Effect of daikenchuto (TU-100) on gastrointestinal and colonic transit in humans


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Submitted 9 February 2010; accepted in final form 1 April 2010

Manabe N, Camilleri M, Rao A, Wong BS, Burton D, Busciglio I, Zinsmeister AR, Haruma K. Effect of daikenchuto (TU-100) on gastrointestinal and colonic transit in humans. Am J Physiol Gastrointest Liver Physiol 298: G970–G975, 2010. First published April 8, 2010; doi:10.1152/ajpgi.00043.2010.—Daikenchuto (TU-100) is a traditional Japanese (Kampo) medicine used to treat postoperative ileus. TU-100 dose dependently increases gastrointestinal (GI) motility by modulating cholinergic and serotonergic mechanisms in animal studies. The aim of this study was to evaluate the effects of orally administered TU-100 on GI and colonic transit and bowel function in healthy humans. In a randomized, parallel-group, double-blind, placebo-controlled, dose-response study, 60 healthy subjects were randomly assigned to placebo or TU-100 2.5 g or 5 g tid ingested immediately before meals for 5 consecutive days. We measured GI and colonic transit by validated scintigraphy and stool frequency and consistency by daily diaries of bowel function. There were overall treatment effects on colonic filling at 6 h without any significant differences between each dose of TU-100 and placebo. There tended to be overall treatment effects on ascending colon (AC) emptying half-time; the TU-100 (7.5 g/day) treatment significantly accelerated AC emptying compared with placebo. There were numerically higher values of GC24 (which reflect overall colonic transit) with both doses of TU-100, but these changes were not statistically significant. There were no significant overall treatment effects on gastric emptying or stool frequency and consistency. One subject, who received 7.5 g/day of TU-100, had elevated creatine phosphokinase following the study. TU-100 (7.5 g/day) significantly accelerated AC emptying. Further randomized controlled trials in patients with functional constipation or irritable bowel syndrome with constipation are warranted to evaluate the clinical efficacy of TU-100 in these disorders.

Traditional Japanese medicine (Kampo medicine); healthy subject; scintigraphy

THE NATIONAL CENTER for Complementary and Alternative Medicine defines complementary and alternative medicine (CAM) as a group of diverse medical and healthcare systems, practices, and products that are not presently considered to be part of conventional medicine (9). An estimated 28.9% of adults in the U.S. use some form of CAM (31). After prayer or spiritual healing, herbal medicine is the second most common CAM therapy: 9.6 to 12.1% of U.S. adults use herbal products, with gross sales surpassing 5 billion dollars annually. There has been a fivefold increase in use of herbal medicines within the last decade (15, 31). Digestive symptoms account for ~10% of the use of herbal therapy. In general, there are few studies documenting the pharmacological effects of such agents.

Daikenchuto (TU-100) is a traditional Japanese medicine (Kampo medicine) that has been used to treat adhesive bowel obstruction (18, 20). TU-100 is a mixture of extract powders from dried Japanese pepper, processed ginger, ginseng radix, and maltose powder. Intra-duodenal and intrajejunal administration of TU-100 (0.5, 1.5, and 3.0 g/dog) increased motility of the duodenum, proximal jejunum, and distal jejunum in conscious dogs in a dose-dependent manner (21). In vivo experiments, the effect of TU-100 on laparatomy-induced or chemically induced intestinal dysmotility was inhibited by treatment with atropine or a 5-HT4 antagonist (30, 36). In vitro experiments, TU-100 stimulated contractions in isolated guinea pig ileum and increased spontaneous contractions of isolated rabbit jejunum (35), but it did not affect uterine motility (28). These effects were completely suppressed by treatment with atropine or tetrodotoxin, and partially suppressed by treatment with a 5-hydroxytryptamine receptor 4 (5-HT4) antagonist (41). TU-100 also stimulated acetylcholine release in ileal smooth muscle (34). These results suggest that the effects of TU-100 in the gastrointestinal (GI) tract are mediated mainly by cholinergic and serotonergic nerves.

No significant safety issues have been identified in preclinical studies of TU-100 in the dosing range intended for human use (1). Using the Functional Observational Battery (FOB) method, TU-100 at 1,800 mg/kg did not have any adverse effects on the general physical condition or behavior of the animals. Safety in humans is illustrated by the observations with widespread use of TU-100 in Japanese patients. Thus only 113 spontaneous adverse events associated with use of TU-100 have been reported from April 1, 1994 until June 30, 2008.

Earlier trials of TU-100 suggested its prokinetic effects may be useful in treating GI hypomotility (17, 39). Previous studies of TU-100 in humans have involved postoperative patients after GI surgery, and they showed TU-100 prevented postoperative ileus (16, 20). The effects of TU-100 in humans without previous major GI surgeries are unclear.

The aim of this study was to evaluate the effects of orally administered TU-100 on GI and colonic transit and bowel function in healthy subjects.

MATERIALS AND METHODS

Participants. Sixty healthy subjects aged between 18 and 65 yr were recruited by advertisement and enrolled in the study. These subjects were either healthy men or nonpregnant, non-breast-feeding healthy women with body mass index (BMI) between 18 and 35 kg/m2 and no alarm indicators suggesting disease or GI symptoms by
a validated self-report GI symptom questionnaire (40). Birth control for female participants was required during this study. Subjects were not allowed to be on any medications except low-dose aspirin (80 mg/day) for cardioprotection, birth control, hormone replacement therapy, and stable thyroid replacement. Over-the-counter drugs were also prohibited. Subjects were excluded if they had a history of allergic reactions to egg, ginseng, ginger, and Sichuan pepper or lactose intolerance. The study was approved by the Mayo Clinic Institutional Review Board, and all participants signed informed consent.

Randomization and concealed allocation. Each subject was assigned a unique patient number to ensure concealed allocation. Two different doses of TU-100 and matching placebo were provided by Tsumura USA. Randomization was stratified on gender and BMI (<25, ≥25 kg/m²). Medication doses were randomly assigned in fixed block sizes according to a schedule provided by an independent statistician in the Department of Health Sciences Research at Mayo Clinic. However, the research pharmacy maintained the randomization schedule in case of emergency. All clinical and laboratory study personnel were blinded throughout the study until all data were analyzed and locked.

Study medications. TU-100 at doses of 2.5 or 5 g or identical placebo were administered orally as a solution three times daily immediately before meals for 5 consecutive days. The protocol-specified dose was dissolved in an ounce of lukewarm water immediately prior to consumption and swallowed over ~1 min maximum.

Study design. This study was a randomized, parallel-group, dose-response, multiple-administration, double-blind, placebo-controlled study evaluating the effects of TU-100 on GI and colonic transit in healthy subjects. Figure 1 shows the study design. Following an initial screening (visit 1), subjects were randomized to 7.5 g/day of TU-100, 15 g/day of TU-100, or matching placebo for 5 days. Each subject underwent validated scintigraphic assessment of gastric, small bowel, and colonic transit of solids. These studies were undertaken over a 48-h period (visits 3, 4, and 5). Each participant was instructed to keep a 5-day medication administration and stool diary. Finally, participants underwent safety monitoring by phone at 7–10 days after the procedure.

GI and colonic transit measurements. Subjects came to the Clinical Research Unit at 6 AM after fasting for a minimum of 8 h (visit 3, day 4 of treatment). A urine pregnancy test was performed in all female subjects within 48 h prior to isotope ingestion for measurement of GI and colonic transit by scintigraphy (3, 4, 6, 7, 10, 11, 32). Indium-111 (111In) absorbed on activated charcoal particles was delivered to the colon by means of a methacrylate-coated, delayed-release capsule ingested with a 3-oz. glass of water. After the capsule emptied from the stomach (documented by its position relative to radioisotopic markers placed on the anterior iliac crests) or 1 h after capsule ingestion, whichever was shortest, a radiolabeled meal was ingested. In this meal, technetium (99mTc)-sulfur colloid was used to label two scrambled eggs that were eaten with one slice of whole wheat bread and one glass of whole milk (300 kcal). This meal facilitated measurement of gastric and small bowel transit. Subjects ingested standardized meals for lunch and dinner at 4 h (550 kcal) and 8 h (750 kcal) after the radiolabeled meal. The subject left the study center at the end of the afternoon and returned the next 2 days (visits 4 and 5) for the images at 24 and 48 h. The images were obtained before breakfast after a minimum of 8 h of fasting on the second and third day of imaging. Relative to the time of breakfast meal ingestion, anterior and posterior gamma camera images were obtained every hour for the first 6 h (the first 4 h for the assessment of gastric emptying), and at 8, 24, and 48 h after ingestion of 111In capsule. The performance characteristics of this test in health and functional gastrointestinal disorders are summarized elsewhere (11, 13).

Transit data analysis. A variable region of interest program was used to quantify the counts in the stomach and each of four colonic regions: ascending (AC), transverse (TC), descending (DC), and combined sigmoid colon and rectum (RS). These counts were corrected for isotope decay, tissue attenuation, and downscatter of 111In counts in the 99mTc window (4, 5, 7, 8, 11).

Geometric mean of counts in anterior and posterior gastric regions of interest was used to estimate the proportionate gastric emptying over time of counts from 99mTc. The proportion of 99mTc reaching the colon at 6 h was estimated as a measure of orocecal (and a surrogate for small bowel) transit.

Geometric center (GC) of colonic counts at 4, 8 and 24 h was estimated using geometric mean of counts in AC, TC, DC, and RS, and stool (weighted by factors of 1 to 5, respectively). The primary variable of interest in overall colonic transit was the GC at 24 h. The GC is the weighted average of counts in the different colonic regions: AC, TC, DC, RS, and stool. At any time, the portion of colonic counts in each colonic region is multiplied by its weighting factors as follows:

![Fig. 1. Study design.](http://ajpgi.physiology.org/)
Table 1. Statistical power statement based on prior studies conducted in healthy subjects

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Mean</th>
<th>SD</th>
<th>CV%</th>
<th>Effect Size (%) Detectable With 80% Power (α = 0.05)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE solids t_{1/2}, min, n = 63</td>
<td>130</td>
<td>29</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Colonic filling at 6 h, %, n = 63</td>
<td>44</td>
<td>29</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>GC at 24 h, n = 62</td>
<td>2.36</td>
<td>0.85</td>
<td>36</td>
<td>33</td>
</tr>
<tr>
<td>AC t_{1/2}, h, n = 50</td>
<td>15.0</td>
<td>8.0</td>
<td>53</td>
<td>48</td>
</tr>
</tbody>
</table>

Effect size is the difference between means as a percentage of listed mean. CV, coefficient of variation; GE, gastric emptying; GC, geometric center; AC, ascending colon. *Based on a 2-sample t-test with a 2-sided α level of 0.05.

Thus, a high GC implies faster colonic transit. A GC of 1 implies that all isotope is in the AC, and a GC of 5 implies that all isotope is in the stool. The AC emptying t_{1/2} was also estimated by plotting the activity-time curve for percent residing in the AC during the first day of transit measurement and 24 h; linear interpolation was used to connect points.

Assessment of stool frequency and consistency. During the study, subjects completed a daily diary to assess stool frequency and consistency using the Bristol Stool Form Scale (25). The diary was dispensed at visit 1 and the completed diary was collected at the conclusion of the study.

Study end points. The primary end points, on which the sample size and statistical power were based, were gastric emptying half-time (GE t_{1/2}) of solid, colonic geometric center at 24 h (GC 24), and ascending colon emptying half-time (AC emptying t_{1/2}). Secondary end points were colonic geometric center at 4 h (GC 4) and 48 h (GC 48), colonic filling at 6 h, stool frequency, and stool consistency.

Sample size assessment and statistical analysis. Table 1 summarizes data for the primary response measures and uses coefficients of variation (%) to estimate the effect size detectable with 80% power based on a two-sample t-test at a 2-sided α level of 0.05. The effect size is the difference in group means as a percentage of the overall mean for each response and assumes 20 subjects per group. It was anticipated that the analysis of covariance (ANCOVA) would provide 80% power to detect similar (pairwise) differences using a pooled estimate of variation across all three groups and potentially even smaller effect sizes by adjusting for important covariates.

Data are expressed as means ± SE or as percentages, as noted. An ANCOVA was used to assess overall treatment effects on GI and colonic transit and bowel function. Dunnett’s test was used for the multiple comparisons of each dose level vs. placebo. P values of less than 0.05 were considered to indicate statistical significance.

Table 2. Participants’ characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 21)</th>
<th>TU-100, 7.5 g/day (n = 19)</th>
<th>TU-100, 15 g/day (n = 20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>34.0 ± 2.8</td>
<td>35.2 ± 3.1</td>
<td>32.8 ± 2.6</td>
<td>0.45</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>11 (52%)</td>
<td>11 (58%)</td>
<td>10 (50%)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.5 ± 0.7</td>
<td>25.3 ± 1.1</td>
<td>25.6 ± 0.7</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE, unless otherwise noted. BMI, body mass index.

RESULTS

Participant characteristics. Sixty-five subjects were initially screened and five subjects were excluded (one because of ineligibility based on medical history, one because of high BMI, and the remaining three because of abnormal screening laboratory data), which resulted in a total of 60 subjects enrolling in the study. Subsequently, 21 subjects were randomized to placebo, 19 to 7.5 g/day of TU-100, and 20 to 15 g/day of TU-100, respectively. Each participant completed the study. The demographic characteristics of the subjects are summarized in Table 2. There were no clinically important differences in age, gender, height, weight, or BMI among the three groups.

Effect of TU-100 on gastric emptying. The mean solid GE t_{1/2} of the placebo group was 125.4 min (±5.98), compared with 134.6 min (±5.74) and 123.9 min (±6.08) of the TU-100 7.5 and 15 g/day group, respectively. There was no significant overall treatment effect of the TU-100 group on gastric emptying (P = 0.45) (Table 3).

Effect of TU-100 on colon filling at 6 h and ascending colon emptying. There were significant overall treatment effects of TU-100 on colon filling at 6 h (P = 0.04). TU-100 (7.5 g/day) tended to accelerate colonic filling at 6 h, which was not statistically significant (P = 0.13 by Dunnett’s test). There tended to be an overall treatment effect of TU-100 on ascending colon emptying t_{1/2} (P = 0.07). In particular, TU-100 (7.5 g/day) significantly accelerated ascending colon emptying compared with placebo (P < 0.05, by Dunnett’s test, that is correcting for two pairwise comparisons of each dose of TU-100 tested vs. placebo). On the other hand, there were no significant effects of TU-100 (15 g/day) on both colonic filling at 6 h (P = 0.64) and ascending colon emptying (P = 0.41) (Table 3, Fig. 2).

Effect of TU-100 on overall colonic transit. The mean colonic GC at 24 h of the placebo group was 2.29 (±0.24), compared with 2.51 (±0.17) and 2.55 (±0.20) of the TU-100 7.5 and 15 g/day group, respectively (P = 0.63). The mean

Table 3. Overall treatment effect of TU-100 on gastrointestinal transit and bowel functions

<table>
<thead>
<tr>
<th></th>
<th>Placebo n = 21</th>
<th>TU-100 (7.5 g/day), n = 19</th>
<th>TU-100 (15 g/day), n = 20</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE t_{1/2}, min</td>
<td>125.4 ± 6.0</td>
<td>134.6 ± 6.0</td>
<td>123.9 ± 6.1</td>
<td>0.45</td>
</tr>
<tr>
<td>GC 4</td>
<td>0.51 ± 0.16</td>
<td>0.71 ± 0.13</td>
<td>0.51 ± 0.11</td>
<td>0.54</td>
</tr>
<tr>
<td>GC 24</td>
<td>2.29 ± 0.24</td>
<td>2.51 ± 0.17</td>
<td>2.55 ± 0.20</td>
<td>0.63</td>
</tr>
<tr>
<td>GC 48</td>
<td>3.43 ± 0.25</td>
<td>3.75 ± 0.23</td>
<td>3.77 ± 0.25</td>
<td>0.64</td>
</tr>
<tr>
<td>Colonic filling at 6 h, %</td>
<td>40.3 ± 7.2</td>
<td>54.9 ± 6.3</td>
<td>34.0 ± 5.4</td>
<td>0.04</td>
</tr>
<tr>
<td>AC emptying t_{1/2}, h</td>
<td>18.8 ± 2.3</td>
<td>13.1 ± 1.3</td>
<td>15.8 ± 1.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Stool frequency, no. per day</td>
<td>1.13 ± 0.49</td>
<td>1.11 ± 0.46</td>
<td>1.21 ± 0.50</td>
<td>0.80</td>
</tr>
<tr>
<td>Stool consistency (BSFS 1–7)</td>
<td>3.63 ± 0.99</td>
<td>3.94 ± 0.79</td>
<td>3.61 ± 0.83</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Values are means ± SE. BSFS, Bristol Stool Form Scale. P value for overall treatment effects, analysis of covariance.
colonic GC at 48 h of the placebo group was 3.43 (±0.25), compared with 3.75 (±0.23) and 3.77 (±0.25) of the TU-100 7.5 and 15 g/day group, respectively (P = 0.64). Although there was a numerical difference in colonic transit on both doses of TU-100, these values were not significantly different from placebo treatment (Table 3).

Effect of TU-100 on bowel function. The mean stool number per day on placebo was 1.13 (±0.49), compared with 1.11 (±0.46) and 1.21 (±0.50) on TU-100 7.5 and 15 g/day, respectively. The mean stool consistency according to Bristol Stool Scale on placebo was 3.63 (±0.99), compared with 3.94 (±0.79) and 3.61 (±0.83) on TU-100 7.5 and 15 g/day, respectively. There were no significant overall treatment effects on stool frequency or consistency.

Adverse events. The proportion of participants developing headache was 42.8% of the placebo group, 36.8% of the 7.5 g/day of TU-100 group, and 40.0% of the 15 g/day of TU-100 group; no treatment differences were detected. In each group, the headache was mild and transient. Although very few adverse events were detected apart from headache, no treatment differences were detected for any of the adverse effects.

One participant who received 7.5 g/day of TU-100 in this study was noted to have an elevated serum creatine phosphokinase level and aspartate aminotransferase and alanine aminotransferase during follow-up approximately 1 mo after receiving the study medication. The patient presented to an emergency department complaining of muscle pain. The patient underwent extensive investigation including serological tests, electromyography, nerve conduction studies, and muscle biopsy. These showed antinuclear antibody 1:80 speckled pattern, normal nerve conduction studies, and mildly small motor unit potentials in a few extremity muscles with no fibrillation potentials or iterative discharges, and simple motor unit morphology compatible with a mild myopathy. However, skeletal muscle biopsy showed evidence of minimal inflammatory reaction with no evidence of myopathy, and detailed studies did not reveal any evidence for metabolic myopathy. At follow-up, 4 mo following ingestion of the study medication, all the biochemical abnormalities were normalized.

DISCUSSION

In this double-blind, randomized, placebo-controlled study, the herbal medication TU-100 accelerated colonic filling at 6 h and AC emptying t1/2, suggesting a promotility effect on small bowel and ascending colon transit in healthy subjects. These data are consistent with previous animal studies (18, 19, 33, 34), which have shown that TU-100 increased dog intestinal motility in vivo (21). TU-100 evokes contractions in isolated intestine of rabbit and guinea pig (19, 33, 34).

One of the important results of the present study is that TU-100 (7.5 g/day) significantly accelerated AC emptying compared with placebo. Stivland et al. (37) showed that in patients with severe constipation the main transit disorder reflects delayed emptying of the proximal colon; in addition, the stimulation of transit in the proximal colon is retarded in irritable bowel syndrome (IBS) patients with constipation (IBS-C) (14). Therefore, significantly accelerated emptying of the proximal colon may lead to therapeutic benefit in patients with functional constipation or IBS-C in whom there is evidence of colonic transit delay (26). Significant acceleration of
AC emptying reduces the time for fluid absorption in this colonic region that has high absorptive capacity (12). Acceleration of AC emptying may therefore change stool consistency. The present study did not show statistically significant change in stool consistency in healthy subjects; however, the study was not powered to detect such a change in stool consistency. Further studies are needed in patients with constipation to assess the therapeutic potential of TU-100.

The observed acceleration of AC emptying may be in part due to the accelerated small bowel transit with delivery of a large volume of chyme to the ascending colon. It is conceivable that this results from its effects on serotonergic and cholinergic mechanisms that control motor functions. TU-100’s effects on small bowel and ascending colon transit may result from stimulation of small intestinal and colonic secretion of water and electrolytes, which may result from effects on serotonergic and cholinergic mechanisms. However, further studies are necessary to determine whether TU-100 promotes activation of chloride channels or induces chloride secretion through the cystic fibrosis transmembrane regulator (2). The present studies cannot differentiate between a primary effect on motility or secretion, with the latter inducing acceleration of transit. It is currently thought that acceleration of colonic transit with lubiprostone and linaclotide is secondary to secretory effects of those medications (38).

In the present study, there was no statistically significant difference between TU-100 at a dosage of 15 g/day and placebo. We considered the possibility of a type II error because of the relatively small sample size ($n \approx 20$ at doses of 7.5 and 15 g/day) treated with TU-100. However, the observed pooled coefficient of variation for AC emptying $t_{1/2}$ was 48%, which was lower than the 53% used to estimate the required sample for the study. Further studies are needed to explore reasons for the lack of efficacy of AC emptying $t_{1/2}$. Another possible explanation for the lack of a significant overall effect of TU-100 on overall colonic transit is that TU-100 has a dual effect on intestinal motility: a direct effect on smooth muscle and an effect on the neural pathways. In previous experimental studies, these effects resulted in either enhancement of normal function or normalization (reduction) of accelerated transit (35). These effects may have resulted in opposing effects on GI transit at the 15 g/day dose, whereby the dual effects resulted in balancing out of its actions, causing no significant difference in transit between TU-100 at a dosage of 15 g/day and placebo.

In previous studies in humans and animals that resulted in accelerated transit (22, 42), TU-100 was administered directly to the colon. It is conceivable that oral administration of TU-100 at doses of both 7.5 and 15 g/day did not result in sufficient concentrations reaching the colon to affect overall colonic transit. A medication delivery system that releases TU-100 in the colon without dilution during transit through the small intestine may be more effective in accelerating overall or distal colonic transit.

There was no significant treatment effect by TU-100 (taken immediately before meals) on gastric emptying of a solid meal, which is consistent with several previous studies (23, 24). The prokinetic effects of TU-100 in an animal study were attenuated during the postprandial state and enhanced during the fasted state (23).

We did not evaluate the plasma levels of neuropeptides in this study. A previous human study showed that the GI motor activity of TU-100 was closely related to changes in plasma motilin levels (29). On the other hand, it was shown that when TU-100 was administered via a long tube, there were no contractions stimulated in the parts of the GI tract proximal to where TU-100 directly contacted the GI mucosa (23). Moreover, TU-100-induced contractions were inhibited by intragastric pretreatment with lidocaine, suggesting a local pharmacological effect mediated at least in part by neural mechanisms (18), rather than depending on systemic absorption and redistribution to the digestive tract humorally.

We focused on bowel function and transit using noninvasive measurements because we have previously shown that these end points are responsive during short-term treatment with prokinetics such as velusetrag (TD-5108) (27). The magnitude of change in AC emptying and colonic filling at 6 h is in the range previously observed by the same methods with the prokinetics, tegaserod (32), prucalopride (3), renzapride (6), neurotrophin-3 (10), and velusetrag (27). Future studies with the same treatment duration and clinical end points, including pain and global IBS symptom relief, should address the clinical efficacy of TU-100 in IBS-C and chronic constipation.

In summary, our study demonstrated that TU-100 has a clinically significant promotility effect in small bowel and ascending colon transit in healthy subjects. TU-100 appears to be safe and well tolerated and is a potential treatment for IBS-C and functional constipation. Additional studies of TU-100 in randomized, controlled trials of subjects with IBS-C or functional constipation using both clinical and validated biomarkers such as small bowel and colonic transit measured by scintigraphy are warranted.

ACKNOWLEDGMENTS

We thank Cindy Stanislav for secretarial support.

DISCLOSURES

The authors have no conflicts of interest. The study was funded by a research grant from Tsumura.

REFERENCES


