Comparison of Physicians’ Compliance, Clinical Efficacy, and Drug Cost before and after Introduction of Asthma Prevention and Management Guidelines in Japan (JGL2003)

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ABSTRACT

Background: This study investigated the variations in the clinical efficacy and drug cost following the introduction of the Asthma Prevention and Management Guidelines in Japan (JGL2003).

Methods: The medical charts of fifty outpatients treated continuously for asthma, aged 16-50 years, from October 2002 to October 2004 at Showa University Hospital were analyzed for physicians’ compliance with asthma guidelines, symptom severity, episodes in various occasions, prescriptions and drug costs.

Results: Physicians’ compliance with the guidelines, which were defined as the number of patient visits treated in conformity with the JGL over the total number of patient visits, was found to be high before (89.4%) and after (90.3%) the introduction of JGL2003, without a statistical difference. On the other hand, the distribution of asthma symptom severity varied significantly \((P < 0.0001)\). Fewer patients were recognized as having more severe asthma symptoms after the introduction of JGL2003. Significantly more patients with severe asthma symptoms were detected in the physicians’ noncompliant group than in the compliant group \((P < 0.0001)\). The number of patients prescribed with oral corticosteroids, long-acting \(\beta_2\)-agonists containing patches, long-acting oral \(\beta_2\)-agonists, short-acting inhaled \(\beta_2\)-agonists, sustained-released theophylline and leukotriene receptor antagonists decreased after the introduction of JGL2003. Furthermore, the total annual drug cost per patient decreased significantly by an average of 16,259 yen \((P = 0.006)\).

Conclusions: The JGL2003 was judged to have improved criteria, which thus resulted in the high compliance of physicians with the guidelines, in the remission of asthma symptoms and in the reduction in the total annual drug cost per patient.

KEY WORDS

asthma management, compliance, drug cost, guideline, JGL

INTRODUCTION

Clinical guidelines are systematically developed statements based on the scientific evidence of therapeutic interventions. They help practitioners to diagnose or to make decisions regarding the appropriate health care under specific circumstances. The Japanese guidelines for the management of asthma were published for the first time in 1998 by a working group in the Ministry of Health, Labour and Welfare, and enti-
tled the Asthma Prevention and Management Guidelines in Japan (JGL1998). Subsequently, the guidelines were updated in 2000 and 2003 as JGL2000 and JGL2003, respectively. The Global Initiative for Asthma (GINA) was launched in 1995 as a collaborative effort between the National Heart Lung and Blood Institute (NHLBI) and the World Health Organization (WHO) and updated in 2002 (GINA2002). Both domestic and international guidelines recommend the use of inhaled steroids in the treatment of asthma. Inhaled corticosteroids (ICS) are found to be effective in controlling the symptoms of asthma, thus reducing asthma mortality rates. Many results support the benefit of inhaled steroids to control asthmatic symptoms. One of the features in JGL2003 is that the ICS is definitely recommended as the first-line therapy in the treatment of mild-to-severe persistent asthma in adults. Another feature in JGL2003 is the introduction of new drugs, such as fluticasone propionate, budesonide and long-acting inhaled β2-agonists. In particular, the descriptions concerning the recommended doses for various ICS depending on the asthma symptom severity were added. The use of long-acting inhaled β2-agonists was also added. Furthermore, it also describes the peak expiratory flow (%PEF) value and forced expiratory volume in the 1st second (%FEV1) value as the definition of asthma symptom severity in order to conform to the GINA2002.

de Marco R et al. reported a positive correlation between good control of the disease and an adequate dose of anti-inflammatory medication, which followed the GINA recommendations. They also reported that the patients treated without following the guidelines experienced significantly more asthmatic attacks and, thereby stressed the importance of compliance with the guidelines. Pont et al. reported that patients treated in accordance with the guidelines showed a significantly higher overall health-related quality of life than those treated without these guidelines.

Accordingly the effect of the guidelines was that standard asthma treatment would become widespread to many physicians. In consequence, asthma control would be improved and asthma treatment would reach a certain targeted level. The guidelines are updated and revised continuously in order to incorporate any novel findings. Although some utility evaluations of the asthma guidelines were investigated, there have so far been no reports comparing the actual conditions before and after the introduction of the asthma guidelines.

Therefore, this study investigated the variations in the clinical efficacy and the drug costs following the introduction of JGL2003, at a university hospital with asthma specialists, where the effect of the guideline revisions would be expected to promptly have an impact.

METHODS

Various aspects of asthma treatment, such as physicians’ compliance with asthma guidelines, symptom severity, episodes in various occasions (i.e. hospital admission, emergency department visit, unscheduled emergency visit), prescription and drug costs were compared between before and after the introduction of JGL2003, which was updated on October 22, 2003.

All outpatients treated continuously for asthma (aged 16-50 years) at Showa University Hospital were selected and their medical charts were surveyed in the present retrospectively study. The term of the surveillance was 1 year before and after October 22, 2003, when JGL2003 was introduced. The outpatients who regularly visited the hospital for more than 6 months before and after the introduction of JGL2003 were selected as the subjects of this study. The medical asthma treatments for adults are different from those for children under the age of 16 and prescriptions for patients aged 51 or over is often affected by the other medicines other than those administered for asthma. Therefore, the subjects were selected within those age cut-offs.

This study employed the method of measuring physicians’ compliance with the guidelines reported by Pont et al. Physicians’ compliance with the guidelines, judged by the conformity to the JGL (Table 1, 2), was surveyed based on medical charts, prescriptions, peak expiratory flows and symptoms for each visit of the patients, and then were recorded as the number of patient visits to be compliant or noncompliant. Physicians’ compliance before and after the introduction of the new guidelines (JGL2003) were assessed based on whether they were compliant with JGL2000 and JGL2003 or not, respectively. Physicians were determined to be noncompliant when their treatments included any violation of JGL. For example, a physician who prescribed only ICS for a patient with severe persistent asthma was judged to be noncompliant, since other drugs should be administered concomitantly with ICS.

The Cochran-Mantel-Haenszel chi square test, stratified by individual patients, was employed to statistically evaluate the three sets of associations between the change in the guidelines and the physicians’ compliance, between the asthma symptom severity and the status of physicians’ compliance, and between the guideline change and the asthma symptom severity. The analyses of prescription or asthma episodes were performed using McNemar’s test. The drug cost and the number of concomitantly administered drugs were analyzed using the Wilcoxon sign rank test. The drug cost was calculated in one-year unit as the annual drug cost per patient. All analyses were performed using the JMP version 6 (SAS Institute, Cary, NC, USA) statistical software package.

With respect to ethical considerations, the protec-
The presence of one or more of the features of severity is sufficient to place a patient in that category; an individual should be assigned to the most severe grade in which any feature occurs.

LTAs, Leukotriene receptor antagonists; SABA, Short-acting β2-agonists; LABA, Long-acting β2-agonists; TXA, Thromboxane A2; DSCG, disodium cromoglycate; H1 blocker, Histamine H1-receptor blocker; CMRI, Chemical mediator release inhibitors.

### RESULTS

Three hundred and sixty-six outpatients treated continuously for asthma from October 2002 to October 2004 at Showa University Hospital were screened. Three hundred and ten of these patients were excluded because the patients had not been treated continuously before 2004. Six pregnant patients were also excluded. As a result, 50 patients were recruited for the study. The patient characteristics are shown in Table 3. The terms of patient observation before and after the introduction of JGL2003 ranged from 9 to 15 months (12 months on average) and from 6 to 15 months (11 months on average), respectively.

The physicians’ compliance accumulated for every treatment day during the period with the adjustment for patients was high before (448 total number of patient visits, 89.4%) and after (334 total number of patient visits, 90.3%) the introduction of JGL2003, respectively. No remarkable difference was observed in the physicians’ compliance before and after the introduction of JGL2003. The physicians’ noncompliant regimes are shown in Table 4.

On the other hand, the distribution of asthma symptom severity, accumulated for every treatment day during the period with the adjustment for patients, differed significantly \( (P < 0.0001) \) before and after the introduction of JGL2003. Fewer patient visits were recognized as having more severe asthma.

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**Table 1** Severity classification and treatment recommendations for JGL2000 ‡

<table>
<thead>
<tr>
<th>Severity classification ‡</th>
<th>Symptoms:</th>
<th>Medication Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild intermittent (Step 1)</td>
<td>Wheeze, Cough, or Dyspnea, once or twice a week Intermittent and brief Night time symptoms: ≤Once or twice a month Lung function (PEF or FEV1): &gt;80% predicted/personal best Variability &lt;20%</td>
<td>Inhaled/oral SABA, or theophylline as needed Inhaled SABA or inhaled DSCG before exercise or exposure of allergen Antiallergic agents 1) LTRAs/TXA receptor antagonist/TXA synthase inhibitor 2) CMRI/H1 blocker/Th2 cytokine inhibitor ICS: BDP 200 μg/day or FP 100 μg/day</td>
</tr>
<tr>
<td>Mild persistent (Step 2)</td>
<td>≥Twice a week Disorder of daily activity and sleep: ≥Twice a month Night time symptoms: ≥Twice a month Lung function (PEF or FEV1): 70-80% predicted/personal best Variability: 20-30%</td>
<td>Low-dose ICS: BDP 200-400 μg/day or FP 100-200 μg/day Sustained-release theophylline Antiallergic agents 1) LTRAs/TXA receptor antagonist/TXA synthase inhibitor 2) CMRI/H1 blocker/Th2 cytokine inhibitor Patches/Oral/Inhaled LABA Inhaled SABA: used as needed (sthird or 4th/day)</td>
</tr>
<tr>
<td>Moderate persistent (Step 3)</td>
<td>Chronic, Almost daily use of inhaled SABA is necessary Disorder of daily activity and sleep: ≥Once a week Night time symptoms: ≥Once a week Lung function (PEF or FEV1): 60-70% predicted/personal best Variability: &gt;30%</td>
<td>Medium-dose ICS: BDP 400-800 μg/day or FP 200-400 μg/day Sustained-release theophylline Patches/Oral/Inhaled LABA Antiallergic agents 1) LTRAs/TXA receptor antagonist/TXA synthase inhibitor 2) CMRI/H1 blocker/Th2 cytokine inhibitor Inhaled anticholinergic drugs Inhaled SABA: used as needed (sthird or 4th/day)</td>
</tr>
<tr>
<td>Severe persistent (Step 4)</td>
<td>Symptoms: Frequent exacerbations, Continual, Limited daily activity Night time symptoms: Frequent (Oral corticosteroids use continuously) Lung function (PEF or FEV1): &lt;60% predicted/personal best Variability: &gt;30%</td>
<td>High-dose ICS: BDP 800-1600 μg/day or FP 400-800 μg/day Oral corticosteroids: Short term: Medium or high-dose, Maintenance dose: Minimum-dose/day or alternate-day Sustained-release theophylline Patches/Oral/Inhaled LABA Antiallergic agents 1) LTRAs/TXA receptor antagonist/TXA synthase inhibitor Inhaled anticholinergic drugs Inhaled SABA: used as needed (sthird or 4th/day)</td>
</tr>
</tbody>
</table>

† If asthma is not controlled on the current treatment regimen, then treatment should be stepped up until control is achieved. When control is maintained for at least three months, treatment can be stepped down.

‡ The presence of one or more of the features of severity is sufficient to place a patient in that category; an individual should be assigned to the most severe grade in which any feature occurs.

Effects of JGL2003 on Asthma Therapy

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symptoms after the introduction of JGL2003 (Fig. 1). The total number of patient visits in mild intermittent and mild persistent asthma increased, while that in moderate persistent asthma decreased, as accumulated for every treatment day during the period.

The number of patient visits in each classification of symptom severity, adjusted by the patients, was found to be significantly different between the compliant and noncompliant groups ($P < 0.0001$, Fig. 2). More severe patients were found in the noncompliant group than in the compliant group, especially for the moderate and severe persistent asthma patients.

There was no significant difference in the incidence of asthma episodes before and after the introduction of JGL2003.

Differences were observed in the prescriptions before and after the introduction of JGL2003 (Fig. 3). The number of patients that were prescribed with oral corticosteroids, long-acting $\beta_2$-agonist containing patches, long-acting oral $\beta_2$-agonists, short-acting inhaled $\beta_2$-agonists, sustained-released theophylline, leukotriene receptor antagonists and APH-S significantly decreased after the introduction of JGL2003, according to McNemar’s test. In contrast, no significant difference was observed in the number of patients receiving prescriptions for ICS, long-acting inhaled $\beta_2$-agonists and antiallergic agents, etc. The median number of concomitantly administered drugs per patient decreased from 3.0 to 2.0 after the introduction of JGL2003, with $P = 0.0014$.

### Table 2  Severity classification and treatment recommendations for JGL2003 †

<table>
<thead>
<tr>
<th>Severity classification ‡</th>
<th>Symptoms:</th>
<th>Treatment recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild intermittent (Step 1)</td>
<td>&lt; Once a week, mild, brief</td>
<td></td>
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<tr>
<td>Night time symptoms:</td>
<td>Once or twice a month</td>
<td></td>
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<tr>
<td>Lung function (PEF or FEV1):</td>
<td>≥ 80% predicted, Variability &lt; 20 %, or PEF ≥ 80% of personal best</td>
<td></td>
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<tr>
<td>Medication recommendations</td>
<td>Low-dose ICS</td>
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<td></td>
<td>Use of the more than one followings with ICS</td>
<td></td>
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<tr>
<td></td>
<td>1) Sustained release theophylline, 2) LTRAs, 3) DSCG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Night time symptoms and persistent airway obstruction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1) Patches/Oral/Inhaled LABA and ICS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atopic asthma: concomitant use of above mentioned medications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1) Concomitant use of oral corticosteroids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asthma attacks: Inhaled SABA, etc.</td>
<td></td>
</tr>
</tbody>
</table>

† If asthma is not controlled on the current treatment regimen, the treatment should be stepped up until control is achieved. When control is maintained for at least three months, treatment can be stepped down.

‡ The presence of one or more of the features of severity is sufficient to place a patient in that category; an individual should be assigned to the most severe grade in which any feature occurs.

LTRAs, Leukotriene receptor antagonists; SABA, Short-acting $\beta_2$-agonists; LABA, Long-acting $\beta_2$-agonists; DSCG, disodium cromoglycate.
The total annual drug cost per patient significantly decreased by 16,259 yen (Mean; \(P = 0.006\)) after the introduction of JGL2003, as seen in Figure 4. According to the Wilcoxon test, each annual drug cost per patient who received long-acting \(\beta_2\)-agonist containing patches, long-acting oral \(\beta_2\)-agonists, sustained-released theophylline and APH-S was found to decrease by 5,297 yen \((P = 0.03)\), 4,615 yen \((P = 0.002)\), 2,087 yen \((P = 0.002)\) and 631 yen \((P = 0.03)\) after the introduction of JGL2003, respectively.

**DISCUSSION**

Akiyama\(^9\) reported that from 30 to 40% of asthma physicians recognized JGL2003 and that over 90% of the physicians knew of the revisions of JGL. Among them, roughly 30% often used the JGL as a reference and over 90% of the physicians partially used the JGL. Lagerløv \textit{et al.}\(^{10}\) found that most physicians agreed with the guideline recommendations, however, the proportion of asthma patients receiving inhaled steroids remained around 44% (31-58%, depending on the state). This may indicate that many physicians still do not recognize the importance of the inflammatory component of asthma. The use of ICS, recommended as the first-line therapy in the treatment of mild-to-severe persistent asthma in adults worldwide, is often used as one of the indices of physicians’ compliance with the guidelines. Only 23% of patients in Europe\(^{11}\) and 18% of patients in Japan\(^{12}\) are reportedly using ICS. Rabe \textit{et al.}\(^{13}\) reported that the use of anti-inflammatory preventative medication, even in patients with severe persistent asthma, is low, ranging from 26% in Western Europe to 9% in Japan. They claim that such a proportion is lower than that overseas and that the use of the standard treatment recommended in the guidelines is not widespread. As just described, the treatment in practice is rarely in conformity with the guidelines for the management of asthma. The method of selecting patients in the previous surveys\(^{11-13}\) was by the random-digit telephone sampling method. On the other hand, by the method of questionnaires given to physicians, the proportion of patients who use of ICS was reported to be 77.4%.\(^{14}\) Makino \textit{et al.}\(^{15}\) reported that JGL was recognized and utilized by most of the Japanese Society of Allergology (JSA) members, but only half of non-
Before the introduction of JGL2003, the hospital surveyed in this study was thought to have conformed to the JGL, thus suggesting that no confusion of JGL in asthma treatment. Treatment in this research hospital was thought to have conformed to the JGL because: 1) the physicians in the current study were able to diagnose the patients’ asthma symptom severity and 2) the selected patients were regular outpatients. No remarkable difference was observed in the physicians’ compliance before and after the introduction of the new guidelines (JGL2003) were assessed based on whether they were compliant with JGL2000 and JGL2003 or not, respectively.

Fig. 1 Comparison of the distribution of asthma symptom severity before and after the introduction of JGL2003. Asthma severity: □ Mild intermittent □ Mild persistent □ Moderate persistent □ Severe persistent. The distribution of asthma symptom severity, accumulated for every treatment day during the period was analyzed by the Cochran-Mantel-Haenszel chi square test stratified by individual patients.

Fig. 2 Comparisons between the physician compliant group and noncompliant group. Asthma severity: □ Mild intermittent □ Mild persistent □ Moderate persistent □ Severe persistent. The numbers of patient visits in each classification of symptom severity was analyzed by the Cochran-Mantel-Haenszel chi square test stratified by individual patients. Physicians’ compliance before and after the introduction of the new guidelines (JGL2003) were assessed based on whether they were compliant with JGL2000 and JGL2003 or not, respectively.

Fig. 3 Prescriptions before and after the introduction of JGL2003. The analyses of prescriptions were performed by McNemar’s test.
† APH-S denotes the fulfilled prescription, including 3 mg clemastine, 0.6 g aminophylline, 3 mg tubocurarine, 60 mg phenobarbital, 0.3 g magnesium oxide; 2 g Neo Umor®, and 1 g dried yeast.

member physicians were aware of JGL, although they utilized JGL after they read it. However, conformity with the guidelines in the hospital observed in the current study was sufficiently high (the physicians’ compliance with guidelines was high with 89.4% even before the introduction of JGL2003). Therefore, the hospital surveyed in this study was thought to be appropriate for investigating the effect of the revision of
Significantly fewer patients were recognized to have more severe asthma symptoms after the introduction of JGL2003, thus indicating that the updated guidelines were properly improved.

There were significantly more patients with more severe asthma symptoms in the physicians’ noncompliant group than in the compliant group (Fig. 2). This result indicates two possibilities. One is that, the more severe the asthma symptoms, the more complicated the disease would be, therefore, it was more difficult to control asthma symptoms by following only the asthma guidelines. Another is that treatment without following the guidelines was unable to control the asthma symptoms.

Differences were observed in the use of prescription medications (Fig. 3). The number of patients that received oral corticosteroids, long-acting β2-agonist containing patches, long-acting oral β2-agonists, short-acting inhaled β2-agonists, sustained-release theophylline and leukotriene receptor antagonists decreased after the introduction of JGL2003. The number of concomitantly administered drugs also decreased. In contrast, the number of patients prescribed with other asthma medicines was not statistically significant.

One of the specific changes in the updated JGL 2003 is that the priority of using long-acting β2-agonists, such as the inhalation, patch and oral medication, was established in this order. This may be the reason why, the number of patients who received prescriptions for long-acting β2-agonist containing patches and long-acting oral β2-agonists was decreased. Meanwhile, the use of oral corticosteroids was limited to the poorly controllable patients even if all other kinds of asthma drugs were used among severe persistent asthma patients. Therefore, it would be natural that the number of patients who received prescriptions for oral corticosteroids decreased.

ICS occupies a more important place in the guidelines after the introduction of JGL2003. However, the number of patients prescribed with ICS was not significantly different after the introduction of JGL2003. This might be due to the effectiveness of ICS, which had been extensively evaluated before the introduction of JGL2003.

After the introduction of JGL2003, ICS was definitely recommended as the best option for first-line maintenance therapy for mild to severe persistent asthma. As a result, the use of drugs other than ICS was reasonably decreased and the number of concomitantly administered drugs also decreased. The remission of asthma symptoms after the introduction of JGL2003 is thought to also contribute to its decrease.

Another factor affecting the administration of prescriptions by physicians would be the launch of new drugs into the market. Generally, there are two such
cases. The first case is that newly approved drugs, in comparison with older ones, are more often prescribed to patients due to the expectation of the new effects. The second case is that newly approved drugs are prescribed less since they are not yet common. In the year before the introduction of JGL2003, Flutide Diskus 100 and 200, Flutide Diskus 50, Flutide Air 50 and Serevent Rotadisk were launched in January 2002, February 2002, March 2003 and June 2002, respectively. In the year after the introduction of JGL2003, Flutide Air 100 and Serevent 50 Diskus were launched in December 2003 and June 2004, respectively. These drugs are classified as ICS or long-acting inhaled β2-agonists. There were no differences in the prescription of drugs after the introduction of JGL2003. The drugs first launched in the year after the introduction of JGL2003, Flutide Air 100 and Serevent 50 Diskus were rarely prescribed in the first 3 and 2 patient visits, respectively. Consequently, the launching of new drugs does not affect the prescription rate.

The total annual drug cost per patient decreased significantly by 16,259 yen (Mean) after the introduction of JGL2003. For this reason, the updated guidelines decreased the burden of patients’ medical costs and contributed to the drug cost reduction. The effect of decreased drug cost associated with generic drugs was not included in this analysis, because there was no prescription of generic drugs in the present study.

Antonicelli et al. reported that asthma severity, as determined by the Global Initiative for Asthma classification, is significantly associated with the use of asthma-related medical resources and the total medical expenses. Van Ganse et al. also reported that medical costs increased significantly with decreasing levels of control, independent of the symptom severity. The present study found that fewer patients were recognized to have more severe asthma symptoms after the introduction of JGL2003, which may have therefore contributed to the reduction of the medical cost.

Although the asthma guidelines may not be perfect, they appear to be the best way to assist primary care physicians and ensure that patients receive the best possible care of their asthma. Despite the above-mentioned advantages of asthma guidelines, patient nonadherence with medication will lead to failure of asthma control; therefore, patient education for asthma is also an important factor in their management. The asthma guidelines were updated in 2006 as JGL2006 in Japan and GINA2006 worldwide. The primary revision in JGL2006 is that only ICS is definitely recommended as the first-line therapy in the treatment of mild persistent asthma in adults. ICS is thus considered to have played a more important role in this sense.

In conclusion, JGL2003 was assessed to have improved criteria, which resulted in the high compliance of physicians with the guideline recommendations, in the remission of asthma symptoms and in the reduction in the total annual drug cost per patient. However, there is a limitation of this study in that the results were obtained at only one university hospital; one must be careful in applying the same results to other university hospitals where physicians need to be aware of JGL2003 to a similar extent.

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