A Comparison of the Efficacy and Safety of Balsalazide (Basazyde®) and Mesalamine (Asacol®) for the Treatment of Acute Exacerbation of Ulcerative Colitis

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Key Words
Balsalazide (Basazyde®);
Mesalamine (Asacol®);
Ulcerative colitis

Purpose. This is a randomized, multi-center, double-dummy, and active-controlled study to evaluate the efficacy and safety of balsalazide as compared to mesalamine for a treatment period of eight weeks in patients with acute exacerbation of ulcerative colitis.

Methods. Subjects with acute exacerbation of ulcerative colitis and had symptomatic grade 2–4 ulcerative colitis after being checked by sigmoidoscopic examination were recruited for the study. Subjects were randomized to received balsalazide (750 mg/cap, 3# tid) and mesalamine (400 mg/tab, 2# tid). Fifty-two subjects were enrolled into the study, forty of them completed eight weeks treatment. Efficacy and safety were evaluated after eight weeks treatment.

Results. Complete remission occurred in 8 of 17 (47.1%) patients in the balsalazide group and 10 of 23 (43.5%) patients in the mesalamine group. Sigmoidoscopic improvement is more significant in the balsalazide group (82.35%) than mesalamine group (47.83%). Adverse event was experienced in 17 of 24 patients (70.8%) in the balsalazide group and 18 of 28 patients (64.3%) in the mesalamine group. There were no clinically significant changes in routine laboratory assessments and vital signs in either treatment groups.

Conclusion. This study confirmed that 8 weeks of treatment with 6.75g daily of balsalazide is safe, well tolerated, and effective for acute ulcerative colitis. Balsalazide is therefore proven to be an effective treatment in the management of ulcerative colitis.

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active ulcerative colitis.\textsuperscript{5-9} For balsalazide to be preferred as an alternative first line in the treatment of acute symptomatic UC, the efficacy, patient tolerability and safety must be demonstrated. Therefore, this study was aimed to compare the efficacy and safety of balsalazide (Basazyde\textsuperscript{\textregistered}) and mesalamine (Asacol\textsuperscript{\textregistered}) in patients with ulcerative colitis. The study was approved by the Institution Review Board, all 7 hospitals participating in the study, and the Department of Health Bureau.

\textbf{Patients and Methods}

This is a randomized, multi-center, double-blind, double-dummy, and active-controlled study to evaluate the efficacy and safety of balsalazide as compared to mesalamine for a treatment period of eight weeks in patients with acute exacerbation of ulcerative colitis. Seven hospitals participated in the study. Written informed consent was obtained from each patient before registration for the study. Patients eligible for this study were those over 18 years old who had symptomatic grade 2-4 ulcerative colitis. The segment of involvement was at least more than 5cm from the anal verge after being checked by sigmoidoscopic examination. Patients were not eligible for the study if they were: pregnant, possibly pregnant, or a nursing mother. Also ineligible were those who had received either: steroids in the past 30 days, an immuno-suppressive agent within the past 3 months, or any mesalamine-releasing compound in the past 5 days. Finally, any patient with Crohn’s disease or specific colitis was excluded. After written, informed consent was obtained and all screening criteria were met, patients were randomized to the study medication in accordance with the randomization schedule.

After randomization, patients were administrated either 3\textsuperscript{\textregistered} of balsalazide (750mg) plus 2\textsuperscript{\textregistered} of mesalamine matching placebo or 2\textsuperscript{\textregistered} of mesalamine (400mg) plus 3\textsuperscript{\textregistered} of balsalazide matching placebo three times daily. The total daily dose was 6.75 g and 2.4 g for balsalazide (Basazyde\textsuperscript{\textregistered}) and mesalamine (Asacol\textsuperscript{\textregistered}) group, respectively. These supply capsules were taken after breakfast, noon, and dinner at about the same time every day. There was no dose change allowed in the study.

All non-steroidal medications required by the patient to manage acute or chronic illness unrelated to ulcerative colitis were permitted. Antibiotics, oral and rectal aminosalicylate, steroid, laxative, anti-diarrheal agent, 6-mercaptopurine and azathioprine etc were not allowed. The immunosuppressive agents and other investigational drugs were also not allowed during the study period. Clinical evaluations included sigmoidoscopic examination, global evaluation, arterial blood pressure (SBP and DBP), and pulse rate. The patient also performed assessments of ulcerative coli-

\begin{table}[!h]
\centering
\begin{tabular}{|l|c|c|c|c|}
\hline
\textbf{Characteristic} & \textbf{All group (N=52)} & \textbf{Basazyde\textsuperscript{\textregistered} (N=24)} & \textbf{Asacol\textsuperscript{\textregistered} (N=28)} & \textbf{p value} \\
\hline
\textbf{Sex} & & & & 0.832 \\
\textbf{Male} & 33 & 15 & 18 & \\
\textbf{Female} & 19 & 9 & 10 & \\
\hline
\textbf{Age (years)} & 43.6 \pm 11.68 & 45.5 \pm 11.15 & 42.0 \pm 12.09 & 0.314 \\
\textbf{BMI (kg/m\textsuperscript{2})} & 22.2 \pm 2.78 & 21.7 \pm 2.23 & 22.7 \pm 3.16 & 0.213 \\
\hline
\textbf{Duration of current episode of symptoms (weeks)} & 14.8 \pm 34.41 & 21.2 \pm 47.15 & 9.2 \pm 16.55 & 0.192 \\
\textbf{Duration of UC symptoms (months)} & 38.4 \pm 49.36 & 42.3 \pm 49.29 & 35.0 \pm 50.08 & 0.719 \\
\hline
\textbf{Result of stool examination} & & & & 0.237 \\
\textbf{Normal} & 48 & 22 & 26 & \\
\textbf{Abnormal} & 2 & 0 & 2 & \\
\textbf{Unknown} & 2 & 2 & 0 & \\
\hline
\textbf{Sigmoidoscopic Examination} & & & & 0.505 \\
\textbf{Grade 2} & 26 & 11 & 15 & \\
\textbf{Grade 3} & 15 & 9 & 6 & \\
\textbf{Grade 4} & 11 & 4 & 7 & \\
\hline
\end{tabular}
\caption{Patient Characteristics at Entry}
\end{table}
tis symptoms daily through the trial period.

At the entry and end of the study, patients underwent sigmoidoscopic examination to classify the extent of disease and to grade the macroscopic appearance of the rectal mucosa. The level of ulcerative colitis was assessed using a 5-point nominal scale (Table 2).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Sigmoidoscopic appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal, vascular pattern clearly visible</td>
</tr>
<tr>
<td>1</td>
<td>Erythema with loss of vascular pattern</td>
</tr>
<tr>
<td>2</td>
<td>Erythema with loss of vascular pattern plus contact bleeding</td>
</tr>
<tr>
<td>3</td>
<td>Erythema with loss of vascular pattern plus spontaneous bleeding</td>
</tr>
<tr>
<td>4</td>
<td>Erythema with loss of vascular pattern plus frank ulceration</td>
</tr>
</tbody>
</table>

The subject’s overall symptoms were assessed periodically at the baseline, 2nd, 4th, 6th and 8th week (study end). The satisfaction with study medication was assessed by physician and subject respectively using the following definitions: 2 meaning much improved, 1 meaning improved, 0 meaning no change, and -1 meaning worse. After 8 weeks of treatment, the physician evaluated the global effectiveness of the treatment.

Patients recorded ulcerative colitis symptoms and other medical problems on their daily diary card. The following variables were recorded: number of visits to the lavatory to pass stool; blood/mucus in stool; fever (> 37.5°C); abdominal pain; need to go to the lavatory and other symptoms interfering with sleep and normal daily activities.

The severity of patients’ ulcerative colitis symptoms was to be graded on the daily card using the following definitions:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel movement</td>
<td>&lt; 4 per day</td>
<td>4-6 per day</td>
<td>&gt; 6 per day</td>
</tr>
<tr>
<td>Blood in the stool</td>
<td>Small</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Fever</td>
<td>None</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Others</td>
<td>Possibly</td>
<td>Possibly</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Patients were considered completely free of symptoms if the responses to all the above variables were none, absent, normal.

Safety was evaluated on the basis of occurrence of adverse events, and changes in vital signs (blood pressure and pulse rate) and abnormality of laboratory tests (blood examination, biochemistry and urinalysis). The intensity of an adverse event was rated as mild, moderate, or severe, based on the investigator’s clinical judgment. A mild adverse event was transient and easily tolerated by the patients. A moderate adverse event caused patient discomfort and interrupted the patient’s usual activities. A severe adverse event caused considerable interference with the patient’s usual activities, and may have been incapacitating or life threatening.

The patient’s demographics and baseline characteristics such as age, weight, and height were tabulated and compared for treatment difference. For continuous variables, a two-way analysis of variance (ANOVA), with treatment and center as fixed effects, was applied to test the homogeneity between the two treatment groups. For categorical variable, the numbers and percentages of subjects in each class were presented, and the CMH test (general association) adjusting for the effects of center was performed. Comparative incidence of adverse events was evaluated using Fisher’s exact test. Laboratory values that fall outside of pre-determined normal range were tabulated and the shift analysis from baseline to follow up visits was performed using Stuart-Maxwell test. Changes in patients’ blood pressure and pulse were compared within treatment by the test and between treatments by the one-way ANCOVA model (baseline value as covariate).

Results

Fifty-two patients were enrolled in the study which started on 4, January, 2002 and ended on 12, July, 2003. Twenty-four patients were randomized to Basazyde® group while 28 patients were randomized to Asacol® group. Forty patients completed the study. Early therapy termination occurred in 7 patients of the Basazyde® group and 5 patients of the Asacol® group. Reasons observed for discontinuation included consent withdrawal (4 patients), adverse event (4 pa-
tients), violation of inclusion criteria (3 patients) and lost to follow up (1 patient).

Twelve patients were excluded from the intent-to-treat population for efficacy analysis due to absence of post-baseline sigmoidoscopic examination or the evaluation of subject’s overall symptoms. Therefore, 40 patients were included in the intent-to-treat population with 17 patients in the Basazyde® group and 23 patients in the Asacol® group. There were two patients in the Asacol® group who missed the scheduled clinic visit during the treatment period due to the SARS outbreak. However, these two patients completed the 8-week treatment period with final sigmoidoscopic examination. Seventeen patients, 10 in Basazyde® group and 7 in Asacol® group, violated the protocol or had early termination. These patients were excluded from the per-protocol population.

Of the 52 randomized patients, the average age was 43.6 years old with range from 26 to 73 years old. Thirty three patients (63.5%) were male. The mean BMI was 22.2 kg/m². The mean duration of current episode of symptoms was 14.8 weeks with range from 1 week to 4 years. The mean duration of UC symptoms was 38.4 months with range from 1 month to 19 years.

The primary endpoint is the proportion of subjects achieving complete remission at Week 8 (Fig. 1). Complete remission is defined as no or mild symptoms with sigmoidoscopic graded 0 or 1, and without the use of rectal steroid enema during last 4 days prior to final visit. For the primary efficacy population, 8 out of 17 (47.06%) patients in the Basazyde® group had complete remission compared to 10 out of 23 (43.48%) patients in the Asacol® group who had complete remission. No statistically significant difference between the two treatment groups in complete remission rate was found ($p$ value = 0.956).

The proportions of patients with sigmoidoscopic graded 0 or 1 were 47.06% for Basazyde® group and 43.48% for Asacol® group. Furthermore, sigmoidoscopic improvement was defined as at least one category improved on the five-category disease activity scale. The analysis revealed a significant difference in sigmoidoscopic improvement between the Basazyde® group (82.35%) and the Asacol® group (47.83%, $p$ value = 0.0280) (Fig. 2 and Table 3).

No statistically significant difference of the overall evaluation of subject’s symptoms at the clinic visit was found between two groups at any clinic visit (Fig. 3). The greater symptomatic remission rate for patients treated with Basazyde® was observed as early as at the second week visit (95.0%) compared with patients treated with Asacol® (77.8%). However, no statistically significant difference was found at any study visit.

![Fig. 1. Primary endpoint-complete remission rate.](image)

**Fig. 1.** Primary endpoint-complete remission rate.

![Fig. 2. Sigmoidoscopic grade improvement rate.](image)

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![Fig. 3. Secondary endpoint-evaluation of subjects’ overall symptom.](image)

**Fig. 3.** Secondary endpoint-evaluation of subjects’ overall symptom.
Among 52 patients enrolled in this study, 13 patients (54.17%) in the Basazyde® group and 17 patients (60.17%) in the Asacol® group experienced at least one day completely free of symptoms during the entire study period. Furthermore, during the 8-week treatment period, the mean cumulative days completely free of symptoms was 11.6 (SD = 17.53) days in the Basazyde® group and 14.9 (SD = 18.63) days in the Asacol® group.

It demonstrated that patients treated with Basazyde® had better improvement of subject’s global evaluation than Asacol®-treated patients after 2 weeks of therapy. Results demonstrated that patients treated with Basazyde® also had better improvement of physicians’ global evaluation than Asacol®-treated patients after 2 weeks of therapy. The physicians’ global evaluation also showed that patients treated with Basazyde® had a higher improvement rate (94.1%) than patients treated with Asacol® (73.9%), although no statistical significance was observed (Fig. 4).

### Adverse Events

At least one treatment adverse event was experienced by 70.8% of subjects in Basazyde® group compared with 64.3% of subjects in the Asacol® group ($p$ value = 0.769). Most reported adverse events were mild in intensity. The most frequently reported adverse events in patients receiving Basazyde® included diarrhea (5 patients, 20.8%) and abdominal pain (4 patients, 16.7%). In Asacol® group, the most frequently reported adverse events were cough (5 patients, 17.9%) and headache (3 patients, 10.7%). Gastrointestinal disorders including abdominal pain and diarrhea were the most frequently observed adverse events. There were two serious adverse events that occurred during the study period. They suffered from severe diarrhea with 15 bowel movement each day following Basazyde® treatment. Four patients (3 in Basazyde®, 1 in Asacol®) were withdrawn because of adverse events. In the Basazyde® group, one patient had nausea and abdominal pain during the first week of therapy and two patients presented with severe diarrhea. The patient treated with Asacol® suffered from rhinorrhea and alopecia.

### Blood Examination, Biochemistry and Urinalysis

Alanine amino-transf erase level was significantly reduced by 7.59 U/L in the Basazyde® group and increased by 2.72 U/L in Asacol® group. Statistically significant difference between two treatment groups
in the change from baseline was noted at the end of the study (p value = 0.0065). BUN level was slightly increased by 0.79 mg/dl in the Basazyde® group and significantly reduced by 1.44 mg/dl in Asacol® group. There was statistically significant difference found between two treatment groups in the change from baseline to the end of study (p value = 0.0142). However, the changes in BUN during the treatment period were within the normal range and therefore were not considered as clinically significant.

**DISCUSSION**

Ulcerative colitis may occur in people of any age, but most often it starts between ages 15 and 30, or less frequently between ages 50 and 70. The most common symptoms of ulcerative colitis are abdominal pain and bloody diarrhea. Patient may also experience fatigue, weight loss, loss of appetite, rectal bleeding, loss of body fluids and nutrients. Treatment for ulcerative colitis depends on the serious of the disease. In severe cases, a patient may need surgery to remove the diseased colon.

In severe cases, the goal of therapy is to induce and maintain remission, and to improve the quality of life for people with ulcerative colitis.

Asacol® is a delayed-release mesalamine formulation with a pH-dependent acrylic resin coating, and is widely prescribed as the maintenance treatment for UC. Despite the widespread use there is some concern over its nephrotoxic potential. Maintenance studies have reported that about forty percent of patients relapse within 6-12 months of treatment. Thus there still remains the clinical need for a better alternative treatment strategy for these patients.

Balsalazide is a prodrug in which 5-aminosalicylic acid (5-ASA) is linked via a diazo bond to 4-aminobenzoyl-β-alanine (4-ABA), an inert and biologically inactive carrier molecule. After oral administration, balsalazide is split into mesalamine and 4-ABA via azo-reduction by the colonic microflora.10,11

The goal of this trial was to evaluate the efficacy and safety of balsalazide (Basazyde®) and mesalamine (Asacol®) in patients with acute exacerbation of ulcerative colitis. Consequently, 52 patients were enrolled and all subjects were subsequently randomized to the trial for a direct comparison of Basazyde® versus Asacol®. Twenty-four patients were randomized to receive Basazyde® and twenty-eight patients to receive Asacol®. No significant difference between the groups in baseline characteristics and the history of ulcerative colitis was noted.

Eight out of 17 (47.06%) patients in the Basazyde® group compared with 10 out of 23 (43.48%) patients in the Asacol® group experienced complete remission. No significant difference in complete remission rate was found (p value = 0.956). Trial results demonstrated a significant difference in sigmoidoscopic improvement between the Basazyde® group (82.35%) and the Asacol® group (47.83%, p value = 0.0280). A greater symptomatic remission rate for patients treated with Basazyde® was observed as early as at the second week visit (95.0%) compared with patients treated with Asacol® (77.8%), although there was no statistically significant difference. The patients treated with Basazyde® had better improvement of subjects’ global evaluation and physicians’ global evaluation than Asacol®-treated patients after two weeks of therapy (95.0% vs. 62.9%; 95.0% vs. 70.4%). Treatment with Basazyde® provided patients with better relief of symptoms of ulcerative colitis during the treatment period, which was shown by a low proportion of patients with severe bloody stool and markedly increased stool frequency (more than 6 times per day). The proportion of patients with fever between the two treatment groups was found to have no statistical difference.

The overall incidence of adverse events showed that at least one treatment adverse event was experienced by 17 of 24 (70.8%) patients in the Basazyde® group and 18 of 28 (64.3%) patients in the Asacol® group (p value = 0.769). There were no significant changes in routine laboratory assessments and vital signs in either of the treatment groups found.

**Conclusion**

This randomized, multi-center, double-blind, double-dummy, and active-controlled trial demonstrated that 8-week treatment with 6.75 g daily of balsalazide
(Basazyde®) is safe, well tolerated and effective for acute ulcerative colitis. Balsalazide (Basazyde®) is therefore proved to be an effective treatment in management of ulcerative colitis.

References