Inhaled Glucocorticosteroid Therapy
—A recent asthma treatment

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Introduction

Recent research has highlighted the prevalence of chronic inflammation of the airways in clinical bronchial asthma. It is also widely recognized that inhaled steroids are the most effective long-term management medicine in the treatment of airway inflammation. The recently published “Global Initiative for Asthma (GINA)” 1 as well as “Asthma Prevention and Management Guideline 2003, Japan” 2 recommend the use of inhaled steroids.

In this report, drawing upon the Japanese guidelines and the recently published results of large-scale clinical trials, we will indicate the method of inhaled steroid use.

Process and Penetration of Inhaled Glucocorticosteroid Use in Japan

Inhaled glucocorticosteroids were developed abroad and introduced to Japan. The Metered Dose inhaler of Beclomethasone dipropionate (BDP) was released in 1972 and introduced in Japan in 1978. Subsequently, the Metered Dose inhaler of Budesonide (BUD) and Dry Powder inhaler were released abroad in 1981 and 1988, respectively. The Dry Powder inhaler was introduced in Japan in 2002. Furthermore, the Fluticasone propionate (FP) rotadisk was released abroad in 1993, followed by the diskhaler in 1994. In Japan, the rotadisk was introduced in 1998, followed by the diskhaler in 2002, and the Metered Dose inhaler in 2003. In Japan, the basic ingredient for Beclomethasone dipropionate was changed from one prepared with chlorofluorocarbon (CFC) to one with hydrofluoralkane (HFA)(Qvar) in 2002.

Twenty years ago Beclomethasone dipropionate was the only inhaled glucocorticosteroid available in Japan. Therefore, the penetration of the medicine to general physicians was retarded as compared with other countries. The reasons for this are as follows: 1) the dosage limit for inhalation was low with 400 μg/day (later on this increased to 800 μg/day), 2) since it required daily inhalation of 4 times, compliance was inadequate, 3) the method of inhalation was difficult, requiring a spacer, and 4) there were many antiallergic agents already developed and available in Japan. However, after the release of Fluticasone propionate in 1998, the dosage limit for the inhalation was lessened. With administration of the inhalant twice a day and the easing of the inhalation procedures, its effectiveness became widely recognized by general physicians.

However, in Japan in 2000, 2 years after the release of Fluticasone propionate, as a result of the 130,000-patient study Asthma Insight & Reality in Japan (AIRJ), 3 in the past year the percentage of patients who experienced asthma

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episodes were as follows: 36% of adult patients and 58% of children experienced an emergency visit, and 30% of adults and 53% of children experienced work/school absence. These results indicate that the daily lives of the patients were considerably limited. Therefore, current asthma treatment does not sufficiently control asthma. In this study, the use of inhaled steroids was low with 12% in adults and 5% in children. The disparity with Europe is quite evident with 22% of adult Europeans and 23% of children using inhaled steroids according to a similar study, “Asthma Insights and Reality in Europe (AIRE)”\(^2\). However, the use of inhaled steroids has been increasing in Japan since 2000 with the penetration of the guidelines.

**Asthma Prevention and Management Guideline 2003, Japan\(^2\)**

Using the international guidelines as a base, the Japanese Guidelines categorize the severity of asthma into 4 steps, according to the characteristics of symptoms, peak expiratory flow rate, and forced expiratory volume in one second: Mild intermittent (Step 1), Mild persistent (Step 2), Moderate persistent (Step 3), and Severe persistent (Step 4). Patients are divided into these strata, based on symptoms at the start of the treatment and past treatment and symptoms in the past. The inhaled glucocorticosteroid is the most effective long-term controller medicine and is the first-line therapy in long-term controllers for persistent asthma patients who are rated Step 2 or above (Table 1).

After achieving the desired treatment outcome with therapies in combination with a bronchodilator or a leukotriene modifier, including other long-term controller medicines, such as long-acting β2-agonists or theophylline, the guidelines indicate it is permissible to step-down the treatment after verifying the stability of control for a minimum of 3 months. If the symptoms are exacerbated or if the current treatment fails to control the symptoms sufficiently, it is necessary to step-up the treatment.

Currently, there are three types of inhaled glucocorticosteroids available clinically in Japan: Beclomethasone dipropionate (BDP), Fluticasone propionate (FP), and Budesonide (BUD). There are 2 types of inhalation methods: the pressurized Metered Dose inhaler (p-MDI) and the Dry Powder inhaler (DPI) with natural inspiration (Table 2).

All of these inhaled glucocorticosteroids have a high affinity with steroid receptors, high uptake quantity to organs and long retention time at the target regions. When excreted to the entire body, it has a characteristic of being swiftly inactivated by the liver enzyme. As for the comparison of effectiveness among medications, there are few comparative studies. Based on the international guidelines, the domestic guidelines advise setting the maximum dose in Step 4 to that permitted by health insurance, the maximum in Step 3 to be half of the maximum in Step 4, the maximum in Step 2 to be the half of the maximum in Step 3, and the rest in the same manner (Table 3).

**The Results of Large-scale Clinical Trials on Asthma Treatment with Inhaled Glucocorticosteroids**

The results of a large-scale Japanese clinical trial called the FINE study\(^5\) was published in 2005. It was carried out in 510 primary care facilities nationwide, with the subjects being patients without previous continuous glucocorticosteroid use, including inhaled glucocorticosteroids. Asthma episodes due to the worsening of asthma symptoms for 6 months before and after the administration of Fluticasone propionate were investigated. 898 cases were studied. The occurrence of asthma episodes decreased from 62.9% before the administration to 24.9% after the administration, with a declining rate of 60.4%. The high declining rate was recorded regardless of patient age, severity of asthma, duration of asthma, or kinds of “add-on” long-term controllers. The percentage of patients who experienced the following episodes declined: hospitalization from 10% to 1.7%, emergency room treatment from 21.9% to 2.9%, unscheduled clinical visit from 49% to 19.1%, and work/school absence from 43.8% to 12.6%. This study validated the efficacy of inhaled glucocorticosteroids against asthma episodes.

The effects of early intervention with budesonide in mild persistent asthma have been investigated and reported abroad. One such study was a large-scale, international double-blind prospective study with approximately 7,000 subjects. The patients received either daily budesonide or a placebo once daily in addition to their usual
### Table 1-1 Classification of asthma severity by clinical features before treatment

<table>
<thead>
<tr>
<th>Severity</th>
<th>Step 1: Mild Intermittent</th>
<th>Step 2: Mild Persistent</th>
<th>Step 3: Moderate Persistent</th>
<th>Step 4: Severe Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics of symptoms</td>
<td>● Asthma symptoms less than once a week  &lt;br&gt;● Symptoms are mild and brief.  &lt;br&gt;● Nocturnal symptoms once or twice a month</td>
<td>● Symptoms more than once a week, but not every day  &lt;br&gt;● Daily life or nocturnal sleep disturbed more than once a month  &lt;br&gt;● Nocturnal symptoms more than twice a month</td>
<td>● Symptom daily  &lt;br&gt;● As-needed use of short-acting inhaled β2-agonists nearly every day  &lt;br&gt;● Daily life or nocturnal sleep disturbed more than once a week  &lt;br&gt;● Nocturnal symptoms more than twice a month</td>
<td>● Frequent exacerbation even under treatment  &lt;br&gt;● Symptom daily  &lt;br&gt;● Frequent nocturnal symptoms</td>
</tr>
<tr>
<td>PEF, FEV1.0</td>
<td>More than 80% of the predicted value, with less than 20% variability, or more than 80% of one's best PEF value</td>
<td>More than 80% of the predicted value, with variability of 20–30%, or more than 80% of one's best PEF value</td>
<td>60–80% of the predicted value, with more than 30% of variability, or 60–80% of one's best PEF value</td>
<td>Less than 60% of the predicted value, with more than 30% of variability, or less than 60% of one's best PEF value</td>
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### Table 1-2 Recommended medications by level of severity: adults

<table>
<thead>
<tr>
<th>Severity</th>
<th>Step 1: Mild Intermittent</th>
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<th>Step 4: Severe Persistent</th>
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<tr>
<td>Long-term controller medicines</td>
<td>● Consider the administration of either one of the following when experiencing asthma symptoms slightly more frequently, for instance once or twice a month, or an increase in the percentage of eosinophils in blood or sputum.  &lt;br&gt;● Inhaled glucocorticosteroid (minimum dose)  &lt;br&gt;● Sustained-release theophylline  &lt;br&gt;● Leukotriene modifier  &lt;br&gt;● Anti-allergic drugs</td>
<td>● Continuous use of inhaled glucocorticosteroid (Low dose)  &lt;br&gt;● Or use continuously or combined with either one of the following:  &lt;br&gt;  • Sustained-release theophylline  &lt;br&gt;  • Leukotriene modifier  &lt;br&gt;  • DSCG  &lt;br&gt;● For nighttime symptoms or lasting airway closure in combination with inhaled glucocorticosteroid  &lt;br&gt;● Long-acting β2-agonists (inhalation/adhesive preparation/oral)  &lt;br&gt;● Leukotriene modifier  &lt;br&gt;● Consider Th2 cytokine inhibitor</td>
<td>● Continuous use of inhaled glucocorticosteroid (Medium dose) In combination with inhaled glucocorticosteroid, use either one or some of the following:  &lt;br&gt;  • Sustained-release theophylline  &lt;br&gt;  • Long-acting β2-agonists (inhalation/adhesive preparation/oral)  &lt;br&gt;  • Leukotriene modifier  &lt;br&gt;● Consider Th2 cytokine inhibitor  &lt;br&gt;● When uncontrolled with the above:  &lt;br&gt;  • Add oral glucocorticosteroid</td>
<td>● Continuous use of inhaled glucocorticosteroid (High dose) In combination with inhaled glucocorticosteroid, use some of the following:  &lt;br&gt;  • Sustained-release theophylline  &lt;br&gt;  • Long-acting β2-agonists (inhalation/adhesive preparation/oral)  &lt;br&gt;  • Leukotriene modifier  &lt;br&gt;● Consider Th2 cytokine inhibitor  &lt;br&gt;● When uncontrolled with the above:  &lt;br&gt;  • Add oral glucocorticosteroid</td>
</tr>
<tr>
<td>In case of exacerbation</td>
<td>Short-acting inhaled β2-agonists, or short-acting oral β2-agonists, short-acting theophylline</td>
<td>Short-acting inhaled β2-agonists, etc.</td>
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(Asthma Prevention and Management Guideline 2003, partially changed)
treatment. The daily budesonide dose was 400 μg for adults and 200 μg for children. The elapsed time to the first severe asthma-related event (SARE) was assessed. The results reported that in the budesonide group, the risk of developing SARE decreased 44% in 3 years (START study, 2003).  

The next study compared two therapies in their achievement level of total control: one with only Fluticasone propionate and the other with Fluticasone propionate in combination with salmeterol. The study was carried out with 3,416 uncontrolled asthma patients over 12 years of age. Based on their inhaled steroid dosage during the 6 months before screening, the patients were divided into 3 groups: stratum 1, previously corticosteroid-free, stratum 2, low-dose corticosteroid users, and stratum 3, moderate-dose corticosteroid users. Patients were administered with either a combination of Fluticasone propionate and salmeterol or only Fluticasone propionate. Treatment was stepped up every 12 weeks until a totally controlled condition was achieved. This totally controlled condition was defined as a condition with morning peak expiratory flow rate reaching 80% of the predicted value every morning, absence of daytime symptoms, nighttime awakenings, acute exacerbations, emergency visits, nor β2-agonist use. The achievement levels after 1 year were compared. As a result, in the group with the combination of Fluticasone propionate and salmeterol, approximately 40% (50% in stratum 1, 44% in stratum 2, 29% in stratum 3) of the patients achieved total control. Furthermore, the results also indicate that the group with Fluticasone propionate and salmeterol achieved total control with less dosage and in a shorter period of time (GOAL study, 2004).  

With most asthma patients, the severity falls into two types: mild intermittent or mild persistent. The current guidelines (GINA) recommend continued administration of inhaled steroids to the Mild persistent asthma patients. In a study on mild persistent asthma patients, a comparison treatment. The daily budesonide dose was 400 μg for adults and 200 μg for children. The elapsed time to the first severe asthma-related event (SARE) was assessed. The results reported that in the budesonide group, the risk of developing SARE decreased 44% in 3 years (START study, 2003).  

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INHALED GLUCOCORTICOSTEROID THERAPY—A RECENT ASTHMA TREATMENT

was made between intermittent and continued use of inhaled glucocorticosteroids, and daily treatment with zafirlukast, a leukotriene-receptor antagonist. The one-year study was carried out with 225 mild persistent adult asthma patients. The patients were divided into 3 groups: one with Budesonide 400 µg/day and a placebo instead of zafirlukast, the 2nd group with zafirlukast 40mg/day and a placebo instead of Budesonide, and the 3rd group with 2 placebos. In the event of exacerbation, the subjects were instructed to intake 1,600 µg/day of Budesonide for 10 days or oral prednisolone 0.5mg/1 kg of body weight for 5 days. In the 3rd group with 2 placebos, glucocorticosteroids were given intermittently and their symptoms were compared to those with continued use. Morning peak expiratory flow rate (PEF), forced expiratory volume in one second (FEV₁) before and after the use of the bronchodilator, the frequency of exacerbations, the degree of asthma control, the number of symptom-free days, and the quality of life (QOL) were evaluated. Compared to the group with continued use of Budesonide and those with intermittent use, the daily budesonide therapy group experienced greater improvements in pre-bronchodilator FEV₁, bronchial reactivity, percentage of eosinophils in the sputum, exhaled nitric oxide levels, scores for asthma control, and the number of symptom-free days, whereas a significant difference was not seen in post-bronchodilator FEV₁ or in the quality of life. Moreover, no differences were observed between the zafirlukast group and the Budesonide intermittent treatment group. In addition, during the 400 days of observation from the start of the trial, no significant difference was seen in the 3 groups in the time leading up to the first exacerbation (IMPACT study, 2005). This report has yet to be confirmed, but also from the point of medical cost, the results may serve to stimulate reconsideration of the current guidelines.

References