Pharmacotherapy Options in COPD According to the New Guidelines of The Japanese Respiratory Society

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Abstract

"Guidelines for the Diagnosis and Treatment of COPD (Chronic Obstructive Pulmonary Disease)" of The Japanese Respiratory Society was revised for the first time in 5 years, and the third edition was published in June 2009. This edition of the guidelines has 4 major purposes, namely: 1) guarantee of high quality healthcare, 2) standardization of healthcare, 3) increased transparency of healthcare, and 4) improved efficiency of medical economics. A comprehensive view of the pharmacotherapy in COPD is as follows. *Pharmacotherapy using bronchodilators as the drugs of first choice is effective to alleviate symptoms, prevent exacerbations, enhance health-related quality of life (HRQOL), and improve exercise tolerance. Therefore, the pharmacotherapy for COPD patients should be actively utilized.* However, the clinical condition of each patient as well as the mechanism of action of each drug must be taken into consideration when treating COPD, using the guidelines as a reference. Accumulation of clinical experience of each physician should lead to future evidence, on which the next version of the guidelines will be prepared.

Key words Long-acting anticholinergic agent, Short-acting bronchodilators, Mucus-regulating drugs, Dyspnea

Introduction

"Guidelines for the Diagnosis and Treatment of COPD (Chronic Obstructive Pulmonary Disease)" of The Japanese Respiratory Society was revised for the first time in 5 years, and the third edition was published in June 2009 (hereinafter referred to as New COPD Guidelines).[1] First, it is necessary to be familiar with the purposes of this New COPD Guidelines, namely the following 4 items:

(1) Guarantee of high quality healthcare
(2) Standardization of healthcare (i.e., standardized healthcare should be available at any medical institution in Japan)
(3) Increased transparency of healthcare (i.e., the reasons for the treatment can clearly be explained to other physicians and patients)
(4) Improved efficiency of medical economics

Although they have not necessarily been achieved at the present time, progress in achieving them should be continually assessed.

As with any guidelines, the COPD guidelines should constantly evolve. Since the content of the guidelines contain the best available evidence at the time of writing, it is necessary to fully understand and investigate the current evidence and decide what evidence should be accumulated in the future.

The definitions of "evidence" and "evidence-based medicine (EBM)" need to be reviewed and precisely defined here. EBM in clinical practice is not only a large collection of randomized controlled trials (RCT), but it involves the clinical expertise of many specialists as well as the clinical experience of each physician. It may be safe to say that the power of the evidence and the universality obtained from an RCT is higher than

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those derived from the clinical experience of an individual. However, the individuality aspect of RCT is not as great as that of the individual clinical experience (**Fig. 1**).[2]

Simply reading New COPD Guidelines does not guarantee that the physicians can provide COPD patient with treatment that is completely satisfactory. What is considered necessary is to treat COPD patient with a comprehensive understanding of COPD, asthma, pulmonary hypertension, respiratory failure, and systemic comorbidities. Since clinicians are providing medical care to individual patients, the clinical condition and characteristics of each patient must be taken into consideration in the treatment, utilizing New COPD Guidelines as a reference.

Long-acting Anticholinergic Agents are the Drugs of First Choice

In New COPD Guidelines, the long-acting anticholinergic agents were selected as the drugs of first choice in the treatment of COPD, instead of the regular administration of long-acting bronchodilators as indicated in the second edition of the guidelines.[3] It is expected that the physicians whose specialty is not respiratory medicine will also realize that COPD is a treatable condition by actively using long-acting anticholinergic agents in the course of treatment.

COPD is, as its definition is indicating, a clinical condition characterized by the manifestation of chronic airflow obstruction. In COPD, the destruction of the lung structure (emphysematous lesions, in which the increased pulmonary compliance causes the loss of elasticity of the lung tissue) and the obstruction of the small airways (peripheral airways) cause hyperinflation of the lungs even at rest. This hyperinflation of the lungs leads to an elevated level of the residual volume, causing air trapping (increased area of un-exchanged air). The most effective drug to alleviate this condition is a long-acting anticholinergic agent that can reduce air trapping by relieving obstruction

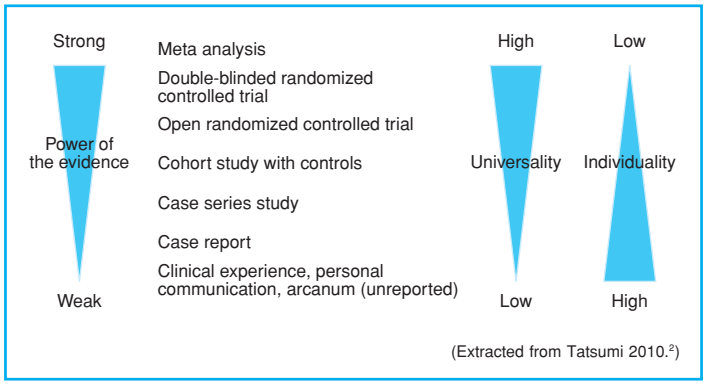

Fig. 1 Evidence in clinical medicine

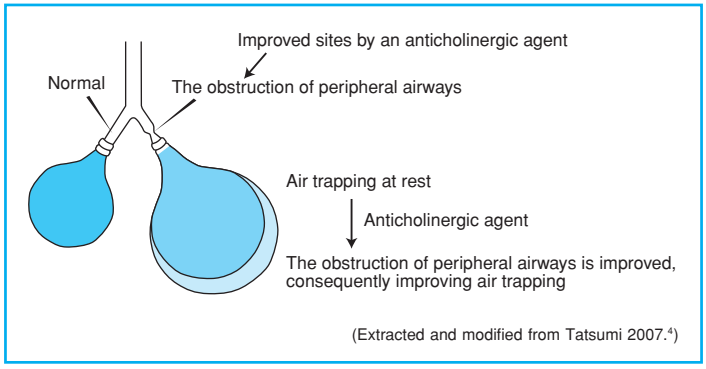

Fig. 2 The sites of action of an anticholinergic agent, using the COPD balloon model

of peripheral airways (**Fig. 2**).[4]

A symptom of COPD that impairs the quality of life (QOL) and causes problems of daily living for COPD patients is shortness of breath on exertion. This symptom is attributed to air trapping that occurs during exertion. The peripheral airway obstruction forces inhalation to start before the air volume in the lungs returns to the resting level, causing the lungs to be hyperinflated compared to the resting state. It is obvious that only a limited volume of air can be inhaled into the lungs that are already hyperinflated. Therefore, the patients feel that they cannot inhale as much air as they expect and start having difficulty breathing, causing an impaired ability to carry out various activities.

This state is referred to as dynamic pulmonary hyperinflation or exercise-induced air trapping (**Fig. 3**).[4] The drug that can treat this condition most effectively is a long-acting anticholinergic

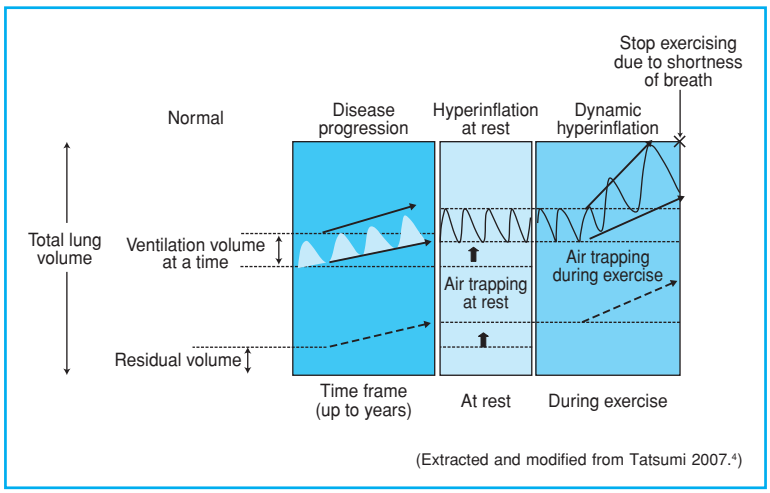

Fig. 3 Why does a patient with COPD have difficulty breathing when actively moving?

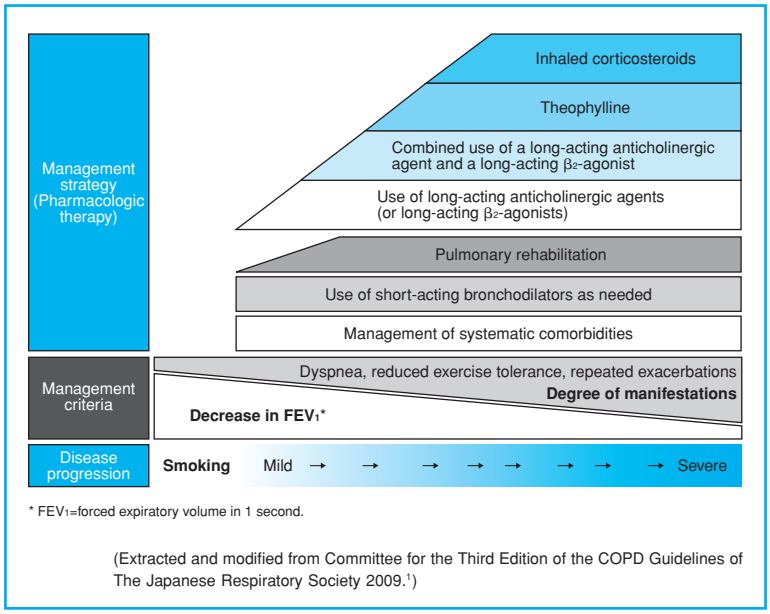

Fig. 4 Pharmacologic therapy in stable COPD

agent. However, in a patient with advanced COPD, monotherapy with one long-acting anticholinergic agent may not achieve a sufficient effect. In such a case, it is necessary to consider an additional drug, taking the clinical condition of the patient into consideration.

Management of Stable COPD

Figure 4 depicting the pharmacotherapy options of stable COPD can be regarded as the fruit of labor of New COPD Guidelines (**Fig. 4**).[1] In the second edition of the guidelines, the progress of the disease was categorized stepwise by using the degree of obstructive ventilation disorder. However, the new edition indicates that the assessment of disease progression should consider the degree of symptoms such as dyspnea, decrease in exercise tolerance, and susceptibility to exacerbation, along with the degree of obstructive ventilation disorder (decrease in forced expiratory volume [FEV_1]).

Unlike the second edition that recommend choosing a pharmacotherapy only according to the stage of the disease, New COPD Guidelines conveys the message that the clinical condition as a whole, including the pulmonary functions and the degree of respiratory symptoms as well as

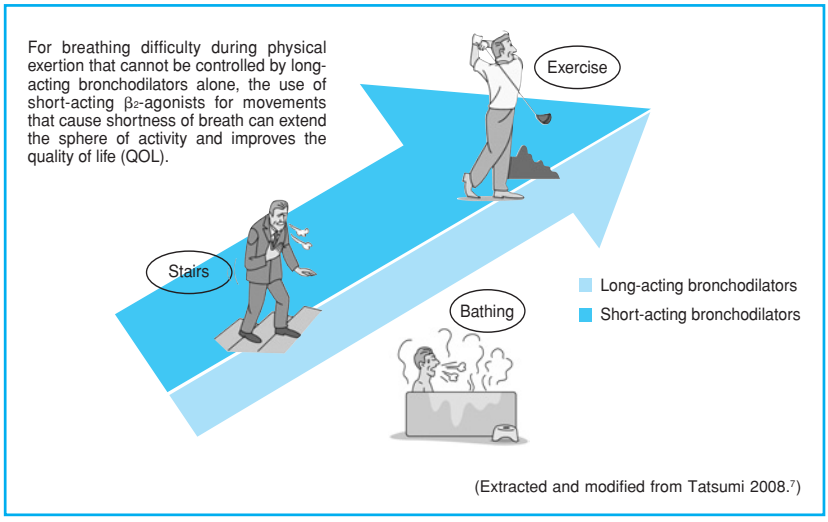

Fig. 5 Active use of short-acting bronchodilators

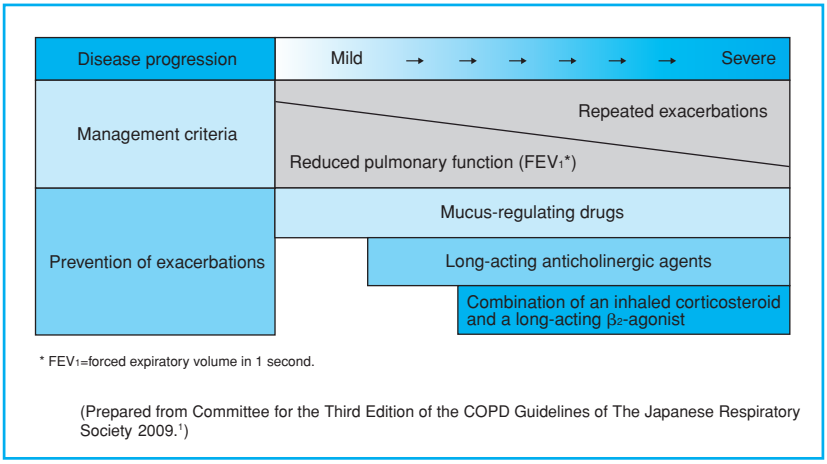

Fig. 6 Pharmacotherapy for the prevention of exacerbations

systemic comorbidity, should be taken into consideration to choose an appropriate course of treatment. In addition, the new edition indicates that pulmonary rehabilitation should also be incorporated into the early stage of treatment in accordance with the symptoms.[5]

The Role of Short-acting Bronchodilators

The second edition of the COPD guidelines recommended to use short-acting bronchodilators as needed, thereby giving the impression that short-acting bronchodilators play a supplementary role to long-acting bronchodilators. In contrast, New COPD Guidelines indicate that β_2-agonists have the advantage of a faster onset of action than anticholinergic agents, although anticholinergic agents produce a better maximal bronchodilation than β_2-agonists. Short-acting bronchodilators are effective in preventing dyspnea on exertion and can control dyspnea in severe COPD patients caused by daily activities like bathing, and physicians should make more active use of them[6,7] (**Fig. 5**).

Pharmacotherapy for the Prevention of Exacerbations

Many COPD patients present with excessive sputum production and difficulty in expectoration. For COPD patients with excessive sputum production, the rate of FEV_1 (i.e., pulmonary function) decrease associated with advancing age is much greater than that in patients with less sputum production, and therefore proper measures must be taken. There are many reports indicating that mucus-regulating drugs do not improve pulmonary functions or dyspnea in COPD patients; however, a study indicates that mucus-regulating drugs significantly reduce the frequency and duration of COPD exacerbations.[8] In addition to improving the sputum viscoelasticity, new findings on the mechanism in which mucus-regulating drugs reduce COPD exacerbations include an antioxidative effect, suppression of mucin gene expression, and suppression of virus infection.

Besides mucus-regulating drugs, other drugs that are useful in the management of stable COPD are also shown to be effective in preventing the exacerbations of COPD (**Fig. 6**).[1]

Conclusion

A comprehensive view of the pharmacotherapy in COPD is as follows. *Pharmacotherapy using bronchodilators as the drugs of first choice is effective in alleviating the symptoms and preventing exacerbations. It is also effective in enhancing health-related quality of life (HRQOL) and improving exercise tolerance. Therefore, pharmacotherapy for COPD should be actively utilized in the course of treatment.*

As mentioned in *Introduction*, the course of treatment in COPD should consider the clinical condition of each patient as well as the mechanism of action of each drug, utilizing New COPD Guidelines as a reference. I believe that the accumulation of clinical experience of each physician will be the basis for future evidence, and further serve as a solid foundation on which the next version of the COPD guidelines will be built.

References

1. Committee for the Third Edition of the COPD Guidelines of The Japanese Respiratory Society. Guidelines for the Diagnosis and Treatment of COPD (Chronic Obstructive Pulmonary Disease). 3rd ed. Tokyo: Medical Review Co., Ltd.; 2009.
2. Tatsumi K. Respiratory Disease: Chinese Herbal Medicine Guide. Rev ed. Tokyo: Kyowa Kikaku; 2010.
3. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008;359:1543–1554.
4. Tatsumi K. Diagnosis and Treatment of COPD in Primary Care. Tokyo: Medical Review Co., Ltd.; 2007.
5. Casaburi R, Kukafka D, Cooper CB, et al. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest. 2005;127:809–817.
6. O'Donnell DE, Laveneziana P, Ora J, et al. Evaluation of acute bronchodilator reversibility in patients with symptoms of GOLD stage I COPD. Thorax. 2009;64:216–223.
7. Tatsumi K. COPD: The Tobacco Disease in the Middle-aged and Elderly. Rev ed. Tokyo: Hokendohjinsha Inc.; 2008.
8. Zheng JP, Kang J, Huang SG, et al. Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE study): a randomised placebo-controlled study. Lancet. 2008;371:2013–2018.