Original article
The effect of mandatory generic substitution on the safety of alendronate and patients’
 adherence

Pauline Siew Mei Lai
Department of Primary Care Medicine, Faculty of
Medicine, University of Malaya, Kuala Lumpur;
Pharmacy Department, University of Malaya Medical
Centre, Kuala Lumpur, Malaysia

Siew Siang Chua
Yah Huei Chong
Department of Pharmacy, Faculty of Medicine,
University of Malaya, Kuala Lumpur, Malaysia

Siew Pheng Chan
Department of Medicine, Faculty of Medicine,
University of Malaya, Kuala Lumpur, Malaysia

Address for correspondence:
Dr Pauline Siew Mei Lai, Department of Primary Care
Medicine, Faculty of Medicine, University of Malaya,
50603 Kuala Lumpur, Malaysia.
Tel.: +603 79492306; Fax: +603 79577941;
pml@ummc.edu.my

Keywords:
Alendronate — Generic — Medication adherence —
Proprietary — Side-effect

Abstract

Objective:
Generic medicines are often used in public hospitals. However, data on the quality of generic alendronate, its
efficacy, side-effects and medication adherence in clinical practice is scarce. Therefore, this study aimed to
compare the side-effects and medication adherence of generic (apo-alendronate®) and proprietary
alendronate (Fosamax®).

Research design and methods:
This prospective study involved two groups of patients: (1) postmenopausal osteoporotic women prescribed
once-weekly Fosamax® (proprietary group) but were switched to apo-alendronate after 2 years (‘switched
over’ group); and (2) patients initiated with once-weekly apo-alendronate (generic group). Participants were
recruited from the Bone Mineral Clinic of a tertiary hospital. Data were collected through interviews.

Main outcome measures:
Side-effects and medication adherence.

Results:
A total of 131 participants were recruited: proprietary group = 64 and generic group = 67. An intergroup
and a within-group comparison were made. Side-effects were reported by 6 (9.4%), 30 (44.6%) and 12
(18.8%) participants in the proprietary, generic and ‘switched over’ groups, respectively. Participants who
were on generic alendronate were at a significantly higher risk of experiencing side-effects compared to
those who were taking proprietary alendronate (odds ratio (OR): 7.84 (95% CI: 2.96–20.65), p < 0.001).
However, no significant statistical difference was found between the ‘switched over’ and the proprietary
group (OR: 2.23 (95% CI: 0.78–6.37), p = 0.127). Four out of 12 (33.3%) patients who experienced side-
effects immediately after switching to generic alendronate discontinued generic alendronate due to
intolerable gastrointestinal side-effects. There was no difference in medication adherence to generic or
proprietary alendronate.

Conclusions:
Medication adherence to both generic and proprietary alendronate appeared similar although patients who
were taking generic alendronate* were significantly more likely to experience side-effects than those on
proprietary alendronate. Therefore, the switch from proprietary alendronate to the generic forms should not
only consider the cost of the products but must also ensure that the generic and proprietary alendronate are
equivalent in all aspects of efficacy and safety.

*Apotex Inc. Toronto, Ontario, Canada.
†Merck Sharp & Dohme Corp., Pavia, Italy.
Introduction

Generic medicines are often used in public hospitals as they are affordable alternatives in a hospital with budget constraints. This resulted in the purchase of generic alendronate (apo-alendronate*), by a public hospital in Malaysia as a substitute for the original product (Fosamax†) as bioequivalence studies showed that these two products were bioequivalent and that the generic product was only one-third the cost of the innovator product. To date, there are seven generic alendronates that have been registered for use in Malaysia.

Drug products are considered bioequivalent if they contain identical amounts of the same active drug ingredient and have the same rate and extent of absorption whereas, they are considered to be therapeutic equivalents only if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

Since 1999, all oral immediate-release solid dosage forms of generic products should have bioequivalence data as a requirement for registration in Malaysia, to ensure that generic products are therapeutically equivalent to the innovators. However, bioequivalence studies alone do not guarantee that two products of the same drug are exactly identical or that they can be regarded as therapeutically equivalent. In the USA, the Food and Drug Administration (FDA) uses the AB rating system to evaluate the different levels of equivalence. Drug products considered to be therapeutically equivalent to other pharmaceutically equivalent products are designated AA (for oral dosage forms), AN (for solutions/powders for aerosolization), AO (for injectable oil solutions), AP (for injectable aqueous solutions) or AT (for topical products). Drug products which are considered not to be therapeutically equivalent to other pharmaceutically equivalent products are designated with the prefix ‘B’ followed by other alphabets such as BC (for extended-release capsules, injectables and tablets), BD (for active ingredients and dosage forms with documented bioequivalence problems), BE (for delayed-release oral dosage forms), BN (for products in aerosol-nebulizer drug delivery systems), BP (for active ingredients and dosage forms with potential bioequivalence problems), BR (for suppositories or enemas that deliver drugs for systemic absorption), BS (for products having drug standard deficiencies), BT (for topical products with bioequivalence issues) and BX (for drug products with insufficient data to determine therapeutic equivalence).

Little is known about the efficacy, side-effects or patient’s adherence to generic alendronate in clinical practice. A recent literature review reported that some generic formulations of alendronate are more poorly tolerated than the innovator product. Since there is no established disintegration time for generic alendronate tablets, it is not possible to ensure that these generics are equivalent to the innovator product in terms of esophageal drug exposure. One laboratory-based study found that the mean disintegration time of 26 different generic alendronate tablets in vitro ranged from 14 to 342 seconds whereas for the proprietary alendronate it was 43 to 78 seconds. Generic drugs are expected to be therapeutically equivalent to the innovator drug, that is to have similar efficacy and safety. However, the higher irritant responses of generic alendronate in rabbits and dogs suggest that important differences may exist between the clinical effects of the innovator and generic alendronate preparations. These indicate that bioavailability studies may not be sufficient for the meaningful assessment of the safety and efficacy of generic alendronate.

The ultimate goal of osteoporosis management is to reduce the occurrence of fracture. Osteoporosis-related fractures account for a significant economic burden. It leads to approximately 432,000 hospital admissions, almost 2.5 million visits to the doctor and about 180,000 nursing home admissions annually in the USA. The cost to the healthcare system associated with osteoporosis-related fractures has been estimated at $17 billion for year 2005; while hip fractures accounted for 14% of the incident fractures and 72% of the fracture costs.

To date, bisphosphonates are the drugs of choice in the treatment of osteoporosis. Previous studies have shown that approximately 50–75% of women who were prescribed any type of anti-osteoporosis innovator drug were no longer taking it persistently 12 months after initiation of treatment. Three retrospective studies have been conducted to compare the side-effects of proprietary and generic alendronate. All three studies found a higher incidence of side-effects with generic than proprietary alendronate which resulted in discontinuation of treatment. Adherence (medication possession ratio) was better with proprietary alendronate, and after 1 year, only 68% of patients on generic alendronate were still on the medication compared to 84% of patients on proprietary alendronate. In addition, the bone mineral density (BMD) of some patients declined after automatic substitution with generic alendronate although these patients previously had stable BMDs while on proprietary alendronate. Poor adherence leads to lower therapeutic efficacy, weaker suppression of bone resorption, smaller increase in BMD, lower reduction in fracture risk, waste, and discontinuation of treatment.

Currently, there is a paucity of data on the impact of generic bisphosphonates in the management of osteoporosis, especially in patients previously stabilized on proprietary alendronate. Therefore, the aim of this study is to determine if there is any difference between generic and

---

*Aptex Inc., Toronto, Ontario, Canada.
†Merck Sharp & Dohme Corp., Pavia, Italy.
proprietary alendronate in terms of side-effects, which may then affect patients' adherence to the medication.

Patients and methods

This prospective study was conducted from 2005 to 2010 at the Osteoporosis Clinic of a tertiary hospital in Kuala Lumpur, Malaysia. The study involved two main groups of patients: (1) Patients who were on proprietary alendronate for 2 years (proprietary group) before being switched to generic alendronate ('switched over' group); and (2) patients who were on generic alendronate only (generic group). This study compared the number and types of side-effects reported, and also medication adherence of (1) the proprietary group before and after automatic substitution to generic alendronate (a within-the-group comparison); as well as (2) the proprietary and generic groups (an inter-group comparison). Data collection were conducted in two parts.

Part A: Compared patients who were initiated on proprietary for 2 years (proprietary group), but were automatically substituted with generic alendronate ('switched over' group)

From 2005 to 2007, patients were prescribed proprietary alendronate. However, in 2007, generic alendronate was introduced into the hospital formulary. All patients were maintained on proprietary alendronate for at least 2 years before automatic substitution with generic alendronate. Participants were followed-up with a telephone call 3 months after they have started on proprietary alendronate, as well as 3 months after they have started on generic alendronate. This was to determine if the participants have experienced any side-effects from their alendronate. Medication adherence was also assessed 3 months after starting alendronate.

Part B: Compared patients who were initiated on proprietary alendronate (proprietary group) with patients who were initiated on generic alendronate (generic group)

Patients newly prescribed alendronate from 2007 to 2010 were supplied with generic alendronate. After 3 months on generic alendronate, participants were contacted via the telephone to determine if they experienced any side-effects. Medication adherence was also assessed at month 3.

Approval from the Medical Ethics Committee of the hospital under study was obtained before commencement of the study. All procedures were in accordance with the Declaration of Helsinki 2008/Malaysian Good Clinical Practice Guidelines.

Sample size

The number of GI side-effects attributed to generic alendronate was 27% higher than proprietary alendronate. Using the sample size calculator, a sample size of at least 64 participants was required in each group to provide an 80% power of detection and a significance level of $\alpha = 0.05$.

Primary outcomes

Primary outcomes measured were: number and types of side-effect as well as medication adherence to once-weekly alendronate.

Telephone interviews were made using structured and also open-ended questions to document side-effects reported by patients. Side-effects captured included specific GI complaints (such as stomach pain/upset, GI upset, nausea, reflux, heartburn, bloating, constipation, diarrhea, rectal bleeding, bowel problems, perforated diverticulum and stomach ulcer) as well as non-GI complaints (chest pain, loss of appetite, general feeling of being unwell, anemia, rash, shortness of breath, bone pain, arthralgia, flank pain and leg cramp).

Medication adherence was assessed by direct-reporting (by asking the participant the number of doses of alendronate she missed for the last 3 months). Medication adherence to once-weekly bisphosphonates was then assessed in 2 ways: (1) absolute medication adherence, defined as when medication was always taken on the same day of the week; or (2) partial adherence, defined as when medication was taken within 2 days of the original day and the patient returned to the original day for taking the medication the following week; or (3) Non-adherence, defined as when medication is not taken at all or taken more than 2 days of the original day, or both. However, the concept of partial adherence has not been formally recognized as it is still under discussion by an ad hoc working group.

Procedure

Patients were screened from a list of female patients attending the osteoporosis clinic of the teaching hospital, using the following criteria: post-menopausal women who had just been diagnosed with osteoporosis (T-score $<-2.5$ at any bone site or a clinically documented low-trauma fracture sustained at or after 45 years of age), were not on any active osteoporosis therapy within the past 6 months [hormone replacement therapy, bisphosphonates, strontium, teriparatide or raloxifene] and had just been prescribed once-weekly proprietary alendronate between 2005 and 2007, or once-weekly generic alendronate.
between 2007 and 2010, and could communicate in English. Patients who had metabolic bone disease or other medical conditions or were on treatment likely to affect bone metabolism, had a history of chronic renal, hepatic or gastrointestinal (GI) disease or traumatic lumbar compression fracture, were excluded from the study.

Informed consent was obtained from patients who agreed to participate in the study. Baseline information such as demographic data, medical history, life-style and medication history were collected when patients were first started on alendronate therapy. Telephone interviews were conducted using a structured questionnaire to document any side-effects reported and medication adherence after 3 months.

Data analyses
All data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS), version 16 (Chicago, IL, USA). Continuous data was expressed as mean ± standard deviation (SD) and median. The Kolmogorov–Smirnov Z-test was used to check for normal distribution of continuous variables. Categorical variables were expressed as absolute (number) and relative frequencies (percentage). The demographic data of participants were compared using the independent sample t-test for continuous variables, while the proportions with side-effects or medication adherence were compared between groups using χ² test. Any association between variables was also analyzed using the χ² test (for categorical variables) or Pearson’s correlation (for continuous variables). A p-value of <0.05 was considered as statistically significant. The odds ratio (OR) of experiencing a side-effect with the generic compared to the proprietary group was also determined.

Results
Response rate
A total of 82 patients who fulfilled the inclusion criteria for the proprietary group were approached. However, only 64 (78%) provided informed consent and completed the telephone interview. For the generic group, 98 patients who fulfilled the inclusion criteria were approached, but only 67 (68.4%) patients completed the study.

Baseline characteristics of participants are shown in Table 1. There was no significant difference between the proprietary and generic groups with respect to their baseline characteristics, except for history of falls, alcohol consumption and frequency of exercise.

Comparison of side-effects reported by the proprietary group (before and after automatic substitution with generic alendronate) and the generic group
Overall, side-effects were reported by 6 (9.4%), 30 (44.8%) and 12 (18.8%) participants in the proprietary, generic and 'switched over' groups, respectively. Participants who were on generic alendronate were at a significantly higher risk of experiencing a side-effect compared to those who were taking proprietary alendronate [OR: 7.84 (95% CI: 2.98–20.65), p < 0.001]. However, no significant statistical difference was found within the proprietary group before and after switched over to generic alendronate [OR: 2.23 (95% CI: 0.78–6.37), p = 0.127]. The number and type of side-effect experienced are shown in Table 2. The most common gastrointestinal (GI) and non-GI side-effects encountered were stomach pain/upset and myalgia, respectively. Four out of 12 patients (33.3%) who experienced side-effects immediately after switching to generic alendronate, discontinued their generic alendronate due to intolerable GI side-effects.

Side-effects were reported within the first month of alendronate therapy and most issues were resolved after 1 month. However, these problems continued for 3 months in the generic group for 13 out of 30 patients who reported side-effects (43.3%). None of the characteristics of the participants shown in Table 1 were significantly related to the occurrence of side-effects due to alendronate (p > 0.05).

Medication adherence
No significant difference in absolute and partial medication adherence was found between the proprietary and generic groups (Table 3). For participants who were considered as non-adherent, they either forgot to take their once-weekly alendronate for that particular week (22, 11.3%), took it on a different day from the original day (50, 25.6%) or both (6, 3.1%). Reasons for non-adherence were similar for both groups (Figure 1). Some (29/131, 22.1%) participants provided more than one reason. No association was found between the occurrence of side-effects and absolute or partial adherence.

Discussion
Most drug molecules developed in recent years were produced at a cost of about $500 million to $2 billion, depending on the type of therapy and the research company. This is because most new molecules are designer drugs, synthesized using the latest technology such as
Table 1. Baseline characteristics of participants.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Proprietary group (n = 84)</th>
<th>Generic group (n = 87)</th>
<th>χ²/T-value*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD (years) [range]</td>
<td>66.41 ± 8.25 [48–97]</td>
<td>66.18 ± 8.55 [45–90]</td>
<td>0.155</td>
<td>0.877</td>
</tr>
<tr>
<td>Age range, years [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>2 (3.1)</td>
<td>2 (3)</td>
<td>0.766</td>
<td>0.943</td>
</tr>
<tr>
<td>50–59</td>
<td>13 (20.3)</td>
<td>10 (14.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>28 (43.8)</td>
<td>30 (44.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>18 (28.1)</td>
<td>21 (31.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥80</td>
<td>3 (4.7)</td>
<td>4 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>13 (20.3)</td>
<td>5 (7.5)</td>
<td>6.293</td>
<td>0.098</td>
</tr>
<tr>
<td>Chinese</td>
<td>38 (59.4)</td>
<td>50 (74.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>13 (20.3)</td>
<td>11 (16.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>1 (1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean BMI ± SD (kg/m²)</td>
<td>23.95 ± 3.95</td>
<td>23.02 ± 3.53</td>
<td>1.417</td>
<td>0.159</td>
</tr>
<tr>
<td>BMI range [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5 (underweight)</td>
<td>4 (6.3)</td>
<td>5 (7.5)</td>
<td>1.928</td>
<td>0.387</td>
</tr>
<tr>
<td>18.5–24.9 (normal)</td>
<td>39 (60.9)</td>
<td>45 (67.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.0–29.9 (overweight)</td>
<td>16 (25.0)</td>
<td>14 (20.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30 (obese)</td>
<td>5 (7.8)</td>
<td>2 (3.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of education [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No formal education</td>
<td>6 (9.4)</td>
<td>4 (5.7)</td>
<td>2.448</td>
<td>0.485</td>
</tr>
<tr>
<td>Primary</td>
<td>13 (20.3)</td>
<td>10 (14.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>26 (40.6)</td>
<td>36 (53.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diploma [tertiary/post-graduate]</td>
<td>19 (29.7)</td>
<td>17 (25.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had a previous fall/fracture [n (%)]</td>
<td>32 (50.0)</td>
<td>18 (26.9)</td>
<td>7.423</td>
<td>0.006*</td>
</tr>
<tr>
<td>Still working [n (%)]</td>
<td>7 (10.9)</td>
<td>11 (16.4)</td>
<td>0.829</td>
<td>0.362</td>
</tr>
<tr>
<td>No. of years menopausal [mean ± SD]</td>
<td>17.97 ± 8.26</td>
<td>17.82 ± 9.10</td>
<td>0.037</td>
<td>0.923</td>
</tr>
<tr>
<td>Family history of osteoporosis [n (%)]</td>
<td>10 (15.6)</td>
<td>11 (16.4)</td>
<td>4.59</td>
<td>0.100</td>
</tr>
<tr>
<td>Alcohol consumption [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occasionally</td>
<td>7 (10.9)</td>
<td>34 (50.7)</td>
<td>24.12</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Never</td>
<td>57 (89.1)</td>
<td>33 (49.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>1 (1.6)</td>
<td>1 (1.5)</td>
<td>1.940</td>
<td>0.370</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>0</td>
<td>2 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>63 (96.4)</td>
<td>64 (95.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3 times/week</td>
<td>31 (48.4)</td>
<td>56 (83.6)</td>
<td>18.13</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>≤3 a week</td>
<td>33 (51.6)</td>
<td>11 (16.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* χ² test was used for all categorical variables while the independent t-test was used for all continuous variables.
SD, standard deviation.

Combinatorial chemistry. Out of 10,000 molecule candidates, only one will make it to the market, and the typical development time is 10–15 years. The sequential process of drug development prior to market approval is to prove the safety and efficacy of the new drug against a target disease. Phase I, II and III clinical trials provide data for the safety and efficacy of the new drug, while phase IV studies document the post-marketing surveillance of the drug. New drugs are patented for 20 years to protect the innovator from unfair competition, to allow recovery from investments and to obtain profit from their invention. Upon expiry of the patent period, it is then possible for other manufacturers to produce the generic version of the drug to be marketed.

The 1984 Hatch–Waxman Amendments gave the Food and Drug Administration (FDA) authority to accept the Abbreviated New Drug Applications (ANDA) for generic versions of drugs whose patents had expired.

Generic medicinal products contain well-known safe and effective active pharmaceutical ingredients that have been on the market for about 10 years. Therefore, an ANDA applicant does not have to prove the safety and effectiveness of the drug product, and are not required to repeat pre-clinical tests and clinical trials on animals and patients. Instead, they have to perform 'bioequivalence studies' to demonstrate that the generic medicine is equivalent to the original product. Bioequivalence studies verify that the active ingredient in a generic drug product will be absorbed into the body to the same extent and at the same rate as its corresponding innovator product. The significance of bioequivalence studies is that when two pharmaceutical products are shown to be bioequivalent, the two products are also considered to be therapeutically equivalent. Therapeutically equivalent products are expected to have the same safety and efficacy profiles, when administered under the approved conditions.
Table 2. Comparison of the number of side-effects events reported by the proprietary, generic and 'switched over' groups.

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>No. of events reported by participants in the proprietary group (n)</th>
<th>No. of events reported by participants in the generic group (n)</th>
<th>No. of events reported by participants in the 'switched over' group (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI side-effects†</td>
<td>Stomach pain/upset 1</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Diarrhea 1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Heartburn 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Nausea 0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Constipation 0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Bloating 0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Reflux 0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Non-GI side-effects†</td>
<td>Mynag 2</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Jaw/gum pain 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Rash 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Bone pain 0</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Headache 0</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dizzy 0</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Statistically significant at p < 0.05.
†some participants reported more than one side-effect.

Table 3. Adherence to once-weekly alendronate for the proprietary and generic groups.

<table>
<thead>
<tr>
<th></th>
<th>Proprietary group (n = 64)</th>
<th>Generic group (n = 67)</th>
<th>χ²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute adherence</td>
<td>28 (43.9)</td>
<td>25 (37.3)</td>
<td>0.563</td>
<td>0.453</td>
</tr>
<tr>
<td>Partial adherence</td>
<td>46 (71.9)</td>
<td>56 (83.6)</td>
<td>2.603</td>
<td>0.107</td>
</tr>
<tr>
<td>Tock medication within 2 days of the original day and returned to the original day the following week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In Malaysia, many generic forms of alendronate are available. Most generic companies provide comparative bioequivalence data with the original product, but not all formulations have been compared in terms of therapeutic equivalence or safety/tolerability. Of particular interest is the GI tolerability of these generic formulations, as bisphosphonates in general have the potential to cause GI irritation. This study found a significantly higher number of participants with GI and non-GI side-effects among those in the generic group compared to the proprietary group, suggesting that the generic and proprietary products of alendronate are not therapeutically equivalent. This may be due to differences in formulation between the innovator and generic products such as drug particle size, excipients, manufacturing process, equipment used, site of manufacture or batch size. These differences may result in different esophageal transit time, which in turn may affect the potential for local irritation of the upper GI tract and tolerability.

Previous studies found that the reported number of GI side-effects increased in patients previously stabilized on proprietary alendronate and then switched to generic alendronate. This finding is similar to the present study, but our results did not reach statistical significance. This may be because participants who were previously on proprietary alendronate are more tolerant to the side-effects of the medication compared to those newly started on alendronate. Previous studies also found that the BMD of some patients declined after automatic substitution with generic alendronate although these patients previously had stable BMDs while on proprietary alendronate. This suggests that mandatory substitution should only be carried out if two products have been shown to be therapeutically equivalent in all aspects of efficacy and safety. However, if health institutions want to purchase generic alendronate...
instead of proprietary alendronate, then close monitoring of side-effects is important to achieve optimal therapeutic outcomes. Existing patients on proprietary alendronate should be continued on the same medication until they no longer need them (which is usually 5-10 years)\textsuperscript{32}. The use of generic alendronate may reduce the purchasing cost of the medicine. However, further studies on cost effectiveness, clinical outcomes and safety should be conducted to confirm the benefits of using generic over proprietary products in terms of financial savings.

**Medication adherence**

Medication adherence to alendronate was less than 50% if absolute adherence was considered. This is similar to that of other studies on chronic diseases\textsuperscript{33,34}. If partial adherence is allowed, then this figure increased to more than 70%. Although medication adherence to generic alendronate appeared lower than that on proprietary alendronate, this did not reach any statistical significance regardless of which type of adherence was considered. Side-effects are a major cause of non-adherence in other studies\textsuperscript{35,36} but this study did not find any significant association between the reporting of side-effects and medication adherence. Rather, the main reason for non-adherence was patients forgot to take their alendronate. Other common reasons cited were that they were busy, there was a change in their daily routine or that they were away from home. This indicates the importance of counseling patients to ensure that they understand the instructions and purpose of alendronate treatment and also to help patients adhere to their dosing regimen.

One of the limitations of this study was that this was an observational study of an existing clinical practice. It was not possible to perform a randomized two-period, two-sequence crossover study with an adequate washout period (to avoid drug carryover effects) in a clinical setting, as the half-life of bisphosphonates is very long (1.5-10 years); which means that these drugs continue to be effective even when the patient stops taking them\textsuperscript{37}. Therefore, the level of evidence of this study may not be as strong. However, since most patients' reported the side-effects within the first month of starting therapy and these were transient in nature, the most important period to assess the tolerability of bisphosphonates is within the first 3 months of starting therapy.

In addition, the side-effects were documented based on patients' self-report, hence reporting bias could not be ruled out. The number of reported adverse events may be an underestimation as patients may not be able to differentiate between muscle ache (myalgia) and bone pain, and would therefore report it as one side-effect instead of two. Another limitation was that only one method was used to assess medication adherence. However, since the same limitation would apply to the proprietary and generic groups, it would not have affected the comparison between these groups. In addition, prior to the mandatory substitution with generic alendronate, patient counseling was not performed to improve acceptance so as to prevent reporting bias.

The BMD of patients were also not assessed in this study and hence the therapeutic impact of the side-effects and subsequent non-adherence to medication could not be assessed. There were also significant differences in terms of past falls, alcohol consumption and level of exercise between the proprietary and generic group at baseline. These major risk factors may potentially affect patient adherence and the clinical outcomes. However, our study focused on the side-effects reported by patients and not the clinical outcomes although an indirect connection between the occurrence of side-effects, poor adherence and clinical outcomes cannot be ruled out.

Only patients who could communicate in English were recruited in this study. However, Malaysia is a multi-racial country and hence, the results may not be generalized to patients who could not read or understand English. In addition, the enrolment of participants was from one center only. Therefore, the sample cannot be considered as population-based. Further studies which use Bahasa Malaysia and Mandarin as a language for communication and enrolment of participants from multi centers are required to enable the results to be more representative of Malaysian postmenopausal women with osteoporosis.

The main strength of this study is that data were collected from real patients in clinical practice settings. This study serves as a 'hypothesis generating' study to alert the relevant authorities of the importance of a more stringent bioequivalence requirement in the pharmacokinetic profile of alendronate since emerging evidences (including the findings in this paper) showed that the variation in formulation may contribute to a higher incidence of GI side-effects. The findings in this study also indicate that drug regulatory authorities should increase the rigor of the country's post-marketing safety studies on generic products that is similarly required of its branded equivalent. Difference in safety aspect (such as the occurrence of side-effects) may occur, which could affect the patients' quality of life. Such consideration is important to ensure that patients obtain optimal benefits from their drug therapy. Therefore, further pharmacoeconomic studies which include the efficacy and safety of the generic versus proprietary alendronate are warranted.

**Conclusions**

Medication adherence to both generic and proprietary alendronate appeared similar although patients who were taking a certain generic alendronate were significantly
more likely to experience side-effects than those on proprietary alendronate. Given the significant increase in side-effects, not all generic alendronates may be as well tolerated as proprietary alendronate. Further studies should be conducted to include clinical outcomes (such as bone mineral density and incidence of fracture) as well as safety and cost effectiveness of generic alendronate before mandatory substitution is performed.

Transparency

Declaration of funding

Funding for research—none.

Declaration of financial/other relationships

The authors declare that they have no competing interests. CMRO peer reviewers on this manuscript have no relevant financial relationships to disclose.

Acknowledgments

We would like to record our appreciation to the staff of the Osteoporosis Clinic of the hospital under study for their assistance and cooperation. Last but not least, we would like to thank all the participants for their involvement in this study.

This material has not been previously published except as an abstract in the 2nd International Conference on Pharmacy and Advanced Pharmaceutical Sciences, Yogyakarta, Indonesia, 19-20 July 2011, abstract no P10:64.

References


8. Denzeriau RJ, Crail DJ, Perkins AC. In vitro disintegration and dissolution studies of once-weekly copies of alendronate sodium tablets (70 mg) and in vivo implications. Curr Med Res Opin 2008;24:1137-45.


34. McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions. JAMA 2002;288:2666-79