Randomized Controlled Study Comparing Two Doses of Intravenous Granisetron (1 and 3 mg) for Acute Chemotherapy-induced Nausea and Vomiting in Cancer Patients: A Non-inferiority Trial

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Received December 21, 2008; accepted March 18, 2009; published online April 24, 2009

Objective: The aim of this study was to assess the non-inferiority of 1 mg to 3 mg granisetron (GRN) injection for the treatment of acute chemotherapy-induced nausea and vomiting (CINV) and to evaluate the tolerability of GRN given at 1 mg in Japanese cancer patients.

Methods: Patients with cancer receiving highly emetogenic chemotherapy were enrolled in this single-blind randomized controlled study. Patients were randomly assigned to receive GRN at a single dose of 1 or 3 mg. The primary endpoint was the rate of complete protection from emetic events (no vomiting, no retching and no need for rescue medication) during the first 24 h following the initiation of chemotherapy.

Results: There were 89 patients in the 1 mg group and 90 patients in the 3 mg group. Complete protection was achieved in 70 patients (78.7%) in the 1 mg group and 73 (81.1%) patients in the 3 mg group. The one-sided test did not reveal non-inferiority of either dose of GRN to the other at a 5% significance level.

Conclusions: Our data failed to show the non-inferiority of 1 mg of GRN to 3 mg of GRN administered as a single dose. However, the rate of complete protection from nausea and vomiting was similar in the two groups. Given the recommended dosage in the guidelines and the economic need for reduction of medical care expenses in Japan, prophylactic administration of GRN at 1 mg may be an appropriate, alternative treatment for acute CINV in cancer patients.

Key words: granisetron – serotonin antagonist – antiemetic – vomiting – non-inferiority trial

INTRODUCTION

Vomiting is one of the most frequently encountered non-hematologic toxicities of cancer chemotherapy. Severe vomiting can lead to problems such as anorexia, dehydration, malnutrition and electrolyte abnormalities, which may lead to refusal of chemotherapy and poor compliance, as well as difficulty in continuing treatment (1,2). The incidence of chemotherapy-induced nausea and vomiting (CINV) depends on the type, dose and administration route of anticancer drugs. For instance, 60–90% of patients receiving carboplatin (a platinum anticancer drug) or doxorubicin (an anthracycline anticancer drug) (>60 mg/m²) and 90% of patients receiving cisplatin (>50 mg/m²) exhibit acute emesis (3). Association between the 5-HT₃ receptor and CINV was first reported in the late 1980s, and 5-HT₃ receptor antagonists began to be applied as antiemetics in the clinical setting from the 1990s. A meta-analysis showed that the risk of CINV associated with cisplatin treatment is reduced to a greater extent by 5-HT₃ antagonists than by conventional antiemetics such as dopamine receptor antagonists and antihistamines (4); thus, 5-HT₃ antagonists are now the drugs of first choice for the prevention of CINV.

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In the USA and Europe, evidence-based antiemetic treatment guidelines have been established by the American Society of Clinical Oncology (ASCO) (5), National Comprehension Cancer Network (NCCN) (6) and European Society of Medical Oncology (ESMO) (7). These guidelines recommend administration of granisetron (GRN) at the dose of 1 mg or 10 μg/kg i.v. or 2 mg orally. In order to determine the optimal effective dose of GRN for the prevention or treatment of CINV in Japanese patients, Furue et al. (8) administered GRN at the dose of 20, 40 or 80 μg/kg once a day and reported that 40 μg/kg administered i.v. once a day was the most appropriate. Therefore, the approved dose of GRN in Japan is set at 40 μg/kg (3 mg i.v.), which differs substantially from the recommendation in the USA and Europe. However, we believe that the results of the aforementioned study could be related to the ambiguous criteria used for defining nausea. We hypothesized that 10 μg/kg of GRN would exhibit equivalent antiemetic efficacy to 40 μg/kg, the approved dose in Japan, and compared the efficacy and safety of 1 mg and 3 mg of GRN from the point of view of clinical rationality.

PATIENTS AND METHODS

This study was a single institutional, single-blind, randomized controlled study conducted to assess whether GRN used at the dose of 1 mg might be non-inferior to the drug used at the dose of 3 mg in regard to complete protection from emetic events. The participants were patients with cancers who were scheduled to undergo chemotherapy and were stratified into the high or moderate emetic risk groups for CINV according to the ASCO guidelines for antiemetic treatment (2006). The study was approved by the Institutional Review Board of the National Cancer Center Hospital. In accordance with a statement from the International Committee of Medical Journal Editors (ICMJE), the study was registered in the University Hospital Medical Information Network (UMIN000000304).

CHEMOTHERAPY SCHEDULE

The chemotherapy was performed according to the following schedule. DC: docetaxel 75 mg/m² on day 1 and carboplatin AUC = 5 on day 1 every 3 weeks, dexamethasone 24 mg/body on day 1; TC: paclitaxel 175 mg/m² on day 1 and carboplatin AUC = 5–6 on day 1 every 3 weeks, dexamethasone 24 mg/body on day 1; weekly TC: paclitaxel 80 mg/m² on day 1 and carboplatin AUC = 2 on day 1 every week, dexamethasone 8 mg/body on day 1; AP: adriamycin 60 mg/m² on day 1 and cisplatin 50 mg/m² on day 1 every 3 weeks, dexamethasone 24 mg/body on day 1 and 20 mg/body on days 2 and 3; CDDP/CPT-11: carboplatin AUC = 5 on day 1 and irinotecan 150 mg/m² on days 1, 8 and 15 every 3 weeks, dexamethasone 24 mg/body on day 1; CDDP/CPT-11: cisplatin 60 mg/m² on day 1 and irinotecan 60 mg/m² on days 1, 8 and 15 every 4 weeks, dexamethasone 24 mg/body on day 1, 8 mg/body on days 2 and 3, 4 mg/body on day 4 and 2 mg/body on day 5; CDDP/GEM: cisplatin 70 mg/m² on day 1 and gemcitabine 1000 mg/m² on days 1, 8 and 15 every 4 weeks, dexamethasone 16 mg/body on day 1, 8 mg/body on day 2, 4 mg/body on day 3 and 2 mg/body on days 4 and 5; AC: adriamycin 60 mg/m² on day 1 and cyclophosphamide 600 mg/m² on day 1 every 3 weeks, dexamethasone 24 mg/body on day 1; CEF: cyclophosphamide 500 mg/m² on day 1, epirubicin 100 mg/m² on day 1 and fluorouracil 500 mg/m² on day 1 every 3 weeks, dexamethasone 24 mg/body on day 1. The following is a single administration. Carboplatin: AUC = 6 on day 1 every 3 weeks, dexamethasone 24 mg/body on day 1; adriamycin: 60 mg/m² on day 1 every 3 weeks, dexamethasone 24 mg/body on day 1; cisplatin: 80 mg/m² on day 1 every 4 weeks, dexamethasone 24 mg/body on day 1 and 8 mg/body on days 2 and 3.

ELIGIBILITY CRITERIA

Patients admitted between January and October 2006 meeting all the inclusion but not falling under any of the exclusion criteria were informed about the study and requested to sign a written consent form. Eligible patients were at least 20 years old and were under treatment with neoplastic agents associated with the high or moderate emetic risk of acute emesis, patients with PS (Eastern Cooperative Oncology Group performance status scale) 0–2 and those meeting each of the following laboratory findings, examined within 3 weeks prior to registration for the study (alanine aminotransferase 100 IU/l lower, creatinine 2.5 mg/dl lower, absolute neutrophil count 1000/μl upper). The ineligibility criteria were known hypersensitivity to 5-HT3 receptor antagonists, treatment with neoplastic agents of the high or moderate emetic risk group for CINV from days 2 to 7 and treatment with the radiation therapy from days 2 to 7. Serious complications, except malignancy (e.g. bowel obstruction, lung fibrosis, cerebrovascular accident, active gastric and duodenal ulcer), inability to precisely record the episodes in a diary were also the ineligibility criteria. The patients were randomly assigned to two treatment arms using the minimization method with correction, including for treatment with a cisplatin-based or non-cisplatin-based regimen and positive/negative history of prior use of the test drug. The randomization of the patients was performed at a participant registry center established at the Division of Biostatistics, School of Pharmaceutical Sciences, Kitasato University. In this study, only patients were blinded to the knowledge of whether they were receiving 1 or 3 mg of GRN. Researchers asked the patients directly or by telephone about whether they experienced any emetic events within 24–36 h following the start of administration of the chemotherapeutic agents that were classified into the high or moderate emetic risk group. Furthermore, patients were asked to record their symptoms for 6 days on a diary card,
and the cards were collected at each visit. Adverse events were evaluated based on the CTCAE v3.0 (JCOG/JSCO Japanese version) (9).

The primary endpoint was the rate of complete response (CR). The rate was complete protection from emetic events (vomiting, retching and need for rescue medications) during the first 24 h following the start of administration of the chemotherapeutic agents classified as high-emetic-risk agents. The secondary endpoints were: rate, the rate was complete protection from nausea and emetic events (no or mild nausea, no vomiting, no retching, no need for rescue medications or premature withdrawals), time-to-treatment success, number of emetic episodes, severity of nausea and severity of adverse events.

**Definitions of the Efficacy Parameters**

Emetic episodes were defined as vomiting or retching. A vomiting episode was considered to have ended when retching or vomiting had ceased for at least 1 min. One or more retching episodes within a 5 min period were defined as one emetic episode. Retching associated with vomiting within a minute interval was defined as one emetic episode within a 5 min period.

Episodes of nausea were recorded by the patients on diary cards, along with the severity of the episodes according to the following four-point scale: 0, none (no nausea); 1, mild (able to take meals as usual); 2, moderate (reduced intake of food) and 3, severe (unable to take either food or water).

Rescue antiemetic medications were defined as follows: the medication for emetic events following chemotherapy that had not previously been prescribed, or temporary medication according to the physical condition in particular patients. Temporary medications were included in rescue antiemetic medications. These medications were used when emetic events or nausea occurred, or the patients desired treatment for these symptoms. Any type or doses of antiemetic agents could be used. Detailed information regarding the use of rescue antiemetic medications, including the date of administration, was recorded when these agents were used. The time of the first rescue antiemetic medication was compared using the $\chi^2$ test. In regard to the safety variables, Grade 3 or more severe non-hematologic toxicities were evaluated. All tests were one-sided, with the statistical significance set at a $P$ value of $<0.05$. The two-sided 95% confidence interval was estimated.

**RESULTS**

**Baseline Demographics**

A total of 182 patients were randomized to the GRN 1 mg group ($n = 90$) or 3 mg group ($n = 92$). Of these, one patient (Patient 106) in the 1 mg group and two patients (Patients 83 and 159) in the 3 mg group withdrew their consent after the randomization. Therefore, 89 patients in the 1 mg group and 90 patients in the 3 mg group were included in the full analysis set (Fig. 1).

**Patient Characteristics**

The characteristics of the patients in the two treatment groups were similar (Table 1). Elderly women were somewhat more likely to be included in the GRN 1 mg group; therefore, that group was slightly disadvantaged at the primary endpoint. The most commonly reported primary cancers in all the treatment groups were: breast cancer ($n = 94$), gynecologic cancer (cervical, endometrial and ovarian cancer) ($n = 64$), primary unknown cancer ($n = 16$), urothelial cancer ($n = 4$) and sarcoma ($n = 3$).

**Efficacy Analysis**

**Primary Efficacy Endpoint: CR Rate**

Table 2 shows the proportion of patients in whom complete protection from emetic events was achieved (no vomiting, no

...
retching and no rescue medications) during the first 24 h following the start of chemotherapy, with the 95% confidence intervals. The one-sided, non-inferiority test at a 5% significance level with a non-inferiority margin of 10% failed to show the non-inferiority of the 1 mg (test dose) dose to the 3 mg (control dose) dose ($P = 0.103$).

**SECONDARY EFFICACY ENDPOINT: CR RATE FOR NAUSEA AND VOMITING**

Table 3 shows the proportion of patients in whom complete protection from nausea and emetic events was achieved (no vomiting, no retching, no rescue medications and no Grade 2 or more severe nausea) during the first 24 h following the initiation of chemotherapy, with the 95% confidence intervals. The one-sided, non-inferiority test at a 5% significance level with a non-inferiority margin of 10% failed to show the non-inferiority of the test group to the control group ($P = 0.108$).

**TIME TO START OF VOMITING**

Episodes of vomiting were observed in eight and six patients in the 1 and 3 mg groups, respectively. The log-rank test showed no statistically significant difference in the time to start of vomiting between the two groups ($P = 0.554$).

**FREQUENCY OF VOMITING AND RETCHING**

Table 4 shows the distribution of the frequencies of vomiting and retching, respectively. The $\chi^2$ test showed the absence of any statistically significant difference in the frequencies of vomiting and retching between the groups ($P = 0.666$ and 0.609, respectively).

**SAFETY ANALYSIS**

In this study, only four patients exhibited Grade 3 or more severe non-hematologic toxicities, as follows: Grade 3 anorexia ($n = 1$) and Grade 3 dehydration ($n = 1$) in the 1 mg group and Grade 3 syncope ($n = 1$) and Grade 3 general malaise ($n = 1$) in the 3 mg group. The investigator did not consider any of these events to be related to GRN treatment.

**DISCUSSION**

In this study, we could not show the non-inferiority of GRN 1 mg to 3 mg; however, the difference in the rate of complete protection from emesis between the two GRN dose groups was only 2.4%. Thus, the failure to show the non-inferiority of the 1 mg dose might be mainly attributable to the lack of sufficient statistical power of the analysis arising from the small sample size. Prior to the start of our study, we expected that the number of patients receiving the target regimens of AC therapy and carboplatin-based chemotherapy would be larger than that of those receiving other regimens. On the basis of this expectation and the results of a study conducted overseas using the above regimen, we assumed that the CR rate with respect to emesis would be 92.6% when calculating the sample size. In this study, patients treated with rescue medications were not included as dropouts, but as patients not showing CR; therefore, the actual CR rate might have been smaller than that estimated when calculating the sample size. Thus, the non-inferiority could not be proved statistically, even though the difference in the CR between the two dose groups was small.

The first study on the effects of GRN has demonstrated the absence of a significant difference in the drug efficacy among groups treated with doses of 40 or 160 $\mu$g/kg in the UK (11–12). Meanwhile, the approved dose of GRN in Japan remains...
Data were analyzed by the Fisher's exact test, the 2-by-2 test. The one-sided non-inferiority test with a 5% significance level did not prove non-inferiority of the 1 mg group to the 3 mg group (P = 0.108). CR, complete response; CI, confidence interval.

There was no statistical difference between the groups (P = 0.666). Frequency of retching during the 5-day period after chemotherapy. There was no statistical difference between the groups (P = 0.609).

40 μg/kg, possibly based on the approved dose in the UK in 1991. This dose of 40 μg/kg has been approved in Japan based on the results of dose-finding study. In the analysis of this trial included not only the objective data of the frequency of emetic episodes, but also the frequency of nausea, which was a subjective variable applied, so that the results depended substantially on the investigators' judgment. Although many studies (13–15) have reported a relationship between the dose and the effectiveness of GRN, the dose of 10 mg/body or 1 mg/body has been approved in the USA. Furthermore, GRN at the dose of 10 μg/kg or 1 mg/body is recommended in the guidelines of the ASCO, ESMO and NCCN. However, the approved dose in Japan remains unchanged. There is a growing global consensus that the doses of antiemetic agents should be minimized to achieve the desired efficacy. Hence, we conducted this study in the hope of achieving efficient use of antiemetic medications in Japan. Physicians in Japan use relatively higher doses of GRN, and the possible medical economic benefit that can be expected with avoidance of the excessive use of these medications has been estimated. For example, we calculated the consumption and purchase price of GRN 3 mg, which has been used at our hospital in 2007. The consumption was 18 455 ampoules each year. The price of each 3 and 1 mg ampoule for injection was 7177 and 3 015 yen in 2007. Thus, if GRN 3 mg were switched to GRN 1 mg, the difference in the purchase price annually would be 76 809 710 yen.

### Table 1. Patient characteristics (n = 179)

<table>
<thead>
<tr>
<th>Gender [n (%)]</th>
<th>1 mg (n = 89)</th>
<th>3 mg (n = 90)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>88 (98.9)</td>
<td>86 (95.6)</td>
<td>0.368†</td>
</tr>
<tr>
<td>Male</td>
<td>1 (1.1)</td>
<td>4 (4.4)</td>
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</table>

<table>
<thead>
<tr>
<th>Type of neoplastic agents [n (%)]</th>
<th>1 mg (n = 89)</th>
<th>3 mg (n = 90)</th>
<th>P value</th>
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<tr>
<td>CDDP included</td>
<td>7 (7.9)</td>
<td>6 (6.7)</td>
<td>0.782†</td>
</tr>
<tr>
<td>Others</td>
<td>88 (98.9)</td>
<td>84 (93.3)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>First cycle [n (%)]</th>
<th>1 mg (n = 89)</th>
<th>3 mg (n = 90)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>36 (40.5)</td>
<td>37 (41.1)</td>
<td>1†</td>
</tr>
<tr>
<td>No</td>
<td>53 (59.6)</td>
<td>53 (58.9)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PS [n (%)]</th>
<th>1 mg (n = 89)</th>
<th>3 mg (n = 90)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>86 (96.6)</td>
<td>87 (96.7)</td>
<td>0.999</td>
</tr>
<tr>
<td>1</td>
<td>2 (2.3)</td>
<td>2 (2.2)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
<td></td>
</tr>
</tbody>
</table>

The chemotherapy was performed according to the following schedule. DC: docetaxel 75 mg/m² on day 1 and carboplatin AUC = 5 on day 1 every 3 weeks, dexamethasone 24 mg/body on day 1; TC: paclitaxel 175 mg/m² on day 1 and carboplatin AUC = 5–6 on day 1 every 3 weeks, dexamethasone 24 mg/body on day 1; weekly TC: paclitaxel 80 mg/m² on day 1 and carboplatin AUC = 2 on day 1, every week, dexamethasone 8 mg/body on day 1; AP: adriamycin 60 mg/m² on day 1 and cisplatin 50 mg/m² on day 1 every 3 weeks, dexamethasone 24 mg/body on day 1 and 20 mg/body on days 2 and 3; CBDCA/CPT-11: carboplatin AUC = 5 on day 1 and irinotecan 150 mg/m² on days 1, 8 and 15 every 3 weeks, dexamethasone 24 mg/body on day 1; CDDP/CPT-11: cisplatin 60 mg/m² on day 1 and irinotecan 60 mg/m² on days 1, 8 and 15 every 4 weeks, dexamethasone 24 mg/body on day 1, 8 mg/body on days 2 and 3, 4 mg/body on day 4 and 2 mg/body on day 5; CDDP/GEM: cisplatin 70 mg/m² on day 1 and gemcitabine 1000 mg/m² on days 1, 8 and 15 every 4 weeks, dexamethasone 16 mg/body on day 1, 8 mg/body on day 2, 4 mg/body on day 3 and 2 mg/body on days 4 and 5; AC: adriamycin 60 mg/m² on day 1 and cyclophosphamide 600 mg/m² on day 1 every 3 weeks, dexamethasone 24 mg/body on day 1; CEF: cyclophosphamide 500 mg/m² on day 1, etoposide 100 mg/m² on day 1 and fluorouracil 500 mg/m² on day 1 every 3 weeks, dexamethasone 24 mg/body on day 1. The following is a single administration. Carboplatin: AUC = 6 on day 1 every 3 weeks, dexamethasone 24 mg/body on day 1; adriamycin: 60 mg/m² on day 1 every 3 weeks, dexamethasone 24 mg/body on day 1; cisplatin: 80 mg/m² on day 1 every 4 weeks, dexamethasone 24 mg/body on day 1 and 8 mg/body on days 2 and 3.

Table 2. CR to the prophylactic therapy against chemotherapy-induced vomiting and to rescue the agents

<table>
<thead>
<tr>
<th>Sample</th>
<th>CR of vomiting [95% CI]</th>
<th>Non-CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg</td>
<td>89 (78.7%) [68.7–86.6]</td>
<td>19</td>
</tr>
<tr>
<td>3 mg</td>
<td>90 (81.1%) [71.5–88.6]</td>
<td>17</td>
</tr>
</tbody>
</table>

The one-sided non-inferiority test with a 5% significance level did not prove non-inferiority of the 1 mg group to the 3 mg group (P = 0.103).

### Table 3. CR to the prophylactic therapy against chemotherapy-induced vomiting and to rescue the agents

<table>
<thead>
<tr>
<th>Sample</th>
<th>CR of nausea and vomiting [95% CI]</th>
<th>Non-CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg</td>
<td>89 (77.5%) [67.4–85.7]</td>
<td>20</td>
</tr>
<tr>
<td>3 mg</td>
<td>90 (80.0%) [70.3–87.7]</td>
<td>18</td>
</tr>
</tbody>
</table>

The consumption was 18 455 ampoules each year. The price of each 3 and 1 mg ampoule for injection was 7177 and 3 015 yen in 2007. Thus, if GRN 3 mg were switched to GRN 1 mg, the difference in the purchase price annually would be 76 809 710 yen.

### Table 4. Frequency of vomiting during the 5-day period after chemotherapy

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Frequency of vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1 3 6 7</td>
</tr>
<tr>
<td>1 mg</td>
<td>89 (91.0%) 3 3 1 1</td>
</tr>
<tr>
<td>3 mg</td>
<td>90 (93.3%) 3 1 2 0</td>
</tr>
<tr>
<td>Frequency of retching</td>
<td>0 1 2 3 4 5 10</td>
</tr>
<tr>
<td>1 mg</td>
<td>89 (87.6%) 4 1 1 2 0</td>
</tr>
<tr>
<td>3 mg</td>
<td>90 (87.7%) 5 4 1 0 0 1</td>
</tr>
</tbody>
</table>

There was no statistical difference between the groups (P = 0.666).
Our results, based on only the objective parameter of complete protection from emetic episodes, showed that the CR rate was similar between the GRN 1 mg and the GRN 3 mg groups. Given the need for promoting efficient use of the limited medical resources and for stemming the rising medical costs in Japan, prophylactic administration of GRN at 1 mg may be the appropriate choice, not expected to be associated with any significant problems. GRN has already been established at a high position among the 5-HT3 receptor antagonist treatment group than in the metoclopramide treatment group (16); therefore, the minimum effective dose of the GRN 1 mg should be recommended in the 5-HT3 receptor antagonist treatment group. Nevertheless, one study indicated a possibly higher incidence of constipation in the 5-HT3 receptor antagonist treatment group than in the metoclopramide treatment group (16). As a result, we have to promote more efficient and cost-effective use of the drugs.

**CONCLUSION**

Our data failed to show the non-inferiority of GRN 1 mg to GRN 3 mg. However, considering the recommendation by the ASCO, ESMO and NCCN guidelines for the administration of GRN at the dose of 1 mg or 10 μg/kg and the economic need for reduction of medical care expenses in Japan, and also the lack of statistical power of the analysis in this study, prophylactic administration of GRN at 1 mg may be the appropriate choice for cancer patients receiving highly emetogenic chemotherapy in Japan.

**Acknowledgements**

We thank all the participating patients. We also thank Masahiro Koseki and Mariko Hochi of the Division of Biostatistics, School of Pharmaceutical Sciences, Kitasato University, for the data analysis, Masashi Ando, Chikako Shimizu, Tsutomu Kohno and Kan Yonemori of the Breast and Medical Oncology Division, National Cancer Center Hospital, for clinical management of the patients.

**Funding**

This research was supported by a grant from the Ministry of Health, Labour and Welfare, Japan.

**Conflict of interest statement**

None declared.

**References**