DA-9601 for erosive gastritis: Results of a double-blind placebo-controlled phase III clinical trial

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Abstract
AIM: To determine the efficacy and safety of DA-9601 on erosive gastritis versus cetraxate as a standard drug by gastrointestinal endoscopy.

METHODS: Five hundred and twelve patients with erosive gastritis were divided into three groups. The groups received 180 mg or 360 mg of DA-9601, or 600 mg of cetraxate (Neuer®) t.i.d. for 2 wk, respectively. Endoscopic observations were performed before and 2 wk after the treatment, and the cure and improvement rates were investigated.

RESULTS: Of the 512 intention-to-treat (ITT) population, 457 patients comprised the per protocol (PP) analysis. Endoscopic cure rate was significantly higher in the DA-9601 group than in the cetraxate group in both the PP (56%, 58% vs 36%; DA-9601 180 mg, 360 mg and cetraxate, respectively) and ITT (52%, 51% vs 35%) populations. Two DA-9601 groups (180 and 360 mg) had significantly higher endoscopic improvement rates than the cetraxate group in both the PP (67%, 65% vs 46%) and ITT (63%, 58% vs 45%) populations. The percentage of symptom relief over the 2 wk was found not significantly different between groups. During the study, both DA-9601 and cetraxate produced no treatment-associated adverse events.

CONCLUSION: From these results, it appears that DA-9601 has excellent efficacy on erosive gastritis. This study also confirms the safety profile of DA-9601.

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INTRODUCTION
Gastritis is a heterogeneous pathological condition, and is one of the most frequent reasons for medical consultation in Asian countries, including Korea and Japan. However, in Western countries, these conditions are diagnosed as non-ulcer dyspepsia (NUD), which affects approximately one in five Americans[1-4]. Gastritis, the “precursor” lesion to mucosal ulceration is both an important clinical entity and an important cause of abdominal pain in children[5]. Inflammation of the gastric mucosa is the end result of an imbalance between mucosal defensive and aggressive factors (i.e., disturbances in gastric acidity and the mucus-bicarbonate barrier), and recently a great deal of attention has been focused on gastric hormones, specifically gastrin, and pepsinogens I and II[6].

Gastritis can be classified into acute or chronic forms based upon Sydney System, and chronic gastritis can be subclassified as nonatrophic, atrophic, and special types[8,9]. Using this Sydney pathologic classification as a guide, Chen et al[10] reported a simplified classification for gastritis based on practical radiologic evaluation, including erosive gastritis (acute and chronic), Helicobacter pylori (H pylori) gastritis, chronic nonspecific gastritis, hyperplastic gastritis, and miscellaneous types (including granulomatous, phlegmonous, eosinophilic, corrosive, other infectious types and rare types).

At present, the exact pathophysiology of this syndrome is poorly understood. However, current evidence suggests that H pylori infection, changes in lifestyles, eating behaviors, and nonsteroidal anti-inflammatory drug (NSAID) ingestion are causative factors in the pathogenesis of gastric mucosal injury in humans[11]. H pylori is known to be a particularly important pathogen in gastric and duodenal inflammation by producing excessive mucosal-reactive oxygen species (ROS), which damage the cell membrane and deplete gastric antioxidants[12].

The current rationale for drug treatment in gastritis is similar to other gastrointestinal disorders (e.g., non-ulcer dyspepsia), and depends mainly on symptomatic relief using gastroprotective agents (e.g., rebamipide, teprenone, ecbacet sodium, sofalcone, cetraxate, etc.), H2 receptor antagonists (e.g., cimetidine, ranitidine, famotidine, etc.), and antacids[13]. However, despite many efforts, the pharmacological treatment of patients with gastritis usually achieves only partial symptomatic relief in the majority of cases.

DA-9601 (StillenTM), a phytopharmaceutical derived from Artemisia asiatica, has been reported to possess antioxidative and cytoprotective actions in various models of gastric mucosal damage[14,16]. Though the mode of action of DA-9601 has not been fully elucidated, this new antioxidative drug scavenges superoxide and hydroxyl radicals, possesses potent anti-inflammatory activities, regenerates mucosal epithelial cells, and enhances the cytoprotective cytokines[17,19].

The present study was designed to assess the therapeutic effects and safety of DA-9601 on gastritis. Cetraxate, which has been shown to have therapeutic effects on gastritis was selected as the standard drug for comparative purposes.

MATERIALS AND METHODS

Patients
The patients examined in this study consisted of 550 erosive gastritis patients who were diagnosed endoscopically between
August 2000 and December 2001. All patients gave their written consent to this study. Out of 550 initially enrolled patients, 512 completed the study. Those 512 patients were subsequently randomized, of whom 326 were allocated to DA-9601 (186 had 180 mg and 140 had 360 mg daily) and 186 to cetraxate 600 mg. The exclusion criteria were: a history of peptic ulcer disease and reflux esophagitis; the presence of a malignant tumor in the digestive tract; the use of drugs capable of interfering with digestive mucosal integrity, gastric secretion or gastrointestinal motility, including H2 receptor antagonists, NSAIDs, muscarinic antagonists, gastroprotective agents (within the previous 14 d); thrombotic patients (cerebral thrombosis, myocardial infarction, thrombophlebitis, etc.); consumption coagulopathy patients; a history of hypersensitivity to drugs (rash, fever, itching, etc.); the presence of major hematological, renal, cardiac, pulmonary, or hepatic abnormalities.

**Methods**
The study was performed as a randomized, double-blind, placebo-controlled, multicenter trial. Subjects were recruited at the following five Korean centers: Inje University of Medicine (Busan), Ulsan University of Medicine (Seoul), Chunnam University of Medicine (Gwangju), Catholic University of Medicine (Seoul), and Ajou University of Medicine (Suwon). Gastrointestinal endoscopies were performed in all patients before starting therapy, and 2 wk later. Patients diagnosed with erosive gastritis were included and divided into 3 groups following initial symptom assessment, and either treated with DA-9601 180 mg or 360 mg, or cetraxate 600 mg t.i.d. for 2 wk. After completing the therapy, endoscopic examinations were conducted according to the following grades: score 1, no erosions; score 2 (mild), erosion number between 1 and 2; score 3 (moderate), erosion number between 3 and 5; score 4 (severe), erosion number more than 6, for the evaluation of cure rate and improvement rate (Table 1). In addition, all patients completed a standardized subjective assessment questionnaire, according to Table 2. Safety surveillance was done at the end of therapy, based on responses to a complaint questionnaire, results of physical examinations and laboratory tests. Blood samples were obtained at the end of therapy to determine concentrations of GPT, GOT, and bilirubin. Complaint questionnaires were recorded for the appreciable harmful or unpleasant reactions experienced by a patient as a result of drug therapy.

**Table 1** Evaluation of efficacy based on endoscopic observations

| Score | Number of erosions |
|-------|--------------------|
| 1 (none) | 0 |
| 2 (mild) | 1–2 |
| 3 (moderate) | 3–5 |
| 4 (severe) | 6< |

**Statistics analysis**
Endoscopic efficacy was analyzed on an intention-to-treat (ITT) and per protocol (PP) basis. Both subjective and objective criteria were analyzed using Duncan’s multiple test. Comparisons between treatment groups were performed using the chi-square test. Data were considered to be significant when $P<0.05$.

**RESULTS**
A total of 512 patients completed the trial. Baseline characteristics of the study populations are detailed in Table 3, which shows that the study groups were comparable with respect to demographics and disease-specific characteristics.

**Table 3** Base-line characteristics of the patients (n, %)

| Characteristic | DA-9601 180 mg (n = 186) | DA-9601 360 mg (n = 140) | Cetraxate 600 mg (n = 186) |
|----------------|--------------------------|--------------------------|--------------------------|
| Male sex       | 89 (47.9)                | 72 (51.4)                | 92 (49.5)                |
| Age (yr)       | 45.9±11.2                | 44.6±12.1                | 46.4±11.5                |
| History <1 wk  | 3 (1.6)                  | 1 (0.7)                  | 3 (1.6)                  |
| 1–4 wk         | 31 (16.7)                | 28 (20.0)                | 29 (15.6)                |
| >4 wk          | 98 (52.7)                | 77 (51.5)                | 97 (52.2)                |
| Unknown        | 54 (29.0)                | 84 (60.0)                | 57 (30.7)                |
| Type           | Erosion 186 (100)        | 140 (100)                | 186 (100)                |
| Bleeding       | 8 (4.3)                  | 4 (2.9)                  | 10 (5.4)                 |
| Redness        | 51 (27.4)                | 47 (33.6)                | 44 (23.7)                |
| Edema          | 2 (1.1)                  | 10 (7.1)                 | 5 (2.7)                  |
| Grade          | Mild 14 (7.5)            | 18 (12.9)                | 21 (11.3)                |
| Moderate       | 50 (26.9)                | 40 (28.6)                | 54 (29.0)                |
| Severe         | 122 (65.6)               | 82 (58.6)                | 111 (59.7)               |

Data values are mean±SD.

**Table 4** Number of patients for ITT and PP assays

|                     | DA-9601 180 mg | DA-9601 360 mg | Cetraxate 600 mg |
|---------------------|----------------|----------------|------------------|
| ITT analysis        | 186            | 140            | 186              |
| PP analysis         | 171            | 120            | 166              |

**Efficacy evaluation**
The ITT population was composed of 512 patients (186 in the DA-9601 180 mg group, 140 in the DA-9601 360 mg group, and 186 in the cetraxate 600 mg group) (Table 4). Endoscopic cure rates in DA-9601 180 mg, 360 mg, and cetraxate 600 mg groups were 52.2%, 51.4%, and 35%, respectively (Figure 1). A significant difference was found between the DA-9601 and cetraxate groups ($P<0.05$), however, no difference in cure rates was found between the DA-9601 groups.

![Figure 1](https://example.com/f1.png)
The PP assay population comprised 457 patients (171 in the DA-9601 180 mg group, 120 in the DA-9601 360 mg group, and 166 in the cetraxate 600 mg group) (Table 4). The estimated cure rates of erosive gastritis by PP analysis in DA-9601 180 mg, 360 mg, and cetraxate 600 mg groups were 55.6% (95/171), 57.5% (69/120), and 35.5% (59/166), respectively (Figure 2). The cure rates between the DA-9601 and cetraxate groups (P<0.05) were significantly different, however, no difference was found between the DA-9601 groups.

Estimated improvement rates by ITT analysis of erosive gastritis patients treated with cetraxate (600 mg) and DA-9601 (180 or 360 mg) showed statistically significant differences (P<0.05); however, no difference was observed between the DA-9601 treated populations (Figure 3). The improvement rates of those treated with DA-9601 180 mg, 360 mg and cetraxate 600 mg were 63.4% (118/186), 75.0% (105/140), and 44.6% (83/186), respectively.

The estimated improvement rates by PP analysis for erosive gastritis treated with DA-9601 or cetraxate were statistically different (P<0.05) (Figure 4). However, no difference was found between the DA-9601 treated groups. The estimated improvement rates were 67.3% (115/171), 65.0% (98/120), and 46.4% (77/166) in the DA-9601 180 mg, DA-9601 360 mg, and cetraxate 600 mg treated groups.

Symptom relief rates
The symptom relief rates determined by the ITT and PP methods showed no statistically significant difference between the study populations. The overall degrees of symptom reduction by the ITT method in the DA-9601 180 mg, 360 mg, and cetraxate 600 mg groups were 77.4% (144/186), 75.0% (105/140), and 73.1% (136/186), respectively (Figure 5), and by PP analysis these were 81.3% (139/171), 81.7% (98/120), and 76.5% (127/166).

Safety
Serious adverse reactions were not encountered during this study. Of the 186 cetraxate 600 mg treated patients, the incidence of adverse effects was 7.5% (11 cases); including heartburn, abdominal pain, acid reflux, headache, itching, skin redness, facial edema, etc. Mild adverse events were observed in 14 of 186 patients treated with DA-9601 180 mg (Table 5). In the case of DA-9601 360 mg group, no notable change was observed.

Table 5 Incidence of adverse events (n, %)

|                        | DA-9601 180 mg | Cetraxate 600 mg |
|------------------------|----------------|-----------------|
| Gastrointestinal       |                |                 |
| Dyspepsia              | 2 (1.08)       | 0               |
| Nausea                 | 2 (1.08)       | 0               |
| Diarrhea               | 2 (1.08)       | 0               |
| Heartburn              | 1 (0.54)       | 1 (0.54)        |
| Abdominal pain         | 1 (0.54)       | 1 (0.54)        |
| Acid reflux            | 0              | 1 (0.54)        |
| Vomiting               | 1 (0.54)       | 1 (0.54)        |
| CNS and ANS            |                |                 |
| Dizziness              | 1 (0.54)       | 0               |
| Headache               | 1 (0.54)       | 1 (0.54)        |
| Skin                   |                |                 |
| Itching                | 1 (0.54)       | 1 (0.54)        |
| Skin redness           | 1 (0.54)       | 1 (0.54)        |
| Facial edema           | 0              | 1 (0.54)        |
| Liver                  |                |                 |
| sGPT elevation         | 1 (0.54)       | 1 (0.54)        |
| sGOT elevation         | 0              | 1 (0.54)        |
| Bilirubin elevation    | 0              | 1 (0.54)        |
| Total                  | 14 (7.53)      | 11 (5.91)       |
either in subjective assessment questionnaire or in clinical examination at the end of the study as compared to DA-9601 180 mg or cetraxate groups. No statistically significant difference was observed between the cetraxate and DA-9601 treated groups.

**DISCUSSION**

Although gastritis is the most common complication in the digestive tract, the definition of gastritis is not consensual due to differences in diagnostic criteria. It has been postulated that gastritis contributes to the natural history of ulcer development due to the decreased protection offered by the mucosal barrier lining the stomach, and increased epithelial cell exposure to hydrochloric acid.

The aim of this study was to demonstrate the efficacy and safety of DA-9601 versus cetraxate, a widely used anti-ulcer drug, for the treatment of erosive gastritis. Cetraxate, which has a mucosal protective effect, was first introduced in 1976 as an anti-ulcer drug[20]. It is widely used clinically in Japan and other Asian countries. The mode of action of cetraxate is ascribed to an increased gastric mucosal blood flow through enhanced nitric oxide synthase activity, and the prevention of a decrease in the mucosal prostaglandin content[21]. The results of the present randomized, double-blind, placebo-controlled, multicenter study demonstrate that orally administered DA-9601 is both effective and well-tolerated in the treatment of erosive gastritis of various etiologies.

Adverse reactions were seen in 7.5% (14/186) of the patients in DA-9601 180 mg treated group and in 5.9% (11/186) of patients in the cetraxate 600 mg treated group. In both groups, the main adverse reactions were vomiting, abdominal pain, headache, skin rash, itching, and sGPT elevation. However, in DA-9601 360 mg treated group, no obvious adverse reactions were observed (0%, 0/140). Therefore, we concluded that there was no drug treatment related adverse reaction based on the lack of dose-response relationship. In the previous four-wk oral toxicity study of DA-9601 in rats at doses of 120, 500, and 2 000 mg/kg.d, no treatment-related alternations, including changes in blood biochemistry were observed[22]. In animal experiments, DA-9601 prevented aceticaminophen, and CCl4-induced hepatic GSH depletion and CCl4-induced increased hepatic MDA (a parameter of lipid peroxidation) in a dose-dependent manner[23,24]. In addition, sGPT and sGOT levels showed a tendency to fall to below the normal range in DA-9601 treated patients (unpublished data).

Conclusively, the present study indicates that DA-9601 has an excellent efficacy and safety profile. Therefore, we believe that DA-9601 is a highly attractive option for the treatment of erosive gastritis, in which a balance between aggressive and defensive factors plays a significant role.

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