Review
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Evolution of Asthma Concept and Effect of Current Asthma Management Guidelines

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Concept of asthma has changed from symptom-complex or airway hypersensitivity to airway inflammation and airway remodeling. Based on this concept asthma management guidelines (JGL) has been developed in Japan. Death from asthma has decreased drastically since the publication of the guidelines, although it is still high in elderly population. Further works are expected for "zero-death" from asthma and for tighter control of airway inflammation and resultant airway remodeling.

Key Words: Asthma; concept; guideline; airway remodeling

FACT OF ASTHMA

Asthma is a chronic inflammatory disease of the airway associated with airway hyperresponsiveness and episodes of airway narrowing. Facts of asthma in WHO website in 2010 said;

- 300 million people suffer from asthma.
- 255,000 people died of asthma in 2005.
- Prevalence of asthma is increased or increasing.
- Asthma is the most common disease among children.
- Over 80% of asthma death occurs in low and lower-middle income countries.
- Asthma is under-diagnosed and under-treated.

in 2005 in the world.[1]

EVOLUTION OF ASTHMA CONCEPT

Treatment of asthma progressed aligned with evolution of concept of asthma.[2] In the middle part of 20th century asthma was called as a disease or symptom complex which showed paroxysmal dyspnea with reversible bronchoconstriction. Spasm of bronchial smooth muscle was thought to be major mechanism of airway narrowing.[3] Accordingly, bronchodilators including epinephrine, isoproterenol and theophyllines were major agents to treat asthma attacks. In 1960s asthma was defined as disease of airway hyperresponsiveness.[4,5] Around 1980s, inflammation of the airway was found to be related with airway hyperresponsiveness and asthma symptoms. Eosinophils are most outstanding cells in the airway of asthma patients. Eosinophils are found to cause or contribute to histological and functional changes in the airway of asthma patients including desquamation of bronchial epithelium and airway hyperresponsiveness.[6-8] Anti-inflammatory agents including corticosteroids, anti-allergic agents, theophyllines, are used to suppress eosinophilia in the airway and has been proved to be effective.[9,10] Following studies on pathophysiology of asthma have shown that many cells and cytokines have roles in the inflammation of the airway of asthma patients in complicated manner.[11] Structural change of the airway due to airway inflammation (airway remodeling) has been shown to contribute to persistent airway narrowing and airway hyperresponsiveness (Fig. 1).[12]

AIRWAY REMODELING AND SMAD PROTEINS

The basic pathological features of bronchial asthma can be explained on the basis of chronic airway inflammation, involving inflammatory cells such as T cells (particularly type 2 helper T, Th2 cells) and mast cells, and airway remodeling. Airway

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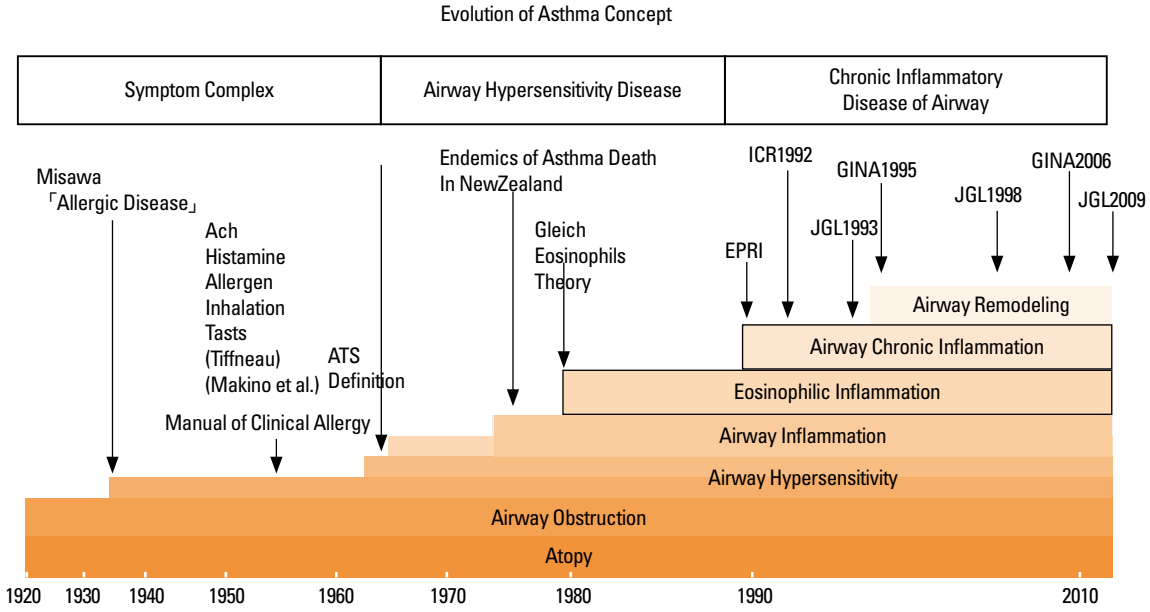


Fig. 1. Evolution of Asthma Concept from Makino S.[2]
ATS, American Thoracic Society; ICR, International Consensus Report; JGL, Japanese Asthma Prevention and Management Guidelines; GINA, Global Initiative for Asthma.

remodeling causes persistent airway narrowing and airway hyperresponsiveness.[12] In fact back to 1966 Makino found that asthma patients with low FEV1/Predicted VC had increased airway responsiveness.[13]

Recent attention has focused on the role of transforming growth factor (TGF)-beta, a fibrogenic cytokine, in airway remodeling. Currently available evidence suggests that airway remodeling is caused by an imbalance in regulatory mechanisms mediated by Smads, a family of signal-transducing molecules of TGF-beta. Smad7 is an intracellular antagonist of TGF-beta signaling, which could determine the intensity or duration of the TGF-beta signal. Sagara, Nakao and others found that the expression of Smad7 in bronchial epithelial cells is inversely correlated to basement membrane thickness and airway hyperresponsiveness in patients with asthma, while the expression of phosphorylated activated Smad2 (p-Smad2) is positively correlated with them.[14,15] Intracellular level of Smad protein is controlled by cytokines. Fueki, Sagara and other found the effects of the Th2 cytokines interleukin (IL)-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF), and the regulatory cytokine IL-10 on the expression of inhibitory Smad7 protein in bronchial epithelial cells IL-10 inhibited the expression of TGF-beta-inducible early gene, which is known to down-regulate Smad7 expression.[16] McMillan and others found budesonide treatment regulated active TGF-beta signaling with a reduction in the expression of Smad2 and the concomitant up-regulation of Smad7 in lung tissue sections of experimental asthma of mice.[17]

These observations suggest that airway remodeling can be controlled by drugs and cytokines which suppress airway inflammation with modulation of signaling of TGF-beta (Fig. 2-1, 2-2).

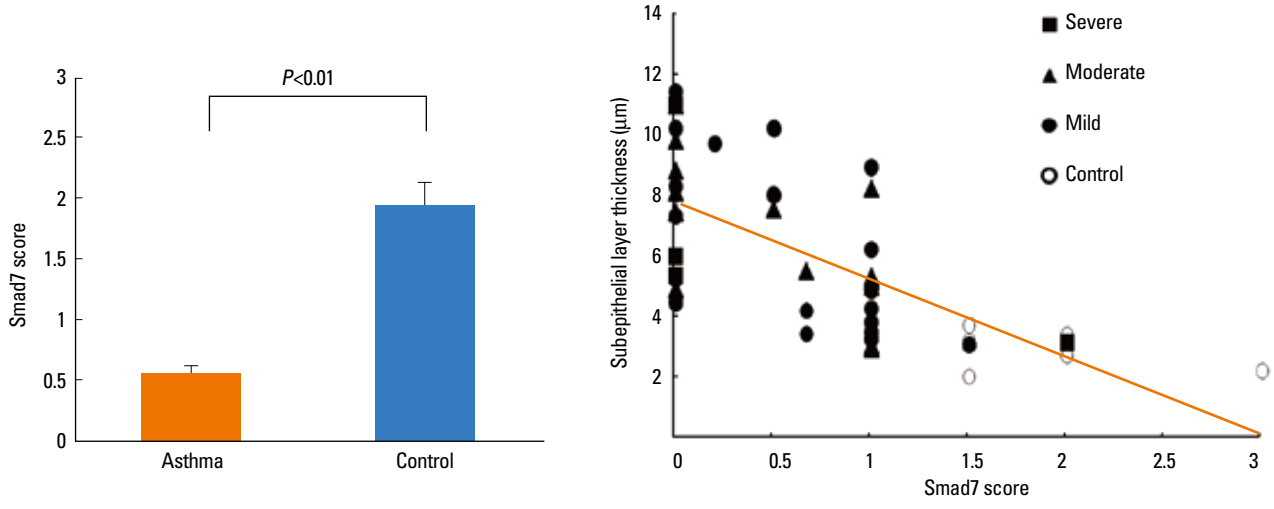
ASTHMA MANAGEMENT GUIDELINES

In 1992 International Consensus Report for the Diagnosis and Management of asthma was released.[18] Global Initiative for Asthma (GINA) started in 1993 and was published in 1995. GINA was developed on the concept of airway inflammation of the airway.[19]

In Japan of 1993, Asthma Prevention and Management Guidelines (JGL) was first developed by Japanese Society of Allergology.[20-22] Like GINA JGL has been produced with the concept that asthma is an inflammatory disease of the airway, and its treatment is aimed at prevention and control of airway inflammation. This concept is new and different from the previous understanding of asthma. Since then JGL has been revised in 1997, 2002, 2006, and 2009, and accepted as the standard of asthma management in Japan.[23]

EVALUATION OF ASTHMA-MANAGEMENT GUIDELINES

Effectiveness of asthma management guidelines can be evaluated by the change of death from asthma comparing before and after implementation of JGL, and trend of medical expenses for the treatment of asthma. The total number of death from asthma for each year was obtained by the report of Ministry of



Smad7 was down-regulated in the airway of asthma patients

Inverse relationship between thickness of BM and density of Smad7 in airway.

Fig. 2-1. Smad7 seems to suppress thickening of bronchial basement membrane in asthma.[15] MB: Basement membrane of the epithelium.

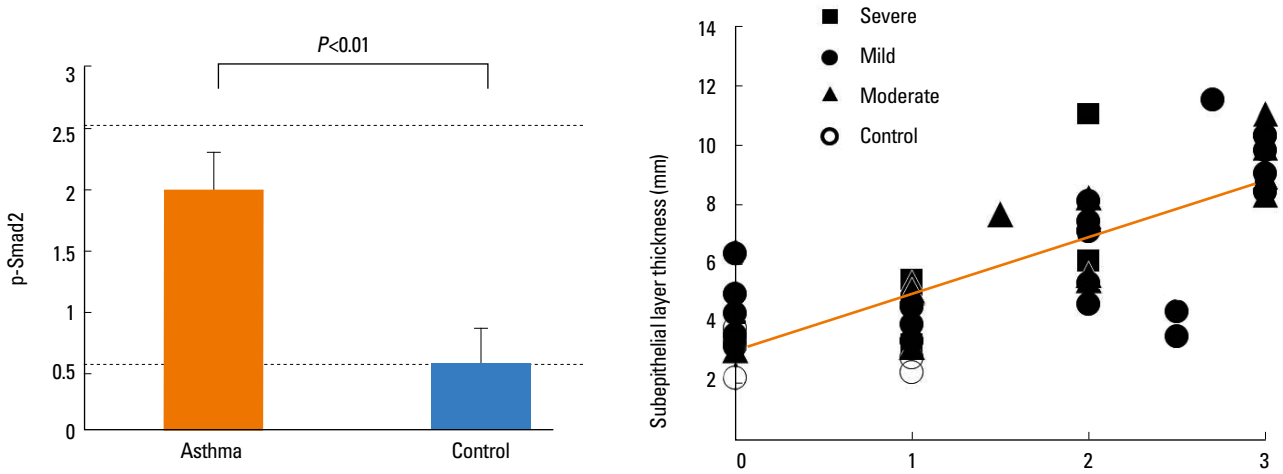


Fig. 2-2. p-Smad2 expression level in bronchial epithelial cells was elevated in asthma. Basement membrane thickness was correlated with Smad2 expression level in the airway of mild to severe asthmatics.[14]

Health, Welfare and Labor, Japan.[24]

Death from asthma seems to have started to decrease continuously around 1997 to 2008. The total number of death from asthma from 1993 to 1998 was approximately 5900, and it was 2300 in 2008. JGL has been widely known in both specialists and non-specialists and widely accepted. Increased use of anti-inflammatory agents including inhaled corticosteroids is thought to be one of causes of this decrease (Fig. 3). [20,23]

GINA has been accepted as a template of national asthma management guidelines in many of countries in Asia Pacific. Implementation of asthma management guidelines with concept that asthma is an inflammatory disease of airway would be effective to decrease of death from asthma in both developed and developing countries.

Another important issue on asthma control is its expense. While in Japan the death from asthma has decreased drastically for the past one decade, direct medical expense for asthma treatment has not increased.[24] This finding suggests that proper implementation of asthma management guidelines is not expensive and would contribute to the social productivity by decreasing work loss and absence for school.

REMAINING PROBLEM: HIGH RATE OF DEATH FROM ASTHMA IN ELDERLY GENERATION

Death from asthma has decreased in children to younger adult populations, while it is still high in elderly population especially 65 years and over. This can be partly due to increase of elderly

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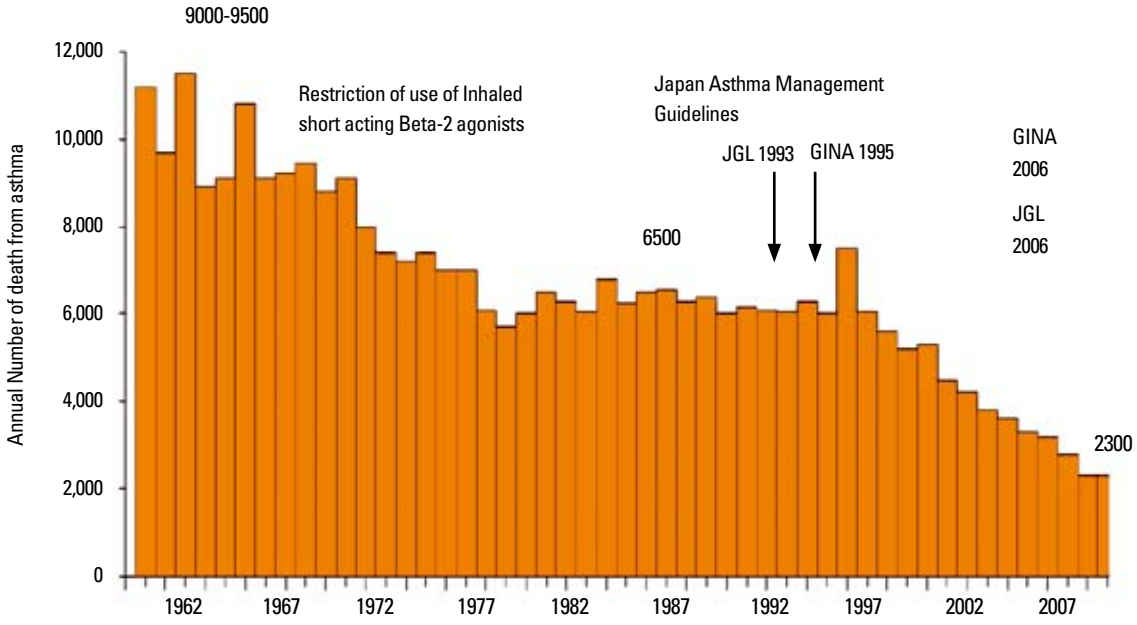

Fig. 3. Time course of decrease of death from asthma in Japan. Five years after JGL publication death from asthma has started to decrease continuously.

population at larger. In fact population 65 years and over is approximately 23% of total Japanese population in 2009. Apparently, control of death from asthma in elderly population is another target of Japanese Guidelines.[25]

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