism, physicians like everyone else, must give good account for the money spent on medications and health care delivery, and they need to be able to justify expenditure in terms of cost benefit analyses. In order to do this, physicians have had to learn the language of the accountant and use the tools of the economist.

The World Allergy Organization is very pleased to present its World Allergy Forum at the 2005 American College of Allergy, Asthma and Immunology meeting in Anaheim. In the symposium, three experts will address the topic “Unmet Needs and Economic Burden of Asthma”.

Dr Michael Blaiss will discuss the ways in which health care costs are considered and will discuss direct, indirect and intangible costs as they apply to the management of patients with severe asthma so that we may then consider the economic burden of this disease upon the individual and the community.

It will become clear that severe asthma consumes a disproportionate share of health care resources with half the costs occurring in the most severe 10% of the asthmatic population. According to Cisternas et al [J Allergy Clin Immunol 2003;111:1212-8], pharmaceuticals are the largest contributor to total health care costs in asthma, particularly in mild asthma. It is interesting to note that as disease severity increases from mild to severe, the percentages of total costs attributed to medication declines from 47% to 19%. Effective controller medications have been demonstrated to reduce other high-cost components of health care including hospitalizations. The expenses of the treatment failures are magnified in both increased need for hospitalization and indirect costs.

Dr Michael Kaliner will present the findings of the TENOR study and discuss insights it has given us into the impact of severe and difficult-to-treat asthma on patients and on the health care system. Despite being on multiple standard-of-care medications, including high dose inhaled CCS, LABA and leukotriene antagonists, the TENOR cohort reports surprisingly high rates of healthcare utilization, most notably patients requiring hospitalization or ER care, as well as a high number of patients with a history of intubation.

The reasons why such patients have problems such as concomitant disease and lack of compliance are explored. The TENOR study highlights the need for every physician caring for patients with severe asthma to optimize management by focusing on issues such as patient education, minimizing the impact of allergic triggers and managing concomitant disease such as GERD, sinusitis and sleep apnoea. In this particular population we must continue to strive for new treatments with the ability to enhance control and decrease asthma exacerbations. In the context of severe asthma, expensive new medications such as omalizumab are potentially cost effective options needing careful consideration. Prof. Carlos Baena-Cagnani will address the treatment of severe asthma and present results of the Investigation of Omalizumab in Severe Asthma Treatment (INNOVATE) study.

Prof. Constance H. Katelaris
World Allergy Organization Treasurer
The Natural History of Severe Asthma

Michael A. Kaliner, MD
Medical Director
Institute for Asthma and Allergy
Chevy Chase and Wheaton, Maryland

Michael Kaliner is Medical Director of the Institute for Asthma and Allergy in Chevy Chase and Wheaton, MD. Among his achievements, Dr. Kaliner has been Head of Allergic Diseases and the Training Program Director of Allergy and Immunology at the National Institutes of Health; President of the American Academy of Allergy, Asthma and Immunology; Chairman of the American Board of Allergy and Immunology; a member of the Executive Committee of the Joint Council of Allergy and Immunology, President of the Allergy and Immunology Section of the American Thoracic Society; and currently is President-elect of the World Allergy Organization. In 2004, he co-founded Strategic Pharmaceutical Advisors, a professional pharmaceutical consulting company.

An avid teacher and researcher, Dr. Kaliner has published more than 475 articles, reviews, and books relating to allergies, sinusitis and asthma. He has edited magazines for patients, such as Breathe Well, which he created, and for physicians, such as The Current Report on Asthma and Allergy, which he also created. He has been Editor or on the Editorial Boards of many allergy and asthma journals, including the Journal of Allergy and Clinical Immunology, Emedicine and the Journal of the World Allergy Organization.

Dr. Kaliner was Head of the Allergy and Asthma Program at the National Institutes of Health for 18 years before founding the Institute for Asthma and Allergy, which is a state-of-the-art research and clinical program designed for difficult-to-manage patients in the mid-Atlantic area of the United States. Dr. Kaliner is recognized on the “Best Doctor” lists of The Best Doctors in America, American Health Magazine, Clinical Guide to Top Doctors, America’s Top Doctors, and The Washingtonian Magazine. In 1995, he received the Gold Key Award from the University of Maryland Medical School as their outstanding alumnus. In 2006 he will be honored to be the recipient of the American Academy of Allergy, Asthma and Immunology’s Distinguished Clinician Award.

Dr. Kaliner earned his MD from the University of Maryland and did his post-graduate training at the Hospital of the University of Maryland, the University of California in San Francisco, and Harvard University School of Medicine.

Abstract

The Unmet Needs in Asthma will cover some epidemiologic and experimental observations that indicate that asthma continues to be a difficult disease to manage, that many patients are not adequately controlled and that even when under excellent care, asthmatics continue to have exacerbations requiring urgent care, emergency room visits, and hospitalizations. While the current medications we employ are excellent, there is a significant portion of patients who do not respond adequately to them or fail to use them properly. Thus, there remains a large segment of the asthmatic population which is under treated and remains at risk. Identifying these unmet needs is the first step towards creating approaches and identifying strategies that work for this large segment of the diseased population.
Unmet Needs in Asthma: 
Asthma “Control” as Seen Through the Tenor Analysis

Michael Kaliner, MD
President-Elect, World Allergy Organization

Asthma Background

- 16 million asthmatics in the U.S.¹
  - 88% of which are estimated allergic asthmatics¹
    - 53% of whom report at least one unscheduled medical visit in a one year period²


Asthma Background

- In 2000, asthmatics had:
  - 10.4 million outpatient asthma visits to private physician offices and hospital clinics¹
  - 1.8 million emergency room visits¹
  - Nearly 500,000 hospitalizations²
  - Mortality of asthma increased 50% from 1980 to the mid-’90s

1) National Ambulatory Medical Care Survey, National Hospital Ambulatory Medical Care Survey, National Hospital Discharge Survey, NHAMCS, CDC
2) National Center for Health Statistics. 2000 National Hospital Discharge Survey, Advanced Data No. 326: June 3, 2002
Asthma Background

Every year an estimated\(^1\)

- $14.0 billion direct and indirect costs
  - $9.4 billion direct costs
    - Inpatient hospital services were the largest single direct medical expenditure (over $3.5 billion)
  - $4.6 billion indirect costs
    - Largest contributor: 10 million+ days of school lost ($1.5 billion)


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Estimated costs of asthma: 2002

<table>
<thead>
<tr>
<th>Cost $ (in billions)</th>
<th>Direct</th>
<th>Indirect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>$6.3</td>
<td></td>
</tr>
<tr>
<td>Morbidity</td>
<td></td>
<td>$2.7</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>$1.0</td>
</tr>
</tbody>
</table>

NHLBI Chartbook

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Annual Per-Patient Direct and Indirect Costs of Asthma

<table>
<thead>
<tr>
<th>Asthma Severity</th>
<th>Meds</th>
<th>Am Care</th>
<th>Hospital Use</th>
<th>Other Medical*</th>
<th>Total Direct Costs</th>
<th>Indirect Costs(^1)</th>
<th>Total Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>47%</td>
<td>7%</td>
<td>4%</td>
<td>5%</td>
<td>$1681</td>
<td>22%</td>
<td>$2646</td>
</tr>
<tr>
<td>Moderate</td>
<td>39%</td>
<td>7%</td>
<td>5%</td>
<td>4%</td>
<td>$2473</td>
<td>33%</td>
<td>$4530</td>
</tr>
<tr>
<td>Severe</td>
<td>19%</td>
<td>7%</td>
<td>17%</td>
<td>8%</td>
<td>$6354</td>
<td>46%</td>
<td>$12,813</td>
</tr>
</tbody>
</table>

\(^{1}\)Lost productivity at work and inability to perform daily activities

**Annual Hospitalizations for Asthma Compared with Other Conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hospital admissions per 10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary atherosclerosis</td>
<td>37.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19.8</td>
</tr>
<tr>
<td>Asthma</td>
<td>16.0</td>
</tr>
</tbody>
</table>


**Asthma Costs in the Developing World**

- Asthma Treatment as a Proportion of Family Income:
  - USA: 5.5 to 14% of total family income
  - India: 9% of per capita income

Source: GINA 2002

**Asthma Prevalence by Age**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Percentage of Asthmatic Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19y</td>
<td>8%</td>
</tr>
<tr>
<td>20-39y</td>
<td>19%</td>
</tr>
<tr>
<td>40-59y</td>
<td>21%</td>
</tr>
<tr>
<td>60+y</td>
<td>12%</td>
</tr>
</tbody>
</table>

An Introduction to TENOR

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens

TENOR Objectives

- Primary Objective:
  - Describe natural history of patients considered by physicians to have ‘severe’ or ‘difficult-to-treat’ asthma

- Secondary Objectives:
  - Examine relationship between features of asthma, treatments and outcome
  - Observe frequency of comorbid conditions
  - Examine the relationship between IgE and disease

TENOR Study Design

- TENOR is an observational study
  - Natural history of severe or difficult-to-treat asthma
  - Patients represent greatest unmet medical need
  - Collects information on factors related to treatment practices and outcomes of interest
  - Provides information on potential risk factors and confounding variables in analyses
TENOR Study Design (cont.)

- TENOR is a three-year, multi-center, observational study
  - Patients continue to receive medications and treatments administered for their asthma as indicated by their physician
- 4,756 patients
  - Aged 6 years or older
  - 283 sites across the U.S.
    - Managed care
    - HMO
    - Community physicians
    - Academic centers

Outcomes of Interest

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare utilization</td>
<td>Number of asthma-related visits to the ER</td>
</tr>
<tr>
<td></td>
<td>Number of asthma-related overnight hospitalizations</td>
</tr>
<tr>
<td></td>
<td>Number of asthma-related regular scheduled office visits</td>
</tr>
<tr>
<td></td>
<td>Number of asthma-related unscheduled office visits/contacts</td>
</tr>
<tr>
<td>Days of school/work missed</td>
<td>Number of days missed because of asthma</td>
</tr>
<tr>
<td></td>
<td>during the 14 days prior to each study evaluation</td>
</tr>
<tr>
<td></td>
<td>For children ≤ 12 years, the number of days of work or school</td>
</tr>
<tr>
<td></td>
<td>or school the parent missed due to their child’s asthma</td>
</tr>
<tr>
<td>Asthma symptoms and control</td>
<td>Measured using the Asthma Therapy Assessment Questionnaire (ATAQ)</td>
</tr>
<tr>
<td>Asthma-related quality of life</td>
<td>Measured using the Juniper MiniAQLQ and PACQLQ(S)</td>
</tr>
<tr>
<td>Living function</td>
<td>Measured by FEV1</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
</tr>
<tr>
<td>Targeted adverse events</td>
<td></td>
</tr>
</tbody>
</table>

Inclusion Criteria

- Subjects must have ‘severe’ or ‘difficult to treat’ asthma in the opinion of the physician
  - Mild or moderate patients were eligible for enrollment if they were considered difficult-to-treat by their physician and met the inclusion/exclusion criteria for the study
- Must have been receiving care from their current physician/provider for at least 1 year
- Must be at least 6 years old
- Must be able to read and understand English
Inclusion Criteria

- In addition, subjects must meet at least one of the following criteria:
  - During the past 12 months, had 2 or more unscheduled care visits for their asthma
  - During the past 12 months, had 2 or more oral steroid “bursts”
  - Currently require chronic daily high doses of inhaled steroids or ≥5mg oral prednisone
  - Currently using 3 or more medications to control asthma

Exclusion Criteria

- Subjects who meet ANY of the following criteria were excluded from TENOR:
  - Heavy smoker (> 30 pack years)
  - Primary diagnosis of cystic fibrosis
  - Severe cardiovascular disease (NYHA class II or greater)
  - Cancer (not including non-melanoma skin cancer or subjects whose cancer has been ‘clear’ for >5 years)
  - Severe psychiatric disorder (not including anxiety or depression)
  - Significant systemic disease (< 2-3 year life expectancy)
  - Known drug abuser

Data Collection

- Data are collected twice yearly.
- Study coordinators conduct interviews and subjects complete a self-administered questionnaire.
- Data are captured on electronic case report forms located on a secure study website.
Data Collection

<table>
<thead>
<tr>
<th>Collected by Study Coordinator</th>
<th>Baseline</th>
<th>Mid-Year Clinic Visit</th>
<th>Annual Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data of Visit/Intervention</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physician Assessment of Severity</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma History</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Care Utilization</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Days of work or school missed in previous 14 days</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medical History (personal and family)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid medical conditions</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication Use</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgE Level</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary function (FEV1/FVC)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted adverse events</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Patient Self-Report</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residential Information</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation Information</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms/Control</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Work Productivity</td>
<td>X</td>
<td></td>
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</tbody>
</table>

Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Adults 18+</th>
<th>Adolescents 12-17</th>
<th>Children 6-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Enrollment (n)</td>
<td>4,756</td>
<td>3,409</td>
<td>497</td>
<td>770</td>
</tr>
<tr>
<td>Age (years; mean)</td>
<td>39</td>
<td>49</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Weight (kg; mean)</td>
<td>75</td>
<td>84</td>
<td>67</td>
<td>41</td>
</tr>
<tr>
<td>BMI (kg/m²; mean)</td>
<td>28</td>
<td>30</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Gender (percent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>62%</td>
<td>71%</td>
<td>43%</td>
<td>34%</td>
</tr>
<tr>
<td>Male</td>
<td>38%</td>
<td>29%</td>
<td>57%</td>
<td>66%</td>
</tr>
<tr>
<td>Race/Ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>78%</td>
<td>80%</td>
<td>65%</td>
<td>65%</td>
</tr>
<tr>
<td>Black</td>
<td>15%</td>
<td>12%</td>
<td>22%</td>
<td>25%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>6%</td>
<td>6%</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>2%</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>M.D. Assessment of Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Moderate</td>
<td>48%</td>
<td>48%</td>
<td>48%</td>
<td>54%</td>
</tr>
<tr>
<td>Severe</td>
<td>48%</td>
<td>48%</td>
<td>48%</td>
<td>38%</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>24%</td>
<td>32%</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Clinical Measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgeL (IU/mL; Geometric mean)</td>
<td>106.0</td>
<td>85.2</td>
<td>223.0</td>
<td>182.5</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>Pre-bronchodilator</td>
<td>77</td>
<td>74</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>Post-bronchodilator</td>
<td>63</td>
<td>73</td>
<td>91</td>
</tr>
</tbody>
</table>

Patient Severity in TENOR

- The overwhelming majority of patients in TENOR have moderate or severe asthma according to physician assessment.
- About half of adolescent and adult patients were considered severe, while only 36% of pediatrics were considered severe.
Asthma Severity in TENOR

Physician Assessment of Treatment Difficulty

- At the baseline visit, physicians were asked if the patient was considered difficult-to-treat.
- The physician identified which of the following reasons made the patient difficult-to-treat (multiple selections were allowed).
- Overall, 96% of patients were considered difficult-to-treat.

Physician Assessment of Treatment Difficulty
The Asthma Therapy Assessment Questionnaire (ATAQ)

- Self-administered at baseline
- Measures patient perceived asthma control and symptoms
  - Scores range from 0 (no control problems) to 4 (maximum number of control problems)

Risk of HCU by Number of Asthma Control Problems

Conclusions

- TENOR confirms the impact of severe and difficult-to-treat asthma on patients and the healthcare system.
- There is a high rate of healthcare utilization among this population, most notably patients requiring hospitalization or ER care in the past 3 months, as well as the high number of patients with a history of intubation.
Conclusions

- Despite being on multiple standard-of-care medications, the TENOR cohort reported high rates of healthcare utilization.
- The most common LTC’s were:
  - Inhaled corticosteroids
  - Long-acting beta-agonists
  - Leukotriene modifiers

Why Are Treatment Goals Not Being Achieved?

- Differences in perception of what constitutes good asthma management between patients and physicians
- Poor understanding of indicators of control
  - Focus on too few variables (e.g., FEV1 only)
  - Failure to appreciate the full impact of asthma on multiple aspects of patients’ lives
- Persistent symptoms despite medication use
- Variability of response to treatment
- Poor adherence to treatment regimens


Mischaracterization of Moderate and Severe Asthma

![Graph showing the mischaracterization of asthma severity](image_url)

- 21% of patients with mild asthma were classified as moderate
- 14% of patients with moderate asthma were classified as severe
- 24% of patients with moderate asthma were classified as severe
- 1% of patients with severe asthma were classified as moderate
- 10% of patients with severe asthma were classified as mild

Pulmonary Function Tests Poor Indicators of Asthma Status

Many Patients* Remain Uncontrolled On Standard ICS and LABA Therapy

Analysis of Inhaled Corticosteroid Responses

*Based on the GOAL Study

1. Malmstrom et al. (n = 895)
2. Adult Study (n = 470)
3. CAMP (n = 311)
4. ACRN (n = 336)
Poor Adherence to Therapy: Nearly 70% of Patients Fail to Refill Their ICS

Adherence as Determined By Prescription Refills After First Prescription

- Leukotriene antagonists: 61%
- LABA: 40%
- ICS: 31%


Adherence to Inhaled Asthma Therapy Decreases Over Time

- Adults with moderate-to-severe asthma (N=50)
- Treated with BID ICS
- Actuation of inhaler monitored electronically

Adherence (%) vs. Week of study


Conclusions

- IgE levels in TENOR patients are elevated compared to non-asthmatic populations
- Decreases across age groups
  - Higher than non-asthmatics
- Higher in males
- Higher in current smokers
  - Consistent across race and gender
- Relationship between IgE and severity among children
Conclusions

- Asthma negatively impacts a large and growing number of patients
- Asthma treatment goals are not being met
- There is significant variability in response to currently recommended asthma controllers
- High-dose ICS and LABA fail to improve asthma for a significant percentage of patients
- Patient adherence to therapy remains less than optimal
- Despite previous treatment advances, there remains a need to improve asthma status and enhance patient well-being

Unmet Needs in Allergic Asthma Treatment

- Optimal treatment needs to:
  - Effectively control symptoms and pathogenesis of allergic disease
  - Reduce the incidence of exacerbations and hospitalizations
  - Enhance health status (quality of life)

What to do?

- Allergy treatment: avoidance and IT
- Treat sinuses
- Treat GERD/LPR
- Educate the patient and family
- Consider omalizumab
Professor Carlos E. Baena-Cagnani, a specialist in allergology, immunology and respiratory medicine, is the President of the World Allergy Organisation (WAO). He is a professor in the Postgraduate Department of the Faculty of Medicine at the Catholic University, Cordoba, Argentina. He is past President of the Latin American Society of Allergy and Immunology and the Argentinean Association of Allergy and Clinical Immunology. He is a member of the Global Initiative for Asthma (GINA) Assembly, and currently Prof. Baena-Cagnani is a member of the Executive Committee and Latin America Chairman for the ARIA–WHO committee. He trained in allergy and respiratory medicine at the University Clinic of the University of Navarra, Pamplona, Spain, and completed his speciality training in clinical research at the South Florida University in Tampa, USA. His main research interests focus on the epidemiology of asthma and allergy, with a particular emphasis on risk factors including allergen exposure. Professor Baena-Cagnani is also involved in clinical trials for the treatment of asthma and rhinitis and their co-morbidities, and sublingual immunotherapy in children. He has presented at more than 250 meetings and seminars throughout the world on such topics as asthma, rhinitis and immunotherapy, and has implemented educational asthma plans in different Latin American countries. Additionally, he has coordinated the phase III International Study of Asthma and Allergies in Childhood (ISAAC) in Argentina. Professor Baena-Cagnani is a member of the editorial board and contributing editor of several international scientific journals, and has published numerous manuscripts in peer-reviewed journals.

**Abstract**

**Severe Asthma**

The prevalence of asthma is rising all over the world and there is evidence that the number of patients suffering from severe asthma has increased. This is a very important issue since patients with severe asthma incur 50 percent of the public health expenditure on asthma. Severe asthma induces a dramatic deterioration in quality of life, with social and economic implications, as well as the anxiety associated with near fatal asthma or the potential of an asthma death.

Options evaluated for the treatment of severe asthma include cyclosporin, methotrexate, gold salts, IVIG, among others, however, the outcomes are variable and unpredictable, and therefore, these medications are not adequate treatment options for severe asthma. Recently, omalizumab, a humanized monoclonal antibody against IgE, has been launched in some countries including the U.S., and it has also recently been approved in the European Union. IgE is pathologically associated with allergic asthma, and omalizumab is recommended for administration in patients with severe allergic asthma.

Clinical studies have clearly demonstrated that omalizumab is effective and safe in patients suffering from severe asthma. Omalizumab significantly reduced emergency room visits as well as unscheduled doctor visits, and also asthma-related hospitalizations in both children and adults. In addition, omalizumab was shown to significantly increase the quality of life of patients suffering from severe asthma. Clinical efficacy was demonstrated by patients being able to reduce corticosteroid doses, and lung function was improved. An anti-inflammatory effect of omalizumab has also been demonstrated. It has an excellent safety profile, with adverse events similar to those found in the placebo group. Omalizumab is an important new option for the treatment of patients with severe allergic asthma.
Severe Asthma: Treatment Options

Prof. C.E. Baena-Cagnani
Faculty of Medicine
Catholic University of Cordoba
Argentina

Severe Asthma: Treatment Options

• What is severe persistent asthma?

• Treatment of severe persistent asthma

• Is there a new therapeutic option for the treatment of severe asthma?

• Omalizumab clinical efficacy

• Quality of Life Results from Pivotal Studies

Severe Asthma: Treatment Options

• What is severe persistent asthma?

• Treatment of severe persistent asthma

• Is there a new therapeutic option for the treatment of severe asthma?

• Omalizumab clinical efficacy

• Quality of Life Results from Pivotal Studies
Severe Asthma, step 4

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Lung Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe persistent</strong></td>
<td>• FEV, or PEF &lt; 60% predicted</td>
</tr>
<tr>
<td>• Continual</td>
<td>• PEF variability &gt; 30%</td>
</tr>
<tr>
<td>• Limited physical activity</td>
<td></td>
</tr>
<tr>
<td>• Exacerbations frequent</td>
<td></td>
</tr>
<tr>
<td>• Night-time symptoms</td>
<td></td>
</tr>
<tr>
<td>frequent</td>
<td></td>
</tr>
</tbody>
</table>

FEV = forced expiratory flow in 1 second; PEF = peak expiratory flow.


Characterization of Severe Persistent Asthma

Severe Persistent Asthma
Features of poor controlled and severe

<table>
<thead>
<tr>
<th>Poorly controlled</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>More transient state of the disease</td>
<td>Not responsive to standard therapy</td>
</tr>
<tr>
<td>The level of symptoms can be improved when standard approaches to therapy are appropriately used</td>
<td>Remaining poorly controlled despite vigorous attempts at management</td>
</tr>
</tbody>
</table>
ATS workshop consensus for definition of severe/refractory asthma

Major characteristics
To achieve control to level of mild-moderate persistent asthma
1. Treatment with corticosteroids
2. Requirement of oral corticosteroids
3. Asthma symptoms on a daily basis
4. Persistent asthma over a 2-year period
5. Oral PEF variability > 20%
6. Three or more oral steroid "bursts" per year
7. A near-fatal asthma event in the past

Definition requires one or both major criteria and two minor criteria

Severe Asthma: Treatment Options

• What is severe persistent asthma?

• Treatment of severe persistent asthma

• Is there a new therapeutic option for the treatment of severe asthma?

• Omalizumab clinical efficacy

• Quality of Life Results from Pivotal Studies

Treatment of severe persistent asthma

• Oral steroids
• Methotrexate
• Gold salts
• Cyclosporin
• Leukotriene receptor antagonists
• IVIG
Severe Asthma: Treatment Options

- What is severe persistent asthma?
- Treatment of severe persistent asthma
- Is there a new therapeutic option for the treatment of severe asthma?
- Omalizumab clinical efficacy
- Quality of Life Results from Pivotal Studies

Omalizumab Characteristics

- Humanized mAb against IgE regardless of specificity
- Binds circulating IgE
- Forms small, biologically inert Omalizumab:IgE complexes
- Does not activate complement

*CDR = complementarity-determining region

Adapted from Boushey H. J Allergy Clin Immunol. 2001;108:S77-83

Severe Asthma: Treatment Options

- What is severe persistent asthma?
- Treatment of severe persistent asthma
- Is there a new therapeutic option for the treatment of severe asthma?
- Omalizumab clinical efficacy
- Quality of Life Results from Pivotal Studies
Asthma Phase III studies

- Randomized, double-blind, placebo-controlled, multicentre, parallel-group
- Omalizumab administered subcutaneously. Dose per 4 weeks calculated according to bodyweight and baseline IgE:
  - 150–300mg: 1–2 injections every 4 weeks (60% of patients)
  - >300–750mg: 2–3 injections every 2 weeks (40% of patients)
- Study populations
  - Adults and adolescents with moderate-to-severe asthma, symptomatic while treated with inhaled corticosteroids
  - Children with moderate asthma, asymptomatic while treated with inhaled corticosteroids

Example of Phase III study design

Omalizumab Pivotal Studies

- Study 1
  

- Study 2
  
Overview of patients in the phase III asthma studies

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
<th>010 (children)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>P</td>
<td>O</td>
</tr>
<tr>
<td>n</td>
<td>268</td>
<td>257</td>
<td>274</td>
</tr>
<tr>
<td>Mean age</td>
<td>39</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>Mean FEV₁ (% predicted)</td>
<td>68</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>Mean BDP dose (µg/day)*</td>
<td>679</td>
<td>676</td>
<td>769</td>
</tr>
<tr>
<td>Severe asthma (%)</td>
<td>22</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Mean IgE (IU/mL)</td>
<td>172</td>
<td>186</td>
<td>223</td>
</tr>
</tbody>
</table>

O = Omalizumab  P = Placebo

Studies 1 and 2: Primary endpoint

- Asthma exacerbations using protocol-defined method in stable steroid phase

<table>
<thead>
<tr>
<th># exacerbation</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Omlzmb</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>n=268</td>
<td>n=257</td>
</tr>
<tr>
<td>0</td>
<td>229</td>
<td>197</td>
</tr>
<tr>
<td></td>
<td>85%</td>
<td>77%</td>
</tr>
<tr>
<td>≥1</td>
<td>39</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>15%</td>
<td>23%</td>
</tr>
<tr>
<td>Difference</td>
<td>8%</td>
<td>18%</td>
</tr>
<tr>
<td>P-value</td>
<td>0.006</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Frequency of Exacerbations: Steroid-stable Phase

**p<0.01, ***p<0.001 vs placebo
Studies 1 and 2: Primary endpoint

- Asthma exacerbations using protocol-defined method in steroid reduction phase

<table>
<thead>
<tr>
<th># exacerbation</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Omizmb</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>n=268</td>
<td>n=257</td>
</tr>
<tr>
<td>0</td>
<td>211</td>
<td>174</td>
</tr>
<tr>
<td></td>
<td>79%</td>
<td>68%</td>
</tr>
<tr>
<td>≥1</td>
<td>57</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>21%</td>
<td>32%</td>
</tr>
<tr>
<td>Difference</td>
<td>11%</td>
<td>14%</td>
</tr>
<tr>
<td>P-value</td>
<td>0.003</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Inhaled Corticosteroid: Median Dose Reduction

<table>
<thead>
<tr>
<th>Percentage reduction</th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 019 (children)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

***p<0.001

Studies 1 and 2: Secondary endpoints

- Number of daily puffs of beta agonist for rescue: Approximately 1-puff/day inter-treatment difference
- Change in dose of inhaled steroid (subjects)

<table>
<thead>
<tr>
<th>BDP dose category</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Omizmb</td>
<td>Placebo</td>
</tr>
<tr>
<td>Cessation</td>
<td>106/268</td>
<td>49/257</td>
</tr>
<tr>
<td></td>
<td>40%</td>
<td>19%</td>
</tr>
<tr>
<td>Difference</td>
<td>21%</td>
<td>25%</td>
</tr>
<tr>
<td>No change</td>
<td>44/268</td>
<td>66/257</td>
</tr>
<tr>
<td></td>
<td>16%</td>
<td>26%</td>
</tr>
<tr>
<td>Difference</td>
<td>10%</td>
<td>17%</td>
</tr>
</tbody>
</table>
Conventional Asthma Parameters

Pediatric Study Design

- Phase III, 28-week, double-blind, randomized, parallel-group, placebo-controlled, multicenter trial
- 334 relatively asymptomatic children (6-12yrs)
- Primary endpoints
  - Safety and tolerability
- Secondary endpoints
  - Corticosteroid requirement
  - Pharmacokinetics/pharmacodynamics
  - Rescue medication use
  - Quality of life
  - Healthcare resource utilization


Pediatric Study: Exacerbation Results

- Placebo
- Omalizumab

![Graph showing exacerbations per patient (mean)](image)

Pediatric Study: Median ICS Reduction

![Graph showing median ICS reduction](image)


---

Extensions of Pediatric Study: Design

- 24-week open-label extension*
- 3-year open-label extension
- Patients randomized to Omalizumab during core study continued drug without interruption
- Patients randomized to placebo during core study switched to Omalizumab

Primary variable
- Long-term safety and tolerability


---

Pediatric Study and Extensions: Conclusions

- Omalizumab has an inhaled corticosteroid-sparing effect
- Omalizumab reduces asthma exacerbations, improves asthma control

- Omalizumab is well tolerated
- Omalizumab 12-month safety profile in children is similar to all other controlled studies
- Omalizumab safety profile is not altered after long-term treatment (approx 3.5 yrs)

Anti-IgE Therapy for Chronic Asthma

Number of Patients with at least one Exacerbation

<table>
<thead>
<tr>
<th>Study</th>
<th>Month 1</th>
<th>Month 6</th>
<th>Month 12</th>
<th>Month 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>EoT with omalizumab</td>
<td>150.7</td>
<td>110.7</td>
<td>90.7</td>
<td>50.7</td>
</tr>
<tr>
<td>EoT with placebo</td>
<td>150.7</td>
<td>110.7</td>
<td>90.7</td>
<td>50.7</td>
</tr>
</tbody>
</table>

 Walker & al, Cochrane Library, 2004

Anti-IgE Therapy for Chronic Asthma

Reduction of ICS use by more than 50%

<table>
<thead>
<tr>
<th>Study</th>
<th>Month 1</th>
<th>Month 6</th>
<th>Month 12</th>
<th>Month 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>EoT with omalizumab</td>
<td>150.7</td>
<td>110.7</td>
<td>90.7</td>
<td>50.7</td>
</tr>
<tr>
<td>EoT with placebo</td>
<td>150.7</td>
<td>110.7</td>
<td>90.7</td>
<td>50.7</td>
</tr>
</tbody>
</table>

 Walker & al, Cochrane Library, 2004

Predicting Response to Omalizumab, an Anti-IgE Antibody, in Patients With Allergic Asthma

Study objective
To determine baseline characteristics predictive of response to omalizumab in patients with allergic asthma

Design
Pooled analysis of two multicenter, double-blind, randomized, placebo-controlled phase III studies with omalizumab

Patients
1070 allergic asthma patients symptomatic despite moderate-to-high doses (mean, 725 µg/d) of inhaled BDP

J Bousquet, S Wenzel, S Holgate, W Lumry, P Freeman, H Fox Chest 2004;125:1378-1386
Response rates
After 16 weeks of treatment

<table>
<thead>
<tr>
<th>Response</th>
<th>Omalizumab</th>
<th>Placebo</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced symptoms</td>
<td>276/671</td>
<td>263/481</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Reduced usage of rescue medication</td>
<td>275/517</td>
<td>199/401</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Improved lung function</td>
<td>167/615</td>
<td>40/486</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Improve QoL</td>
<td>184/647</td>
<td>129/414</td>
<td>0.082</td>
</tr>
<tr>
<td>Composite definition</td>
<td>334/521</td>
<td>235/488</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* According to definition of response


Patients who benefit most when omalizumab is administered as add-on therapy are those:

- Receiving high doses of BDP
- With a history of frequent ER asthma treatment
- With poor lung function

Patients should be treated with omalizumab for a minimum duration of 12 weeks

J Bousquet, S Werzel, S Holgate, W Lushey, P Freeman, H Fox
Chest 2004; 125:1378-1386

Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE

M. Humbert, R. Beasley, J. Ayres, R. Slavin, J. Hebert, J.
Bousquet, K.-M. Beeh, S. Ramos, G. W. Canonica,
S. Hedgecock, H. Fox, M. Blogg, K. Surrey

Allergy 2005; 60: 308 - 316
Investigation of Omalizumab in Severe Asthma Treatment

- A 28-week randomized DBPC study to assess the efficacy and safety of omalizumab add-on therapy in patients (GINA 2002) with severe persistent asthma (SPA)
  - Inadequately controlled despite high doses of ICS (>1,000mcg) and LABA

The combination of the current level of symptoms and the current maintenance treatment step should enable the establishment of the patient’s asthma severity and the corresponding appropriate maintenance treatment

GINA 2002

GINA-based Definition of Asthma Severity

<table>
<thead>
<tr>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe persistent</td>
<td>Moderate persistent</td>
<td>Severe persistent</td>
</tr>
<tr>
<td>≤500 μg BDP or equivalent</td>
<td>500–1000 μg BDP or equivalent</td>
<td>&gt;1000 μg BDP or equivalent</td>
</tr>
</tbody>
</table>

Global Initiative for Asthma (GINA) 2012. NIH Publication No. 02-3659
Inclusion criteria

- Patients (12-75 yrs) with allergic asthma
- FEV₁ reversibility ≥12%
- Inadequate asthma control demonstrated by
  - FEV₁ ≥40% ≤80 at randomization
  - Meaningful asthma symptoms in the 4 weeks prior to randomization despite high-dose of ICS & LABA
  - Clinically meaningful exacerbations in the previous year
    - Either 2 exacerbations requiring systemic corticosteroids OR
    - a severe exacerbation (PEF or FEV₁ ≥60% personal best requiring systemic corticosteroids and requiring ER treatment or hospitalization)

Significant unmet need despite GINA step 4 therapy

- Median FEV₁ of 62% of predicted value
- 67% of patients at high-risk of asthma-related mortality according to GINA definition (previous intubation or ER visit or hospitalization in past year)
- Approximately 2 clinically significant asthma exacerbations per patient per year and 5 unscheduled doctor’s visits
- Average of 31 school/work days missed in the past year
- Meaningful impact from asthma on patients QoL

Primary efficacy variable

- Rate of clinically significant asthma exacerbations
  - Worsening of asthma symptoms requiring treatment with systemic corticosteroids meeting at least one of these criteria:
    - 2/3 consecutive night awakenings
    - PEF or FEV₁ ≥80% personal best
    - >20% drop in PEF on 2/3 days
    - >50% increase in rescue use on 2/3 days
Other efficacy variables

- Severe exacerbation rate
  - PEF or FEV <60% personal best

- Emergency visit for asthma
  - Hospital admission
  - ER visits
  - Unscheduled doctor’s visits

- Asthma related QoL
Omalizumab is well tolerated

- The percentage of patients who experienced AEs was similar in both treatment groups
  - Omalizumab (72.2%), placebo (75.5%)
- Fewer serious AEs in the omalizumab group
  - Omalizumab (11.8%), placebo (15.6%)
- AEs were generally mild or moderate in nature and of short duration

INNOVATE
Conclusions

- In patients with SPA, omalizumab therapy as add-on to best available treatment:
  - Decrease Exacerbation rate
  - Reduction of severe exacerbation rate
  - Reduce ER visit due to Asthma worsening
  - Improvement of asthma QoL
- Omalizumab add-on therapy was well tolerated with a safety and tolerability profile similar to that of placebo

Omalizumab in Patients With Allergic Asthma
(With High Risk of Serious Asthma-Related Event)

![Graph showing the comparison between Omalizumab and Placebo in patients with allergic asthma](image-url)
The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma

- Pooled analysis from 7 studies
- To examine the effect of omalizumab on exacerbations
- 4,308 patients with severe persistent asthma
- 2,511 treated with omalizumab


Analysis of asthma exacerbations using Poisson regression for individual studies and pooled data (ITT population)

More than 90% of patients met the criteria for severe persistent asthma set out by GINA 2002


Relative rates of asthma exacerbations across subgroups in pooled studies

The rate of hospitalizations and other unscheduled visits for the pooled population using Poisson regression

<table>
<thead>
<tr>
<th>Type of visit</th>
<th>Rate per year</th>
<th>Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total emergency visits</td>
<td>0.332</td>
<td>0.433</td>
<td>0.251</td>
</tr>
<tr>
<td></td>
<td>0.531</td>
<td>0.469</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>0.036</td>
<td>0.446</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>0.414</td>
<td>(0.344, 0.493)</td>
<td>0.041</td>
</tr>
<tr>
<td>Emergency room visits</td>
<td>0.006</td>
<td>0.466</td>
<td>0.040</td>
</tr>
<tr>
<td></td>
<td>0.417</td>
<td>(0.347, 0.498)</td>
<td>0.013</td>
</tr>
<tr>
<td>Unscheduled doctor visits</td>
<td>0.252</td>
<td>0.743</td>
<td>0.511</td>
</tr>
<tr>
<td></td>
<td>0.568</td>
<td>(0.417, 0.734)</td>
<td>0.0866</td>
</tr>
</tbody>
</table>

Data for study 2 were not included. Randomized patients who did not receive study medication were excluded from the Poisson regression analysis.


These data from controlled clinical studies in patients with severe persistent asthma show that omalizumab is highly efficacious as add-on treatment to concomitant asthma therapy


Severe Asthma: Treatment Options

- What is severe persistent asthma?
- Treatment of severe persistent asthma
- Is there a new therapeutic option for the treatment of severe asthma?
- Omalizumab clinical efficacy
- Quality of Life Results from Pivotal Studies
Mean AQLQ Change from BL to End Steroid Stabilization Period

All Randomised Patients (Study 008)

Mean AQLQ change score

Activities  Emotions  Symptoms  Exposure  Overall Score

P = 0.083  P = 0.011  P = 0.001  P = 0.004  P < 0.001

OMA  Placebo

Mean AQLQ Change from BL to End Stabilization Period

All Randomised Patients (Study 009)

Mean AQLQ change score

Activities  Emotions  Symptoms  Exposure  Overall Score

P = 0.004  P < 0.001  P < 0.001  P = 0.062  P < 0.001

OMA  Placebo

Asthma-Related Quality of Life
Pivotal Studies

Patients with ≥ 0.5 and ≥ 1.5 units change in AQLQ overall score at end of steroid-reduction phase, %

P < .001  P < .001  P = .002

OMALizumab  0.5 Placebo  1.5 Placebo

Data not included in full prescribing information.

Management of asthma: updating the GINA guidelines

<table>
<thead>
<tr>
<th>Asthma severity</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Intermittent</td>
<td>Avoidance of risk factors, immunotherapy, short-acting beta-2 agonists as needed</td>
</tr>
<tr>
<td>Mild Persistent</td>
<td>Low-dose inhaled steroids</td>
</tr>
<tr>
<td>Moderate Persistent</td>
<td>Combination of long-acting beta2 agonists with low dose inhaled steroids</td>
</tr>
<tr>
<td>Moderate Persistent</td>
<td>Combination with higher doses inhaled corticosteroids, theophylline, antileukotrienes</td>
</tr>
<tr>
<td>Severe Persistent</td>
<td>Systemic steroids</td>
</tr>
</tbody>
</table>

From: Fabbri LM 2004

---

GOAL Study
Frequency of patients achieving well-controlled asthma

![Graph showing frequency of patients achieving well-controlled asthma]

Bateman ED et al. AJRCCM 2004; 179: 836-844

---

Omalizumab is of clinically relevant efficacy in difficult-to-treat patients and should be considered add-on treatment for patients with severe persistent asthma who continue to suffer with inadequately controlled asthma despite **best available therapy**

Bousquet J, et al. Allergy 2006; 60: 302 - 308
Thank you!

University of Cordoba
Lights Block Jesuits
Cordoba, Argentina
Humanity Cultural Heritage
UNESCO
Economic Analysis of the Cost of Treatments for Severe Asthma

Michael Steven Blaiss, MD  
Clinical Professor of Pediatrics and Medicine  
University of Tennessee Health Sciences Center College of Medicine  
Memphis, Tennessee

Dr. Michael S. Blaiss is Clinical Professor of Pediatrics and Medicine at the University of Tennessee Health Sciences Center in Memphis and in private practice in Memphis at Allergy & Asthma Care.  He has presented at more than 250 meetings and seminars throughout the world on such topics as allergic rhinitis, asthma, socioeconomic subjects in allergy and asthma and issues in compliance and adherence. Dr. Blaiss has written for several peer-reviewed journals, including Journal of Pediatrics, Journal of Allergy and Clinical Immunology, and JAMA and several allergy textbooks.  He has co-edited one text, Atlas of Allergic Diseases.  In addition, he is a member of the editorial board for the Journal of Asthma, The World Allergy Organization Journal, Allergy and Asthma Proceedings, and the Annals of Allergy, Asthma and Immunology. Dr. Blaiss is a fellow of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology. He served on the Board of Directors for the American Board of Allergy and Clinical Immunology and is Immediate Past-President of the American College of Allergy, Asthma, and Immunology. Dr. Blaiss received his medical degree from the University of Tennessee Center for Health Sciences.  After completing his residency at Le Bonheur Children’s Medical Center, he completed a fellowship in allergy/immunology at Ochsner Medical Foundation in New Orleans, Louisiana.

Abstract
Economic Analysis of the Cost of Treatments for Severe Asthma

Severe asthma consumes a disproportionate share of asthma health care resources. We need treatment strategies that minimize exacerbations which may decrease the need for unscheduled medical services, reduced ED visits, and minimize hospitalizations should be cost-effective in asthma care.

Direct Medical Costs:
1) The amount of money spent on medical services directly due to an illness. This includes hospital care, pharmaceutical products, physician care, nursing services, etc.
2) The amount of resources consumed directly to produce a certain outcome such as personnel time, equipment, supplies, etc.

Direct Non-medical Costs:
1) Expenditures outside the medical market such as costs borne by patients seeking care. This includes costs such as transportation, child care, and lodging, etc.

Indirect Costs:
1) Costs resulting from a patient being unable to perform normal activities due to illness and therefore borne by the patient, the patient’s family, or an employer.
2) Expenditures or losses as an indirect consequence of illness or consumption of medical care. Examples include lost earnings, decreased productivity.
3) Economic value of changes in health status as measured by lost wages, willingness to pay, or human capital theory.

Intangible Costs:
1) Include humanistic measures of changes in health status such as quality of life and satisfaction.

Costs disproportionately affects those with most severe disease:
- severe asthma 50% costs (10% population)
- mild asthma 20% costs (70% population)

Medical management can lead to cost savings in severe asthma. Combination therapy with inhaled corticosteroids and long-acting beta agonist has been documented to decrease ED visits and hospitalizations. In severe and difficult-to-treat asthmatics, omalizumab prevented the development of exacerbations in 17 additional patients for every 100 treated. This corresponds to a prevented fraction of 50% in the incidence of exacerbations in patients randomized to omalizumab. In the INNOVATE study (Humbert M, Beasley R, Ayres J et al. Allergy 2005; 60:309-16), omalizumab decreased hospital admission rate to 1 admission for every 8 treated patients per year compared to 1 admission for every 4 placebo patients per year. Further studies are needed to measure economic outcomes in the treatment of severe asthma.
Economic Analysis of the Cost of Treatments for Severe Asthma

Michael S. Blaiss, MD
Clinical Professor of Pediatrics and Medicine
University of Tennessee Health Science Center
Memphis, Tennessee USA

Introduction

• Severe asthma consumes a disproportionate share of asthma health care resources
• Treatment strategies that minimize exacerbations which may decrease the need for unscheduled medical services, reduced ED visits, and minimize hospitalizations should be cost-effective in asthma care

US Health Care Spending/GNP

[Graph showing the percentage of US Health Care Spending/GNP from 1970 to 2010]

CMS, Office of the Actuary
Components of Cost

Direct Medical Costs

expenditures on tangible health care products or services, which contribute to the gross national product

Cost Data

Components of Cost

Direct Medical Costs
(Medications, hospital days, tests, procedures, etc.)

Cost Data

Components of Cost

Other Direct (non-medical) Costs

expenditures on tangible products or services, which contribute to the gross national product. They are needed to obtain care, but they do not directly contribute to health care.

Cost Data
Components of Cost

Other Direct (non-medical) Costs
(transportation to the doctor’s office, hiring a baby sitter so a parent can visit the doctor, etc.)

Components of Cost

Unpaid resource commitment. Cost of morbidity and mortality.

Components of Cost

Indirect Costs
(Unpaid assistance, days lost from work, decreased productivity, etc.)
Components of Cost

Cost Data

Intangible Costs
(Pain, suffering, etc.)

Measurement of resource use

Direct Medical Costs
(Medications, hospital days, tests, procedures, etc.)

Other Direct (non-medical) Costs
(Transportation to the doctor’s office, hiring a baby sitter so a parent can visit the doctor, etc.)

Indirect Costs
(Unpaid assistance, days lost from work, decreased productivity, etc.)

Cost Data

Intangible Costs
(Pain, suffering, etc.)

Burden of Asthma

Cost of Disease: Direct

- Total Direct Cost (M)
  - 1994 $6,106
  - 1998 $7,365

Cost in $ Millions

- Hospital Inpatient
- Emergency Department
- Hospital Outpatient
- Physician Inpatient
- Physician Office Visits
- Prescriptions

Burden of Asthma
Cost of Disease: Indirect

Cost in $ Millions

- School Days Lost
- Lost Work - Men
- Lost Work - Women
- Housekeeping
- Mortality


Cost of Asthma to Employers

- Medical
- Pharmacy
- Absenteeism
- Disability

Control

- Other care
- Respiratory
- Other care
- Other respiratory
- Asthma care

$ per year


Presenteeism: At Work-But Out of It

Paul Hemp

Harvard Business Review
October 2004
Hidden Costs of Presenteeism

- Direct Costs
  - Medical and Pharmaceutical-24%
- Indirect Costs
  - Absenteeism-6%
  - Short-Term Disability-6%
  - Long-Term Disability-1%
  - Presenteeism-63%

Annual Data 2000 from Bank One

Economic burden

Direct costs: associated with medical treatments

Indirect costs: non-medical output losses resulting from illness

Disproportionately affects those with most severe disease:

- severe asthma 50% costs (10% population)
- mild asthma 20% costs (70% population)

Global Burden of Asthma. Allergy 2004

Annual Per-Patient Direct and Indirect Costs of Asthma

<table>
<thead>
<tr>
<th>Asthma Severity</th>
<th>Meds</th>
<th>Am Care</th>
<th>Hospital Use</th>
<th>Other Medical *</th>
<th>Total Direct Costs</th>
<th>Indirect Costs¹</th>
<th>Total Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>47%</td>
<td>7%</td>
<td>4%</td>
<td>5%</td>
<td>$1661</td>
<td>22%</td>
<td>$2646</td>
</tr>
<tr>
<td>Moderate</td>
<td>39%</td>
<td>7%</td>
<td>5%</td>
<td>4%</td>
<td>$2473</td>
<td>33%</td>
<td>$4530</td>
</tr>
<tr>
<td>Severe</td>
<td>19%</td>
<td>7%</td>
<td>17%</td>
<td>8%</td>
<td>$6354</td>
<td>46%</td>
<td>$12,813</td>
</tr>
</tbody>
</table>

¹Lost productivity at work and inability to perform daily activities

TENOR Study

- On-going 3 year multi-center observational cohort study (not a clinical trial)
- Evaluating “Difficult to Treat” asthma
- Sponsored by Genentech and Novartis

Healthcare Utilization and Missing Work/School Days By Asthma Severity

<table>
<thead>
<tr>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missed 1+ days of work/school in past 2 weeks*</td>
</tr>
<tr>
<td>Unscheduled office visit in past 3 months*</td>
</tr>
<tr>
<td>Regular office visit in past 3 months*</td>
</tr>
<tr>
<td>Steroid burst in past 3 months*</td>
</tr>
<tr>
<td>Hospitalization in past 3 months*</td>
</tr>
<tr>
<td>ER visit in past 3 months*</td>
</tr>
<tr>
<td>Ever intubated</td>
</tr>
</tbody>
</table>


Types of Economic Analysis

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost minimization</td>
<td>Cost in $; identical effects</td>
<td>Choose product with lower price</td>
</tr>
<tr>
<td>Cost effectiveness</td>
<td>Cost in $; different effects</td>
<td>Cost per number of cures or years life saved</td>
</tr>
<tr>
<td>Cost benefit</td>
<td>Cost and benefit in $</td>
<td>$ spent vs. $ gain</td>
</tr>
<tr>
<td>Cost utility</td>
<td>Cost in $; different effects weighted by utilities</td>
<td>Cost per quality-adjusted life years</td>
</tr>
</tbody>
</table>

Inhaled corticosteroids plus salmeterol or montelukast: Effects on resource utilization and costs

David A. Stempel, MD, John C. O’Donnell, PhD, and Jay W. Meyer, PhD. Seattle, Wash, Research Triangle Park, NC, and Eden Prairie, Minn.


Design: 2-Year Pre-Post Retrospective Cohort Claims Study

<table>
<thead>
<tr>
<th></th>
<th>FP + salmeterol (n = 261)</th>
<th>ICS + salmeterol (n = 703)*</th>
<th>ICS + montelukast (n = 216)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-index period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-index period</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All observations made between 1996 and 1999.

* ICS + salmeterol group included FP users.
† ICS + montelukast group included FP users.
‡ Index event was the first filled prescription for salmeterol or montelukast.


Pre-Index Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>FP + Salmeterol</th>
<th>ICS + Salmeterol</th>
<th>ICS + Montelukast</th>
<th>P-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Yr)</td>
<td>39.0 (11.1)</td>
<td>49.3 (18.3)</td>
<td>39.9 (13.9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Female (%)</td>
<td>60.9</td>
<td>61.5</td>
<td>52.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Respiratory comorbidty † (%)</td>
<td>26.1</td>
<td>23.0</td>
<td>22.2</td>
<td>NS</td>
</tr>
<tr>
<td>Short-acting beta-agonist (refills)</td>
<td>5.8 (6.6)</td>
<td>5.7 (6.8)</td>
<td>5.6 (6.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Oral steroid use (refills)</td>
<td>1.8 (2.2)</td>
<td>1.3 (2.0)</td>
<td>1.5 (2.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Emergency department visit (% with ≥ 1)</td>
<td>17.2</td>
<td>13.9</td>
<td>13.9</td>
<td>NS</td>
</tr>
<tr>
<td>Inpatient admission (% with ≥ 1)</td>
<td>4.6</td>
<td>4.4</td>
<td>4.2</td>
<td>NS</td>
</tr>
<tr>
<td>Inpatient adm and ED visit (% with ≥ 1)</td>
<td>10.0</td>
<td>16.9</td>
<td>15.3</td>
<td>NS</td>
</tr>
<tr>
<td>Pharmacy asthma cost ($)</td>
<td>358 (355)</td>
<td>378 (359)</td>
<td>450 (437)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total asthma cost ($)</td>
<td>1036 (1300)</td>
<td>1020 (1063)</td>
<td>1216 (1820)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Mean(±SD) or percent. P-value from F or chi-square tests of the null hypothesis of no significant difference among groups.
† P-value, ICS + Montelukast versus ICS + Salmeterol
‡ Identified with International Classification of Diseases (9th revision) codes (chronic obstructive pulmonary disease and other respiratory conditions).

Level of Control Achieved with 1 Year of Therapy with Combination Fluticasone/Salmeterol 500/50 BID: The GOAL Study

- % Subjects not well controlled
- % Subjects not totally controlled

- Steroid naive
- Low Dose ICS
- High Dose ICS


Omalizumab and Costs of Treatment

- **Risk difference**: Omalizumab prevented exacerbations in about 17 additional patients for every 100 treated
- **Prevented fraction**: 50% of potential exacerbations were prevented by treatment with Omalizumab
- **Number needed to treat**: 5.7 patients needed to be treated with Omalizumab to maintain 1 patient free of an exacerbation


**TABLE II. Mean daily treatment costs (per person; 2003 dollars)**

<table>
<thead>
<tr>
<th></th>
<th>Omalizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>0.04</td>
<td>0.28</td>
</tr>
<tr>
<td>ED visits</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Physician office visits</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>Rescue albuterol</td>
<td>0.42</td>
<td>0.52</td>
</tr>
<tr>
<td>Inhaled BDP*</td>
<td>0.69</td>
<td>1.19</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>38.66</td>
<td>—</td>
</tr>
<tr>
<td>Total daily costs</td>
<td>39.85</td>
<td>2.07</td>
</tr>
</tbody>
</table>

*ED, Emergency department.
*Based on study 009 only.

Oba and Saltzman; JACI 2004
Review

- Omalizumab is cost-effective if there are 5 hospitalizations a year or > 20 days per year hospitalized
- Based on RCT and not “real world” studies
  - Low hospitalization rate due to being in RCT
- Not based on QALY, but AQLQ
- Did not look at indirect costs associated with asthma

Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE.

Humbert M, Beasley R, Ayres J et al.
Allergy 2005; 60:309-16.

GINA Classification of Asthma Severity by Daily Medication Regimen and Response to Treatment

<table>
<thead>
<tr>
<th>Current Treatment Step</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms + 1 x wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturnal symptoms + 12 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung function normal between exacerbations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Intermittent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mild Persistent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Moderate Persistent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Severe Persistent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms + 1 x wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturnal symptoms + 1 x wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung function normal between exacerbations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mild Persistent</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>- Moderate Persistent</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>- Severe Persistent</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Step 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturnal symptoms + 1 x wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung function normal between exacerbations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Moderate Persistent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Severe Persistent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent nocturnal symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity +10% placed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Severe Persistent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Severe Persistent</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>- Severe Persistent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Investigation of Omalizumab in Severe Asthma Treatment: INNOVATE

• A 28-week randomized, double-blind, placebo-controlled study to assess the efficacy and safety of omalizumab add-on therapy in patients with severe persistent asthma (GINA 2002) inadequately controlled despite high doses of inhaled corticosteroids (>1,000 µg/day) and long-acting $\beta_2$-agonists

INNOVATE

• Primary objective:
  ▪ To determine the effect on clinically significant asthma exacerbation rate of omalizumab compared to placebo as add-on to GINA step-4 therapy

• Secondary objectives:
  ▪ QOL, clinical symptom score, morning PEF, and asthma rescue medication
  ▪ Frequency of hospitalization, ER visit, and unscheduled doctor visits
  ▪ Evaluate safety and tolerability

Demography

<table>
<thead>
<tr>
<th></th>
<th>Omalizumab (n = 209)</th>
<th>Placebo (n = 210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) Mean (SD)</td>
<td>43.4 (13.29)</td>
<td>43.3 (13.49)</td>
</tr>
<tr>
<td>Sex n (% Female)</td>
<td>141 (87.6)</td>
<td>138 (85.7)</td>
</tr>
<tr>
<td>Weight (kg) Mean (SD)</td>
<td>81.2 (19.75)</td>
<td>79.2 (17.48)</td>
</tr>
<tr>
<td>IgE (IU/ml) Mean (SD)</td>
<td>197.6 (145.2)</td>
<td>189.6 (153.1)</td>
</tr>
<tr>
<td>FEV1 % Pred. Mean (SD)</td>
<td>61.0 (14.42)</td>
<td>61.6 (13.83)</td>
</tr>
<tr>
<td>FEV1 Rev. Mean (SD)</td>
<td>28.9 (23.27)</td>
<td>24.5 (23.27)</td>
</tr>
<tr>
<td>ICS Daily Dose Mean (SD)</td>
<td>2359 (1210)</td>
<td>2301 (878)</td>
</tr>
<tr>
<td>LABA Use (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Daily OCS Use (%)</td>
<td>23.4</td>
<td>20.0</td>
</tr>
<tr>
<td>Theophylline (%)</td>
<td>30.6</td>
<td>24.3</td>
</tr>
<tr>
<td>Antileukotriene (%)</td>
<td>35.4</td>
<td>34.3</td>
</tr>
</tbody>
</table>
Primary Analysis of Asthma Exacerbation Rate

- Primary Analysis Adjusted for Baseline Exacerbations
  - P = 0.043
- Primary Analysis Without Adjustment for Exacerbations
  - P = 0.153

Unscheduled Visits Due to Asthma Worsening Are Significantly Reduced
(unadjusted for baseline exacerbations)

<table>
<thead>
<tr>
<th>Type of visit</th>
<th>Omalizumab (n = 209) Rate/26 wks</th>
<th>Placebo (n = 210) Rate/26 wks</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall unscheduled emergency visit</td>
<td>0.24</td>
<td>0.43</td>
<td>0.038</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>0.06</td>
<td>0.12</td>
<td>0.117</td>
</tr>
<tr>
<td>ER visits</td>
<td>0.04</td>
<td>0.06</td>
<td>0.480</td>
</tr>
<tr>
<td>Unscheduled doctor visits</td>
<td>0.13</td>
<td>0.24</td>
<td>0.090</td>
</tr>
</tbody>
</table>

- Hospital admission rate equates to
  - 1 admission for every 4 placebo patients per year
  - 1 admission for every 8 omalizumab patients per year

Conclusions

- One needs to consider costs in looking at asthma outcomes in the severe asthmatic patient
- Optimal treatment
  - Effectively control symptoms
  - Reduce asthma variability especially exacerbations and hospitalizations
  - Enhance health status (Quality of Life)
- Because the severe asthmatic consumes a high percentage of the health care dollar in ED visits and hospitalizations, it is important that we continue to use and develop new treatments that decrease asthma exacerbations