Problems of elderly patients on inhalation therapy: Difference in problem recognition between patients and medical professionals

Daiki Hira, a,*, Yuko Komase b, Setsuko Koshiyama c, Tetsuya Oguma d, Tetsuo Hiramatsu e, Akira Shiraki f, Masanori Nishikawa g, Masanori Nakanishi h, Takao Tsui i, Hisako Matsumoto j, Koichi Ichimura k, Takashi Iwanaga l, Miwa Morikawa m, Hirotaka Yasuba n, Fumiko Sugaya o, Yukako Arakawa p, Yoshiki Kobayashi q, Toshiyuki Kato r, Yutaka Futamura s, Fumio Tsujito t, Tomohiro Terada a

a Department of Pharmacy, Shiga University of Medical Science Hospital, Shiga, Japan
b Department of Respiratory Internal Medicine, St. Marianna University, School of Medicine, Yokohama-City Seibu Hospital, Kanagawa, Japan
c Kinki-Chozai Kadono Sanjo Pharmacy, Kyoto, Japan
d National Hospital Organization Higashi-Ohmi General Medical Center, Shiga, Japan
e Hiramatsu Clinic, Aichi, Japan
f Department of Respiratory Medicine, Ogaki Municipal Hospital, Gifu, Japan
g Fujisawa City Hospital, Kanagawa, Japan
h Third Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan
i Department of Respiratory Medicine, Tokyo Medical University Ibaraki Medical Center, Ibaraki, Japan
j Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan
k Ichimura Clinic, Tokyo, Japan
l Department of Respiratory Medicine and Allergology, Faculty of Medicine, Kinki University, Osaka, Japan
m Third Department of Internal Medicine, Faculty of Medical Sciences, University of Fukui, Fukui, Japan
n Department of Airway Medicine, Mitsubishi Kyoto Hospital, Kyoto, Japan
o Department of Respiratory Medicine, Teine Keijinkai Hospital, Hokkaido, Japan
p Sleep and Respiratory Disease Center, KKR Takamatsu Hospital, Kagawa, Japan
q Department of Otolaryngology, Kansai Medical University, Osaka, Japan
r Department of Respiratory Medicine and Allergology, Kariya Toyota General Hospital, Aichi, Japan
s Kagawa Pharmaceutical Association, Kagawa, Japan
t Suita Municipal Hospital, Osaka, Japan

A R T I C L E    I N F O

Article history:
Received 8 December 2015
Received in revised form 24 March 2016
Accepted 3 April 2016
Available online 5 May 2016

Keywords:
Asthma therapy
Elderly patient
Inhalation instruction
Inhalation medicine
Nationwide questionnaire survey

Abbreviations:
COPD chronic obstructive pulmonary disease
NRS numerical rating scale

A B S T R A C T

Background: There is no systematic analysis to identify problems involved with instruction on inhalation therapy for elderly patients. We conducted a nationwide questionnaire survey for patients and medical professionals.

Methods: A questionnaire survey was conducted of adult patients on inhaled drugs (ages 18–92 years, 820 individuals) and medical professionals (pharmacists or nurses) who provided instruction on inhalation therapy to these patients in 23 institutions in Japan to investigate the technique and the level of understanding (knowledge) of the inhalation therapy. Changes in the recognition of performance of inhalation technique and inhalation knowledge with increasing age were analyzed.

Results: According to patients’ subjective assessment, there was no deterioration in the performance of the inhalation technique or loss of the knowledge with increasing age. On the other hand, medical professionals’ objective assessment revealed a significant loss of both inhalation technique and knowledge with increasing age. Not many elderly patients noticed their own problems themselves, revealing a great perception gap between elderly patients and medical professionals. Thus, there was concern that patients would unconsciously practice the inhalation procedure improperly. On the other hand, in comparison with non-elderly patients, elderly patients were less resistant to continuation of therapy, suggesting that they would be more likely to accept instruction on inhalation therapy.

* Corresponding author. Department of Pharmacy, Shiga University of Medical Science Hospital, Seta-Tsukinowa-cho, Otsu, Shiga 520-2192, Japan.
E-mail address: hirad@belle.shiga-med.ac.jp (D. Hira).
Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2016.04.002
1323-8930/© 2016, Japanese Society of Allergology. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Introduction

Inhalation therapy plays an important role in the treatment of asthma and chronic obstructive pulmonary disease (COPD). Inhaled drugs, unlike oral drugs, should be delivered to the target site by inhalation by the patient; therefore, an appropriate inhalation technique is indispensable to achieve an adequate therapeutic effect. However, there have been a number of reports regarding cases of inappropriate inhalation techniques. Factors reported as causing inappropriate inhalation techniques include age, sex, and the types of inhalation devices. In particular, age is considered to be an important factor. Age-related problems may include decreased cognitive function and physical function according to increased age that interfere with the proper performance of the inhalation technique. In addition, the mortality from asthma is higher in the elderly than in the young. Therefore, to decrease the overall mortality from asthma, implementation of appropriate inhalation therapy in elderly patients is important.

Moreover, if problems specific to elderly patients in relation to inhalation therapy are apparent, it is possible to expect improved quality of inhalation therapy through the provision of proper instruction on inhalation therapy to elderly patients who tend to have poor inhalation technique. In this context, we focused on the divergence of recognition between patients and medical professionals in elderly patient, and conducted a multicenter questionnaire survey aimed at comparing the results of subjective assessment by patients and the objective assessment by medical professionals to identify problems particular to elderly patients.

Methods

This study was conducted between February 2014 and March 2015 and covered 23 institutions nationwide that participated in activities of the Association of Inhalation Therapists which is a nonprofit organization consist of doctors and pharmacists who works in the area of inhalation therapy. Patients meeting the inclusion criteria were surveyed by using a questionnaire about age, sex, the knowledge and technique of inhalation therapy, person who provided instruction, presence/absence of gargling, and specific problems (continuity, technique, manipulation, actual sensation of inhalation, understanding of the necessity of therapy, side effects), and medical professionals who provided instruction on inhalation therapy to these patients (mainly pharmacists and nurses) were also surveyed by questionnaire about the patient’s knowledge and technique of inhalation therapy and specific problems (understanding of the technique, physical problems involved in manipulation, living environment including solitary living, and understanding of the necessity of therapy) (Supplementary Table 1). All participants gave oral informed consent.

Inclusion criteria: Patients aged 18 years or older who were on inhaled drugs for the treatment of asthma or COPD and had been using inhaled drugs continuously for at least two weeks were included in this study.

Exclusion criteria: Patients were also not eligible if it was difficult for them to respond to the questionnaire because of decreased cognitive function.

The data obtained were stratified by 5-year age groups to analyze the results of patients’ subjective assessment and medical professionals’ objective assessment about the knowledge and technique of inhalation therapy rated by the NRS. The difference in recognition between patients and medical professionals was also examined, based on the calculation according to Eq. (1) shown below:

\[
\text{Difference in recognition between patients and medical professionals} = \text{medical professionals’ objective assessment} - \text{patients’ subjective assessment}
\]

Variations in NRS scores with increasing age were analyzed by the Jonckheere–Terpstra test at a significance level of \( P < 0.001 \).

Concerning inhalation knowledge and technique, when patients’ subjective assessment was better than medical professionals’ objective assessment (misconception of poor performance as good: difference in recognition between patients and medical professionals < 0), the difference was defined as a negative divergence. In this case, the effects of age as a determinant for causing a negative divergence of recognition between patients and medical professionals were studied by receiver operating characteristic (ROC) analysis, and the cutoff value (age at the maximum value of Youden’s index = sensitivity – [1 – specificity]) was calculated.

The inhalation technique may vary according to the type of inhalation device. In this regard, multivariate logistic analysis was conducted to evaluate the confounding effect of age and the inhalation device in cases where there was a negative divergence of recognition regarding inhalation technique between the patients and the medical professionals. The presence/absence of a negative divergence was used as the dependent variable, and age and the type of inhalation device (devices used by at least 10% of all patients: Diskus, Turbuhaler, pMDI) and the count of all inhalation device were used as explanatory variables.

Patients were divided into two groups by the cutoff value obtained by ROC analysis, and the frequencies of specific problems found by subjective and objective assessment were compared between the groups. The frequencies of specific problems in these two groups were compared by the chi-squared test or Fisher’s exact test at a significance level of \( P < 0.01 \). SPSS ver. 22 (IBM Corp., Armonk, NY, USA) was used for processing statistical analyses. This study was conducted with the approval of the Ethics Boards of Saint Marianna University School of Medicine as a representative of all participating institution (Approval number: 2562). Some participating institutions, including Shiga University of Medical Science (Approval number: 26–37), independently obtained the approval of each Ethics Boards as needed.

Results

The completed questionnaires of 867 patients from 23 institutions located nationwide were collected. Among these respondents, 36 patients who provided incomplete data that lacked information on age or NRS scores, and 11 patients who were under 18 years of age were excluded, and a total of 820 patients were
subjected to analysis. The evaluable patients ranged widely in age from 18 to 92 years. Among the prescribed inhalation devices, powder inhalers such as Diskus and Turbuhaler were predominant (Table 1). When the patients were stratified by 5-year age groups, the number of patients were comparable across all age groups, with each group reaching an adequate number of patients, i.e., more than 40 patients.

Figure 1A,B shows the relationship between age and patients’ subjective assessment or medical professionals’ objective assessment regarding the knowledge and technique of inhalation therapy. According to patients’ subjective assessment, there were no significant changes in either inhalation knowledge or inhalation technique with increasing age. In contrast, the objective assessment of medical professionals revealed a significant decrease in NRS scores for both inhalation knowledge and inhalation technique with increasing age (Jonckheere–Terpstra test, \( P < 0.001 \)); the decrease was particularly prominent in patients who were \( \geq 70 \) years of age. As shown in Figure 1C, it also became apparent that the difference in NRS scores for both inhalation knowledge and inhalation technique between patients and medical professionals decreased significantly with increasing age. Thus, it was suggested that increase in patient age would be a causative factor for divergence of recognition between patients and medical professionals. Subsequently, ROC analysis was performed to obtain the cutoff value for negative differences in recognition between patients and medical professionals (Fig. 2). The results showed that age was a significant determinant to produce a negative difference in recognition of both inhalation knowledge and inhalation technique between patients and medical professionals, and the cutoff value for age was 66.5 years for both knowledge and technique (Table 2). In addition, it was suggested that knowledge might be more susceptible to increasing age than technique.

Table 1
Patient characteristics.

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Mean ± S.D. (Min–Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–30</td>
<td>57.7 ± 17.5 (18–92)</td>
</tr>
</tbody>
</table>

Range of age (y) Number of patients

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–30</td>
<td>55</td>
</tr>
<tr>
<td>31–35</td>
<td>48</td>
</tr>
<tr>
<td>36–40</td>
<td>76</td>
</tr>
<tr>
<td>41–45</td>
<td>78</td>
</tr>
<tr>
<td>46–50</td>
<td>45</td>
</tr>
<tr>
<td>51–55</td>
<td>49</td>
</tr>
<tr>
<td>56–60</td>
<td>48</td>
</tr>
<tr>
<td>61–65</td>
<td>81</td>
</tr>
<tr>
<td>66–70</td>
<td>89</td>
</tr>
<tr>
<td>71–75</td>
<td>100</td>
</tr>
<tr>
<td>76–80</td>
<td>95</td>
</tr>
<tr>
<td>81–92</td>
<td>56</td>
</tr>
</tbody>
</table>

Sex (M/F) 336/484

Type of Inhalation device

| Turbuhaler | 322 (39.3%) |
| pMDI       | 236 (28.8%) |
| Diskus     | 215 (26.2%) |
| Respinmat  | 64 (7.8%)   |
| Breezhaler | 42 (5.1%)   |
| Handihaler | 31 (3.8%)   |
| Twisthaler | 18 (2.2%)   |
| Ellipta    | 10 (1.2%)   |
| Clickhaler | 7 (0.9%)    |
| Rotadisk   | 3 (0.2%)    |
| Swinghaler | 1 (0.1%)    |

Count of inhalation device

| Unknown/1/2/3 | 6/688/114/12 |

Fig. 1. Relationship between patient’s age and (A) knowledge of inhalation therapy, (B) inhalation technique, and (C) the difference in recognition between patients and medical professionals. (A, B) Black lines denote patients’ self-assessment, and gray lines denote medical professionals’ objective assessment. (C) The black line, gray line, and N represent inhalation technique, knowledge of inhalation therapy, and the number of patients in each group, respectively. *Statistically significant decrease in NRS scores with increasing age (Jonckheere–Terpstra test, \( P < 0.001 \)).

The results of logistic analysis using the divergence of recognition of inhalation technique as the dependent variable showed that the type of inhalation device was not a significant factor, whereas age and the count of inhalation device were significant factors for deterioration in the performance of the inhalation technique even when the effects of the type of inhalation device were taken into account (Table 3).

Using the cutoff value, 66.5 years, obtained by ROC analysis as the criterion, patients were divided into two groups, i.e., an elderly...
CI, Con
medical professionals' assessment decreased with increasing
that scores for inhalation technique and inhalation knowledge on
struction on inhalation therapy. The results of this study showed
inhalation therapy and medical professionals who provided in-
divergence of recognition between patients and medical pro-
Discussion
in the non-elderly group.
problems related to continuation of medication was more frequent
patients' subjective assessment showed that the reporting of
technique were particularly frequent in the elderly. In contrast,
objective assessment revealed that problems related to inhalation
professionals was greater in the elderly group. Medical professionals'
have some problems on the objective assessment of medical pro-
elderly group; on the contrary, the number of patients judged to
their subjective assessments was signi

table comprising subjects
Table 2
Table 3
Table 4
patient age, although patients were not aware of the decrease. The
influences of increasing age on inhalation technique have been
studied widely, and Molimard et al. demonstrated that the inci-
dence of erroneous operation increased with increasing age.16 In
recent years, several dry powder inhaler devices with simplified
operation have been developed, and some easy-to-use devices are
available for patients who begin using an inhalation device.11
However, in the actual clinical setting, various inhalation devices
are in use, and it has been reported that inappropriate use of these
devices leads to unsatisfactory results.8,9 As shown in Table 1, the
820 patients who participated in this study were also using a va-
riety of inhalation devices, demonstrating the diversity of inhala-
tion devices currently in use.
In this study, the divergence of recognition between patients' self-assessment and medical professionals' objective assessment
was evaluated to determine the effects of increasing age. The study
participants were distributed evenly over a wide range of ages,
representing an optimal population to evaluate the effects of
increasing age. Within the scope of our knowledge, there have been
no previous studies that quantitatively evaluated patients' self-
assessment in comparison with medical professionals' objective
assessment. Therefore, we believe that this study provides useful
information for identifying problems involved in inhalation ther-
apy for elderly patients in the actual clinical setting.
As shown in Figure 1, there were no significant changes in the
scores of either inhalation knowledge or inhalation technique on
patients' subjective assessment with increasing age. However, the
objective assessment of medical professionals revealed a decrease
in the scores of both inhalation knowledge and inhalation tech-
nique with increasing age. Because the divergence of recognition
between patients and medical professionals increased with
increasing age, it was suggested that more aggressive instruction
on inhalation therapy would be useful for elderly patients.
Although ROC analysis revealed that age served as a determi-
nant for both knowledge and technique of inhalation, technique
seems to be more susceptible to the effects of increasing age, as
shown in Table 2. Some inhalation devices require complicated
manipulation or a certain level of strength for operation.11 The

Fig. 2. The receiver operating characteristic (ROC) curve of the effects of age on
inhalation knowledge (gray line) and inhalation technique (black line).

Table 2

<table>
<thead>
<tr>
<th>Area</th>
<th>P value</th>
<th>95% CI</th>
<th>Cutoff</th>
<th>Youden index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technique</td>
<td>0.697</td>
<td>&lt;0.001</td>
<td>0.656</td>
<td>0.739</td>
</tr>
<tr>
<td>Knowledge</td>
<td>0.638</td>
<td>&lt;0.001</td>
<td>0.596</td>
<td>0.681</td>
</tr>
</tbody>
</table>

Table 3

Multivariate logistic analysis of causative factors for divergence of recognition be-
tween patients and medical professionals.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age†</td>
<td>1.040 (1.028–1.051)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type of inhalation device†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diskus</td>
<td>0.844 (0.521–1.366)</td>
<td>0.665</td>
</tr>
<tr>
<td>Turbuhaler</td>
<td>0.718 (0.447–1.155)</td>
<td>0.237</td>
</tr>
<tr>
<td>pMDI</td>
<td>0.684 (0.430–1.089)</td>
<td>0.105</td>
</tr>
<tr>
<td>Count of inhalation device</td>
<td>2.104 (1.419–3.120)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI, Confidence interval.
† Per 1-year increase.
‡ Inhalation device used/not used = (0/1).

Discussion
The current study was a novel study that aimed to analyze the
divergence of recognition between patients and medical pro-
fessionals based on a questionnaire survey involving patients on
inhalation therapy and medical professionals who provided in-
struction on inhalation therapy. The results of this study showed
that scores for inhalation technique and inhalation knowledge on
medical professionals' assessment decreased with increasing

<table>
<thead>
<tr>
<th>Subjective assessment by patients</th>
<th>Non-elderly &lt;66.5 yrs</th>
<th>Elderly ≥66.5 yrs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with some problems</td>
<td>267/504 (53.0%)</td>
<td>106/316 (33.5%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Continuation of medication</td>
<td>145/504 (28.4%)</td>
<td>38/316 (12.0%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Lack of understanding of operating the inhalation device</td>
<td>2/504 (0.4%)</td>
<td>7/316 (2.2%)</td>
<td>0.032†</td>
</tr>
<tr>
<td>Difficulty in operating the inhalation device</td>
<td>12/504 (2.4%)</td>
<td>14/316 (4.4%)</td>
<td>0.103</td>
</tr>
<tr>
<td>Lack of understanding of meaning of therapy</td>
<td>106/504 (21.0%)</td>
<td>33/316 (10.4%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Less sensation of inhalation</td>
<td>11/504 (2.2%)</td>
<td>6/316 (1.9%)</td>
<td>0.781</td>
</tr>
<tr>
<td>Concern about adverse effects</td>
<td>50/504 (9.9%)</td>
<td>32/316 (10.1%)</td>
<td>0.924</td>
</tr>
</tbody>
</table>

Objective assessment by medical staff

| Patients with some problems      | 63/504 (12.5%)         | 82/316 (25.9%)   | <0.001* |
| Lack of understanding of operating the inhalation device | 4/504 (0.8%) | 19/316 (6.0%) | <0.001* |
| Difficulty in operating the inhalation device | 3/504 (0.6%) | 6/316 (1.9%) | 0.095† |
| Environmental problem such as nursing care | 0/504 (0.0%) | 4/316 (1.3%) | 0.022† |
| Lack of understanding of meaning of therapy | 19/504 (3.8%) | 19/316 (6.0%) | 0.137   |

*Statistically significant (P < 0.01).
† Analyzed by Fisher exact test.
results of our study may be explained by a distinct deterioration of inhalation technique derived from arthritis or decreases in muscular strength, vision, dexterity, and cognitive function, among other factors with increasing age.4,27

Logistic analysis has shown that age and the count of inhalation device are significant factors that lead to diminished inhalation technique, even when the type of inhalation device is taken into account (Table 3). Although it has been previously reported that the type of the inhalation device, in addition to age, causes a difference in the performance of the inhalation technique,4,27 this divergence seems to be attributable to individual patients or to differences in the method of evaluation. In the current study, patients of a variety of ages were recruited without bias to determine the effects of age as primary endpoints. However, in regard to the inhalation device, the secondary endpoint, various inhalation devices including the aforementioned three devices used by many patients are currently available, and the prominent effects of age on inhalation devices could be detected, but it was also possible that the influences of inhalation devices were hardly detected. On the other hand, the count of inhalation device is the significant factor of inhalation technique independent from age. Therefore, to prevent mistakes, we should choose same device for same patient as possible. Thus, it is presumed that confirmation of inhalation technique is important for elderly patients, regardless of the type of inhalation device. In recent years, inhalation devices with simplified operation have become available,11 and it is expected that the development of inhalation devices associated with fewer operational errors will be further promoted according to advances in pharmaceutical technology.

Table 4 shows the results of comparison between the two groups of patients, i.e., the elderly group (≥66.5 years of age) and the non-elderly group (<66.5 years of age), in regard to the frequencies of specific problems. Similar to the NRS scores, the number of patients who reported some problems on their subjective assessment was significantly greater in the non-elderly group, whereas those with problems were more frequent in the elderly group on the objective assessment of medical professionals, showing a divergence. Thus, these results highlighted the lack of awareness of problems among elderly patients. Medical professionals’ subjective assessment revealed that patients who had problems in inhalation technique were predominant particularly in the elderly group. In contrast, patients’ subjective assessment showed that there were more patients who had difficulty continuing medication in the non-elderly group. In general, older age in patients is reported to be associated with low adherence to treatment because of decreased cognitive and physical function.18 On the other hand, it has been reported that elderly patients have higher respect for medical professionals and are more likely to visit a hospital regularly, and therefore medical professionals play an important role in the patients’ acceptance of treatment.18 The results of this study also suggest that tolerance to continuation of medication, i.e., motivation for treatment, remained undiminished. The decrease in resistance to continuation of treatment might also be derived from the fact that elderly patients are more likely to be unemployed and thus have fewer temporal restrictions than non-elderly patients. There are some limitations in this study. (1) Medical professionals’ assessment was not based on a checklist, and therefore the rating scale might have varied among different raters. However, the variance among individual raters is presumed to be great enough to affect the relationship between age, primary endpoint, and the technique or knowledge of inhalation. (2) The present study was not complete survey, and therefore there is potential for bias that the participants are likely to be health-conscious patients. Despite those health conscious patients, increasing age spoils their light recognition for inhalation therapy. (3) Because the present study is a questionnaire survey, we could not capture the detailed patients information, such as activities of daily living (ADL) and complications. However, in the present study, patients were not eligible if it was difficult for them to respond to the questionnaire because of decreased cognitive function. Therefore, patients who have extremely low ADL were not included in the present study. Generally, the ADL associates with the age of patient. In the present study, we considered that the influence of ADL on inhalation therapy was included in the influence of age.

In conclusion, medical professionals’ objective assessment showed the patients to have diminished inhalation technique and knowledge with increasing age. However, patients’ self-assessment revealed that they were not aware of the diminished inhalation technique, and this trend was particularly prominent in patients aged ≥66.5 years. Namely, when confirming the inhalation technique, hearing from the patient about his or her self-assessment at the hospital or pharmacy is not adequate. In particular, it has become apparent that, in elderly patients, actual implementation of face-to-face instruction regarding inhalation therapy will help detect problems of which patients are not aware. On the other hand, elderly patients accepted the continuation of medication well, suggesting that implementation of more frequent and careful instruction on inhalation therapy in elderly patients than in non-elderly patients facilitates the practice of quality inhalation therapy.

Acknowledgments

This study was supported by the Association of Inhalation Therapists (ASSISTS). The authors express their sincere gratitude to all pharmacies and medical institutions for their cooperation in this questionnaire survey.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.alit.2016.04.002.

Conflict of interest

YKom and HM received lecture fees from GlaxoSmithKline and AstraZeneca, respectively. TI received research funding from Kyorin Pharmaceutical and Astellas Pharma. The rest of the authors have no conflict of interest.

Authors’ contributions

DH, YKom, SK, and TO designed the study. TH, AS, MN, MNa, TTs, HM, KI, TI, MM, HY, PS, YA, YKoh, TK, YF, and FT contributed to data collection. DH, YKom, and TT performed the statistical analysis and wrote the manuscript. All authors read and approved the final manuscript.

References


