Efficacy and tolerability of oral budesonide in Japanese patients with active Crohn's disease: A multicentre, double-blind, randomized, parallel-group Phase II study

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Received 9 December 2011; received in revised form 8 June 2012; accepted 8 June 2012

Abstract

Background and aims: Current treatments for Japanese patients with active Crohn's disease have not proved optimal, and new treatment options are required. The present study therefore evaluated the efficacy and tolerability of oral budesonide in Japanese patients with mild-to-moderate active Crohn's disease.

Methods: In this multicentre, double-blind, randomized, parallel-group, Phase II study, patients (18–65 years) with baseline Crohn's Disease Activity Index (CDAI) score ≥ 200 were randomized to once-daily (od) oral budesonide 9 mg or 15 mg, or matching placebo, for 8 weeks. Concomitant therapy with sulfasalazine or 5-aminosalicylic acid, and nutritional therapy, was allowed. The rate of remission (defined as CDAI score ≤ 150) after 8 weeks' treatment (primary variable), health-related quality of life (assessed using the Inflammatory Bowel Disease Questionnaire [IBDQ]), and tolerability were assessed.

Results: 77 patients were randomized and 63 completed the study. The proportion of budesonide-treated patients with remission after 8 weeks' treatment was higher compared with placebo (23.1%, 28.0%, and 11.5% for budesonide 9 mg, 15 mg, and placebo, respectively; no significant difference). The mean change from baseline to week 8 in CDAI total score (−48.0, −58.2, and

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doi:10.1016/j.crohns.2012.06.006
1. Introduction

Crohn’s disease is a chronic inflammatory disease of the gastrointestinal tract characterized by periods of remission and relapse; however, its underlying pathology is unknown. Its clinical presentation can include diarrhea, abdominal pain, fever, bowel obstruction, and passage of blood and/or mucus. In Japan, guidelines indicate that a definite diagnosis of Crohn’s disease depends on the presence of: an intestinal longitudinal ulcer or deformity induced by a longitudinal ulcer or cobblestone pattern; intestinal small aphthous ulcerations arranged in a longitudinal pattern for ≥3 months, plus non-caseating granulomas; or multiple small aphthous ulcerations in the upper and lower digestive tract for ≥3 months, plus non-caseating granulomas. Ulcerative colitis, ischaemic enterocolitis, and acute infectious enterocolitis must also be excluded.

Crohn’s disease is currently less prevalent in Japan than in Western countries; however, while its prevalence appears to be stabilizing in Western countries it is rapidly increasing in Japan. For example, the age-standardized prevalence of Crohn’s disease in Japan has increased from 16.3 per 100,000 persons in 2003 to 21.2 per 100,000 persons in 2005. Crohn’s disease mainly affects younger people in Japan, with a sharp increase reported for patients in their early 30s and a higher incidence in men than women. While the life expectancy of Japanese patients with Crohn’s disease is slightly reduced compared with age- and sex-matched controls, relative survival rates are similar to those seen in Western countries.

Nutritional therapy (enteral nutrition with complete bowel rest) is regarded as the basis of first-line (acute) treatment for Crohn’s disease in Japan, with pharmacotherapy recommended as second-line therapy. To date, however, current treatments have not proved optimal in Japanese patients with mild-to-moderate active Crohn’s disease, and new treatment options are required. One possibility is oral budesonide, a glucocorticosteroid characterized by a high topical anti-inflammatory effect on intestinal tissue that has been widely studied in the acute treatment of Western patients with active mild-to-moderate active Crohn’s disease, and new treatment treatments have not proved optimal in Japanese patients with mild-to-moderate active Crohn’s disease, and new treatment experience with oral budesonide outside of Western countries, ileocolonic Crohn’s disease. However, there is limited clinical experience with oral budesonide outside of Western countries, including Japan.

The aim of the present placebo-controlled study, therefore, was to evaluate the efficacy and tolerability of oral budesonide in Japanese patients with mild-to-moderate active Crohn’s disease affecting the ileum, ileocecal region, and/or ascending colon.
2.2. Assessments

During screening and treatment periods, patients were required to keep a daily diary card to record: the number of liquid or very soft stools; intensity of abdominal pain (none, mild, moderate, or severe); general well-being (generally well, slightly under par, poor, very poor, or terrible); body temperature (if a patient felt feverish); and intake of loperamide or other opiates for diarrhea. Intake of study medication during the treatment period was also recorded. The CDAI score was subsequently calculated as previously described.\(^\text{16}\)

Health-related quality of life (HRQL) was assessed at baseline and after 2, 4, 8, and 10 weeks' treatment using the validated Japanese version of the Inflammatory Bowel Disease Questionnaire (IBDQ).\(^\text{17}\) The IBDQ consists of 32 items separated into four subscales (systemic symptoms; bowel symptoms; emotional function; and social function) with each item scored on a 7-point Likert scale based on a 2-week recall. Higher scores reflect better HRQL.

Morning plasma cortisol levels at baseline and after 2, 4, 8, and 10 weeks' treatment, and plasma cortisol levels following adrenocorticotropic hormone (ACTH) tests at baseline and after 8 weeks' treatment, were also assessed. For the ACTH test, which was performed prior to dosing, blood samples were drawn before intramuscular injection of Cortrosyn® (250 μg) and at 30 and 60 min afterwards; plasma cortisol levels were subsequently compared between the three samples.

All adverse events (AEs) were recorded. Measurements of clinical laboratory variables (including hematology, clinical chemistry, and urinalysis), vital signs (pulse, blood pressure, and body temperature), and electrocardiography (ECG) were also undertaken during the study.

2.3. Statistical analysis

Analysis of efficacy was completed for the full analysis set (all randomized patients who took at least one dose of study medication and had evaluable data). The primary variable was the rate of remission (defined as CDAI score ≤ 150) following 8 weeks' treatment; differences with placebo were evaluated using Fisher's exact test.

Secondary variables included the rate of remission after 2 and 4 weeks' treatment, change in CDAI score, and time to first remission (defined as the number of days from randomization to first remission). The Newcombe–Wilson score method without continuity correction\(^\text{18}\) using two-sided 90% confidence intervals (CIs) was used to assess remission rates for each treatment group. A linear mixed-effect model was used to calculate least square means and 90% CIs for the change in CDAI scores after 8 weeks' treatment. The model included the CDAI score at randomization as a covariate, along with fixed effects for time, treatment group, and the interaction between time and treatment group, and random effect for patient. Time to first remission was analyzed by the Kaplan–Meier method, with cumulative remission rates and 90% CIs after 2, 4, and 8 weeks' treatment.

The rate of clinical improvement (defined as remission [CDAI score ≤ 150] or a decrease in CDAI score of ≥ 100 from baseline) and CDAI total scores were reported using descriptive statistics, along with change in IBDQ scores and tolerability findings/safety evaluations.

The assumed remission rate after 8 weeks' treatment was 52.5% for budesonide 9 mg and 20% for placebo (estimated from the results of five Western studies\(^\text{9–11,19,20}\)), based on the assumption that the efficacy and safety of budesonide were not significantly different between Japanese and Western
patients. In order to detect a significant between-group difference (two-sided 10% significance level) with 75% power, approximately 75 patients were to be randomized to ensure at least 23 evaluable patients for each treatment group.

3. Results

In total, 90 patients were screened for enrolment and 77 were randomized to treatment. Mean (± standard deviation) disease duration was 4.9 (±5.3) years, 40.3% of patients had colonic involvement, and 94.8% used concomitant therapy (most commonly nutritional therapy in combination with 5-ASA). There were no patients using sulfasalazine. Treatment groups were well balanced in terms of baseline characteristics (Table 1). Fourteen patients withdrew prematurely leaving 20, 21, and 22 of budesonide 9 mg, 15 mg, and placebo recipients to complete the study, respectively (Fig. 2).

The mean (standard deviation) duration of study treatment was similar between treatment groups: budesonide 9 mg, 63.1 (±15.2) days; budesonide 15 mg, 63.5 (±16.7) days; and placebo, 65.3 (±12.6) days. All patients had acceptable compliance (≥75% of medication taken).

### Table 1

<table>
<thead>
<tr>
<th>Disease Location</th>
<th>Budesonide 9 mg od (n=26)</th>
<th>Budesonide 15 mg od (n=25)</th>
<th>Placebo (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n (%)</td>
<td>9 (34.6)</td>
<td>7 (28.0)</td>
<td>6 (23.1)</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>37.7 (18–63)</td>
<td>35.4 (18–56)</td>
<td>36.4 (18–57)</td>
</tr>
<tr>
<td>Disease duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 years, n (%)</td>
<td>22 (80.8)</td>
<td>22 (88.0)</td>
<td>20 (76.9)</td>
</tr>
<tr>
<td>≥10 years, n (%)</td>
<td>5 (19.2)</td>
<td>3 (12.0)</td>
<td>6 (23.1)</td>
</tr>
<tr>
<td>Disease location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileum only, n (%)</td>
<td>17 (65.4)</td>
<td>15 (60.0)</td>
<td>14 (53.8)</td>
</tr>
<tr>
<td>Colonic involvement</td>
<td>9 (34.6)</td>
<td>10 (40.0)</td>
<td>12 (46.2)</td>
</tr>
<tr>
<td>Disease severity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDAI&lt;300</td>
<td>18 (69.2)</td>
<td>21 (84.0)</td>
<td>20 (76.9)</td>
</tr>
<tr>
<td>CDAI≥300</td>
<td>8 (30.8)</td>
<td>4 (16.0)</td>
<td>6 (23.1)</td>
</tr>
<tr>
<td>Concomitant therapy, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutritional therapy</td>
<td>1 (3.8)</td>
<td>1 (4.0)</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>5-ASA therapy</td>
<td>2 (7.7)</td>
<td>9 (36.0)</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td>Nutritional therapy and 5-ASA</td>
<td>22 (84.6)</td>
<td>15 (60.0)</td>
<td>17 (65.4)</td>
</tr>
</tbody>
</table>

ASA, 5-aminosalicylic acid; CDAI, Crohn’s Disease Activity Index; od, once daily.

3.1. Efficacy

At week 8, the proportion of patients in remission was higher with budesonide treatment compared with placebo (Fig. 3); however, the absolute differences in remission rates were not statistically significant between budesonide 9 mg and placebo (11.5%; 90% CI: −6.1, 28.7), or between budesonide 15 mg and placebo (16.5%; 90% CI: −2.1, 34.2). Overall, patients with colonic involvement had numerically higher remission rates at week 8 than patients with ileal Crohn’s disease; 33.3% versus 17.6% and 50.0% versus 13.3% for budesonide 9 mg and 15 mg, respectively.

Compared with baseline, the mean change in CDAI total score after 8 weeks’ treatment was greater for budesonide-treated patients versus placebo recipients (Fig. 4). The difference in mean change from baseline to week 8 was similar between the budesonide treatment groups (−9.0; 90% CI: −7.0, 29.1). Decreases in CDAI items liquid or soft stools, abdominal pain, and general well-being (−15.5, −15.0, and −25.5 for budesonide 9 mg and −9.4, −17.5, and −34.4 for budesonide 15 mg, respectively) were major contributors to the decrease in CDAI total scores.

It was not possible to calculate the median time to first remission as <50% of patients achieved this outcome. The cumulative rate of remission at week 8 was 38.5% for budesonide 9 mg, 36.0% for budesonide 15 mg, and 19.2% for placebo; at all time points a higher proportion of patients were in remission for budesonide treatment groups than placebo (Fig. 5).

Clinical improvement rates at week 8 were higher for patients treated with budesonide than placebo recipients; 23.1%, 36.0%, and 15.4% for budesonide 9 mg, 15 mg, and placebo, respectively. This proportion was 23.1%, 24.0%, and 19.2% at week 4 and 7.7%, 24.0%, and 0% at week 2, respectively.

3.2. Health-related quality of life

Mean (± standard deviation) IBDQ total score improved from baseline to week 8 for all treatment groups, most notably among budesonide recipients (10.8±33.6, 23.2±24.6, and 6.5±29.4 points for budesonide 9 mg, budesonide 15 mg, and placebo, respectively). When separated into IBDQ subscales, bowel symptom scores showed the largest mean improvement at week 8 (5.1±10.8, 8.0±8.3, and 1.5±9.2 points, respectively).

3.3. Tolerability

All 77 randomized patients were included in the safety analysis set. In total, 43 patients experienced at least one AE, which were typically of mild-to-moderate intensity: budesonide 9 mg, n=19; budesonide 15 mg, n=14; and placebo, n=10. The most commonly reported AEs in budesonide recipients were deterioration of Crohn’s disease (n=5; 9.8%), anemia (n=5; 9.8%), nasopharyngitis (n=5; 9.8%), acne (n=4; 7.8%), rash (n=3; 5.9%), and pharyngolaryngeal pain (n=3; 5.9%). There were no apparent dose-related trends among budesonide-treated patients.
Drug-related AEs were reported for 16 patients (budesonide 9 mg, n=5; budesonide 15 mg, n=8; and placebo, n=3), and typically comprised skin and subcutaneous tissue disorders and laboratory abnormalities (Table 2). Glucocorticosteroid-related AEs were infrequent among budesonide recipients (9 mg: acne [n=1; 3.8%]; 15 mg: acne [n=2; 8.0%], acne aggravated [n=1; 2.0%], and moon face [n=1; 2.0%]), and no patients discontinued due to such events. There were no glucocorticosteroid-related AEs among placebo recipients. Four patients experienced a serious AE (SAE) during the study, including ileus and deterioration of Crohn’s disease in the budesonide 9 mg group (1 patient each), and perianal abscess and deterioration of Crohn’s disease in the placebo group (1 patient each). With the exception of perianal abscess, SAEs were not considered to be drug-related.

AEs leading to withdrawal from the study occurred in 6 (23.1%), 2 (8.0%), and 2 (7.7%) patients receiving budesonide 9 mg, 15 mg, and placebo, respectively. Of these, only one AE (perianal abscess, placebo group) was considered to be drug-related. There were no deaths during the study.

Over the 8-week treatment period, mean morning plasma cortisol levels decreased for both budesonide 9 mg and 15 mg, with lower mean morning plasma cortisol levels for budesonide 15 mg than 9 mg, but remained relatively constant for placebo (Fig. 6). Thereafter, cortisol levels generally returned to baseline during the 2-week tapering period, but remained below baseline for those who received budesonide 15 mg during the 8-week treatment period. There were no clinically relevant differences between budesonide treatment groups and placebo with regard to ACTH test findings following 8 weeks’ treatment, stratified according to whether the test was normal or abnormal at baseline (Table 3).

No clinically important trends were noted in clinical laboratory tests, vital signs, and ECG observations during the study.
4. Discussion

Western clinical studies have shown oral budesonide to be effective and well tolerated in the treatment of acute Crohn’s disease; however, there is limited clinical experience of oral budesonide in Japan. In this study, patients treated with oral budesonide showed a greater (numerically, but not statistically) improvement for all efficacy variables compared with placebo, including higher remission rates and faster time to remission, which were paralleled by HRQL improvements. While budesonide 9 mg and 15 mg were similar in terms of efficacy, budesonide 9 mg was better tolerated. These results suggest that budesonide 9 mg od (for up to 8 weeks) may therefore offer a useful treatment option for Japanese patients with mild-to-moderate active Crohn’s disease, consistent with dosing recommendations in Western countries.

In the treatment of Crohn’s disease, other pharmacotherapy options evaluated in Japan include infliximab and antibiotics (clarithromycin and metronidazole plus ciprofloxacin). A single intravenous infusion of infliximab proved effective in the treatment of patients with moderate-to-severe Crohn’s disease who were resistant to first-line treatment, while a retrospective analysis demonstrated a significantly higher efficacy for infliximab treatment within 12 months of diagnosis compared with a diagnosis of >12 months. Results were encouraging in the assessment of antibiotics as add-on therapy, though larger studies are warranted. The present study therefore adds to knowledge of pharmacotherapy for the treatment of acute Crohn’s disease in Japan, in that it provides (to our knowledge) the first report of the use of oral budesonide in such patients.

The remission rate seen in this study was lower than that reported in other studies of 8 weeks’ oral budesonide treatment in Western populations, including a comparative study versus mesalamine. In the current trial, the remission rate was 23%, 28%, and 11.5% for budesonide 9 mg, 15 mg, and placebo, respectively. In comparison, other placebo-controlled trials in Western patients report remission rates of 48%, 53%, and 33% with budesonide 9 mg od, 4.5 mg twice daily, and placebo, respectively (differences between the groups were not significant); and 51%, 43%, 33%, and 20% with budesonide 9 mg od, 15 mg od, 3 mg od, and placebo, respectively (P<0.01 for budesonide 9 mg and 15 mg versus placebo). In the comparative study mentioned above, patients treated with budesonide 9 mg/day achieved clinical remission in 69.5% of cases (versus 62% with mesalamine). However, while the primary end point and major inclusion/exclusion criteria were similar to the current study, the use of concomitant therapy was prohibited in the placebo-controlled Western studies. As most of the patients in the present study were also using concomitant therapy (which could not be considered when the sample size calculation was made), this may have contributed to the relatively low response rate across treatment groups and the
non-statistically significant difference in efficacy between budesonide and placebo. However, in order to enroll patients into a placebo-controlled study in Japan, the design had to reflect current clinical practice and therefore allowed for the use of sulfasalazine, 5-ASA, or nutritional therapy. It is likely that if this study had been conducted with the same design as the Western placebo-controlled studies, similar results would have been obtained. It should also be emphasized that the current study included patients with mild-to-moderate active Crohn’s disease who continued to have symptoms despite receiving primary therapy. Hence the higher remission rate with budesonide, when compared with placebo, is noteworthy for this largely refractory population, enrolment of whom might account for the comparatively low remission rates versus Western studies.

A decrease in CDAI score of ≥70 from baseline has been used as the primary efficacy end point in other studies that have assessed treatment of active Crohn’s disease. A post-hoc analysis showed that the proportion of patients who achieved this criteria at week 8 was higher with budesonide treatment compared with placebo (48.0%, 23.1% and 19.2% for budesonide 15 mg, 9 mg, and placebo, respectively); differences were statistically significant between budesonide 15 mg, 9 mg, and placebo, respectively; but not between budesonide 9 mg and placebo (3.8%; 90% CI: −14.8, 22.2). This post-hoc analysis further supports the effectiveness of budesonide in the treatment of Japanese patients with mild-to-moderate Crohn’s disease.

Higher rates of remission with budesonide were paralleled by greater improvements in HRQL compared with placebo, as determined by the Japanese version of the IBDQ. The mean improvement from baseline in total score was 23.2 points; corresponding values for budesonide 9 mg and placebo were 10.8 and 6.5 points, respectively. Notably, the improvement in HRQL with budesonide was particularly apparent in bowel function subscale, in accordance with higher rates of remission. These findings are generally in accordance with other studies reporting numerically or statistically significant improvements in HRQL for oral budesonide compared with placebo, conventional glucocorticosteroids, or mesalamine. Taken together, these findings indicate a HRQL benefit of budesonide therapy in patients with acute Crohn’s disease, and additional studies are warranted in the Japanese patient population to clarify the incremental benefit.

The development of drug-related AEs is a major consideration in the treatment of Crohn’s disease. With glucocorticosteroids, particular concerns include (but are not limited to) the development of cushingoid features (moon face, buffalo hump), osteoporosis, acne, and thinning of the skin. In general, oral budesonide is associated with fewer glucocorticosteroid-related AEs than other agents of this class. This is most likely explained by rapid absorption of budesonide within the gut mucosa (where it has a high intrinsic activity) and rapid first-pass metabolism via the cytochrome P450 3A4 pathway. Its metabolites have minimal (<1%) activity compared with that of the parent compound and are excreted via the kidneys. This pharmacokinetic profile is likely to explain the favorable tolerability of oral budesonide in the present Japanese population of patients with acute Crohn’s disease, for whom relatively few drug- and glucocorticosteroid-related events were reported. Moreover, comparison of the two active treatment groups showed that budesonide 9 mg appeared to have a more favorable tolerability profile than the 15 mg dose. The low frequency of glucocorticosteroid-related events with budesonide was paralleled by no clinically relevant effect on adrenal suppression in ACTH tests. Among 20 patients randomized to budesonide (9 or 15 mg) who had ‘normal’ test findings at baseline, for example, 60% (12 out of 20) had ‘normal’ results at Week 8; similar findings were apparent for those randomized to placebo (62.5%). In addition, there was no dose-related trend in the budesonide groups. Such findings, while suggestive of no clinically relevant effect on adrenal suppression, should be interpreted with caution in view of small patient numbers.

Limitations of the study include the lack of a statistically significant difference between budesonide and placebo for efficacy end points, which may be explained by the fact that the sample size was based on the results from Western studies. In fact, the actual remission rates after 8 weeks in

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Table 3  Plasma cortisol levels following adrenocorticotropic hormone tests after 8 weeks’ treatment, stratified according to whether the test was normal or abnormal at baseline (safety analysis set).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Test result at baseline</th>
<th>Test result at week 8, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Budesonide 9 mg od</td>
<td>10</td>
<td>2 (20.0) 8 (80.0)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>4 (66.7) 2 (33.3)</td>
</tr>
<tr>
<td>Budesonide 15 mg od</td>
<td>10 100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>3 (37.5) 5 (62.5)</td>
</tr>
<tr>
<td>Placebo</td>
<td>8</td>
<td>5 (62.5) 3 (37.5)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2 (40.0) 3 (60.0)</td>
</tr>
<tr>
<td>od, once daily.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
the current study were approximately 50% lower than expected in both budesonide and placebo groups. Consequently, the study was underpowered. One possible explanation as to why the remission rates were lower in Western studies could be the relatively short duration of the study (i.e. 12 weeks may have been preferable) and/or the patient population, as highlighted above. Indeed, the present study included a high proportion of patients who were receiving concomitant treatment with 5-ASA and/or nutritional therapy, and many of these patients were symptomatic (i.e. refractory) in spite of usual first-line treatment. Previous use of glucocorticosteroids may have also contributed to the study findings (in terms of lower remission rates), although information on the prior use of such therapies was not collected during the baseline assessment. The study also included a large proportion of patients with ileal involvement, stratified analysis showing that such patients achieved lower remission rates than those with colonic disease (i.e. disease in the ileum was relatively difficult to treat). However, the proportion of patients with ileal involvement was largely comparable to that observed in Western studies, and does not therefore explain the observed lower remission rates in the present study.

In conclusion, Western clinical studies have shown oral budesonide to be effective and well tolerated in the acute treatment of patients with Crohn's disease, hence there is a strong desire to introduce budesonide into Japanese medical practice. We show here that, in Japanese patients with mild-to-moderate active Crohn's disease, budesonide was numerically (but not statistically) superior to placebo for induction of remission, improved HRQL, and was well tolerated. The lack of significance was most likely secondary to the requirements of the study design, which took into account the unique circumstances regarding treatment of Japanese patients with Crohn's disease. However, in view of the observed remission rate (more than double compared with placebo), the possibility remains that budesonide may offer a new treatment option for such patients and a dose of 9 mg od may be most suitable based on its favorable tolerability profile. Further investigation is required to confirm the efficacy of budesonide in this setting.

Conflict of interest statement

- Yasuo SUZUKI: no conflicts to declare.
- Satoshi MOTOYA: lecture fees (Abbott Japan and Tanabe Mitsubishi); research funding (Abbott Japan, Ajinomoto Pharma and Janssen Pharmaceutical KK).
- Masakazu TAKAZOE: no conflicts to declare.
- Tadashi KOSAKA: no conflicts to declare.
- Masataka DATE and Masahiro NII: employees, AstraZeneca KK.

Acknowledgments

The authors wish to acknowledge the patients and their family members, medical practitioners, and hospital staff who were involved in this study. This study was supported by AstraZeneca (Osaka, Japan), the manufacturer of Entocort® (budesonide). The authors thank Melanie Gatt and Steve Winter from inScience Communications, Springer Healthcare who provided medical writing support funded by AstraZeneca.

Appendix A

The following centers participated in this study: Hokkaido P.W.F.T.A.C Sapporo-kosei General Hospital; Keio University Hospital; Social Insurance Central General Hospital; Tokorozawa Proctologic Hospital; Toho University Sakura Medical Center; Kannai-Suzuki Clinic; Yokoyama Hospital for Gastroenterological Disease; Matsunami General Hospital; Daiwa Hospital; Tachibana Medical Corporation, Higashiumiyoshiyomito Hospital; Kinki Central Hospital of the Mutual Aid Association of Public School Teachers; Kyoto University Hospital; Toyama University Hospital; The Hospital of Hyogo College of Medicine; Hiroshima Prefectural Hospital; Hiroshima University Hospital; National Hospital Organization Fukuyama Medical Center; Kawasaki Medical University Hospital; Fukukusa University Chikushi Hospital; Kurume University Hospital; Kurume Coloproctology Center.

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