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Efficacy and Safety of Ilaprazole in the Treatment of Patients with Non-Erosive Reflux Disease: A Randomized Clinical Trial

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1. Abstract

1.1. Background and Aims

Non-erosive reflux disease (NERD) is a common phenotype of gastroesophageal reflux disease (GERD) and is associated with a substantial health burden. Ilaprazole, a new-generation benzimidazole proton pump inhibitor (PPI), has been shown to be safe and effective in the treatment of duodenal ulcer and erosive reflux esophagitis. This study aimed to evaluate the efficacy and safety of ilaprazole in patients with NERD.

1.2. Methods

A prospective, randomized, controlled trial was conducted. Eighty-two patients with reflux symptoms and normal upper gastrointestinal endoscopic findings were enrolled and randomized to receive either ilaprazole 20 mg or omeprazole 40 mg once daily for 4 weeks. Clinical efficacy was assessed using the Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease (FSSG) before and after treatment. Adverse events, drug compliance, and laboratory test results were also evaluated after completion of treatment.

1.3. Results

Among the 82 patients enrolled, 78 patients (40 in ilaprazole group and 38 in omeprazole group) completed the study. Baseline characteristics were comparable between the two groups, with no significant differences. The primary outcome, changes in FSSG scores, showed significant improvement after treatment in both groups (ilaprazole: from 24.10 ± 3.30 to 5.12 ± 1.34; omeprazole: from 24.45 ± 3.05 to 5.26 ± 1.43; $P < 0.0001$). However, there was no statistically significant difference in FSSG score improvement between the ilaprazole and omeprazole groups.

1.4. Conclusion

Ilaprazole 20 mg once daily for 4 weeks significantly improved reflux symptoms in patients with NERD and showed efficacy and short-term safety comparable to those of omeprazole 40 mg. Further large-scale studies are needed to confirm these findings.

2. Introduction

Gastroesophageal reflux disease (GERD) is a common digestive disorder characterized by the reflux of gastric contents into the esophagus due to an incompetent lower esophageal sphincter. The prevalence of GERD is estimated to be approximately 10–20% in Western populations and 3–5% in East Asian populations. However, there has been an increase in GERD-related symptoms as well as a rising prevalence of esophagitis in Asian countries [1-3]. The most typical symptoms of GERD are heartburn and regurgitation. In addition, patients may present with extraesophageal manifestations such as chest pain, coughing, hoarseness, and dysphagia. These symptoms, whether typical or atypical, substantially impair patients' quality of life.

Subtypes of GERD include erosive reflux disease (ERD) and non-erosive reflux disease (NERD). Non-erosive reflux disease (NERD) has been defined as reflux-related symptoms with the absence of esophageal mucosal erosions or breaks at conventional endoscopy and without recent acid-suppressive therapy [4]. Approximately two-thirds of patients presenting with typical symptoms of gastroesophageal reflux disease (GERD) exhibit no evidence of erosive changes on endoscopy. The complex pathophysiology of NERD and mechanism of its association with symptoms are not clear [4,5]. Still, Given that a comparable reduction in quality of life is observed in these patients, non-erosive reflux disease (NERD) should not be regarded as a merely mild manifestation of reflux.

The treatment of GERD primarily focuses on reducing gas-

tric acidity and decreasing the reflux of gastric contents into the esophagus. Proton pump inhibitors (PPIs) have been shown to be more effective than histamine-2 receptor antagonists (H2RAs) in achieving esophageal mucosal healing and providing symptom relief [6]. Standard-dose PPIs are generally recommended for 4 to 8 weeks as the initial therapy for GERD [7]. However, compared with patients with ERD, those with NERD generally show lower response rates to PPI therapy for symptom relief, highlighting the need to explore additional therapeutic options for symptom control in this population [8, 9, 10].

Ilaprazole, a new-generation benzimidazole PPI, has been shown to be unaffected by CYP2C19 gene polymorphism in human metabolism, thereby providing more consistent efficacy and improved safety for patients [11]. Furthermore, phase I and II clinical studies of ilaprazole have demonstrated its safety and effectiveness, supporting its use in the treatment of peptic ulcer disease and gastroesophageal reflux disease (GERD) [12, 13, 14]. However, clinical data regarding the efficacy and safety of ilaprazole in patients with NERD remain limited.

In this study, we aimed to evaluate the efficacy and safety of ilaprazole in the treatment of patients with non-erosive gastroesophageal reflux disease (NERD).

3. Materials and Methods

3.1. Study Design

This study was a 4-week single-centre, prospective, open-label trial designed to evaluate the efficacy and safety of ilaprazole in the treatment of NERD. Patients were recruited from the outpatient gastroenterology department of Daejeon St. Mary's Hospital between September 2022 and June 2025. Participants were screened according to predefined inclusion and exclusion criteria and subsequently prescribed the investigational drugs. After completion of treatment, adverse reactions, drug compliance, and laboratory test results were assessed. All participants provided written informed consent. Following the acquisition of informed consent, patients were randomly assigned to two treatment groups to receive either ilaprazole 20 mg once daily or omeprazole 40 mg once daily for 4 weeks. Randomization was performed using a computer-generated list of random numbers. The severity of symptoms was evaluated using the FSSG questionnaire at baseline and after 4 weeks of treatment.

This study was approved by the Institutional Review Board of the Catholic University of Korea (IRB no. DC19MEDVD053).

3.2. Inclusion Criteria

Patients were eligible for enrolment if they were older than 18 years, had persistent reflux symptoms suggestive of GERD, and showed no evidence of erosive esophagitis or other significant abnormalities on upper gastrointestinal endoscopy.

3.3. Exclusion Criteria

The exclusion criteria were as follows: allergy or hypersensitivity to the test drugs; pregnancy, breastfeeding, childbearing age, and not using appropriate contraception; uncontrolled diabetes mellitus (DM) or hypertension (HTN); drug or alcohol abuse; history of malignancy within the last 5 years (excluding those who underwent endoscopic curative resection for gastric dysplasia or early gastric cancer); history of surgery such as esophagectomy or gastrectomy; hereditary diseases such as galactose intolerance, lactase deficiency, and glucose-galactose malabsorption; and current participation in another clinical trial. Furthermore, we excluded subjects who had the following laboratory abnormalities: (1) ≥1.5 times the upper limit of normal in terms of total bilirubin and creatinine (Cr) levels and (2) ≥2 times the upper limit of normal in terms of aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), and blood urea nitrogen (BUN) levels.

Several participants were excluded from the study. Subjects were withdrawn due to (1) revoked their consent to participate, (2) received concomitant medication that adversely affected the efficacy or safety of the investigational drugs during the study, and (3) demonstrated less than 80% compliance with the study medication. In addition, subjects who experienced critical adverse reactions requiring hospitalization or developed laboratory abnormalities exceeding 1.5 times baseline values-regardless of whether these were related to the investigational drugs-were also withdrawn.

3.4. Symptom Severity: Frequency Scale for Symptoms of GERD (FSSG)

Treatment response was assessed based on changes in reflux symptom severity. Symptom severity was evaluated using the Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease (FSSG), a standardized questionnaire based on the frequency of GERD-related symptoms [15]. The total FSSG score was calculated as the sum of individual item scores. Each item was rated on a 5-point scale as follows: never, 0; occasionally, 1; sometimes, 2; often, 3; and always, 4. Higher scores indicated more severe reflux-related symptoms.

3.5. Drug Compliance and Adverse Events

Drug compliance and adverse events were monitored during scheduled visits and telephone follow-ups. Significant compliance was defined as intake of more than 80% of the study medication, and participants with less than 80% compliance were planned to be excluded. Adverse events were graded according to the requirement for medical intervention or hospitalization.

3.6. Endpoints

The primary endpoint was improvement in reflux symptoms after 4 weeks of treatment, as assessed by changes in the total FSSG score from baseline. The secondary endpoint was safety during the study period, assessed by adverse events, drug compliance, and laboratory test results.

3.7. Statistical Analysis

Calculations were performed using SPSS statistical software, version***(IBM Corp., Armonk, NY, USA). Continuous variables are presented as means ± standard deviation or median, and discrete variables are expressed as numbers and percentages. The baseline characteristics of the patients in the two groups were compared using the chi-squared test or Fisher's exact test for categorical data,

and the independent t-test or Mann-Whitney U test for continuous data. Paired comparisons of parameters before and after treatment were performed using a paired t-test or a Wilcoxon signed-rank test. Results are presented as differences in proportions, 95% confidence intervals (CI), and p values. $p \leq 0.05$ was considered statistically significant.

Originally, a sample size of 69 patients per group was required to achieve 80% statistical power with a one-sided significance level of 5% and a non-inferiority margin of 19%. However, as the final enrolment (n = 82) was lower than planned, the present study was interpreted in an exploratory and supportive manner. Consequently, the analysis focused on the estimation of treatment effects and descriptive clinical response patterns rather than definitive confirmatory hypothesis testing.

4. Results

4.1. Baseline Characteristics of The Patients

Baseline characteristics of the subjects are shown in Table1. A total of 82 patients diagnosed with non-erosive reflux disease (NERD) were enrolled and randomized into ilaprazole and omeprazole treatment groups, with 41 patients each group. In the ilaprazole group, one patient excluded due to loss of follow-up, while three patients in the omeprazole group were excluded for the same reason. Consequently, 78 patients completed the study protocol (Figure 1).

The mean age of each group was 62.80 ± 8.0 in the ilaprazole group and 63.2 ± 8.6 in the omeprazole group. Male patients accounted for 35.0% and 31.6% of each group. The mean BMI was 23.5 ± 2.5 in the ilaprazole group and 23.7 ± 2.2 in the omeprazole group. There was no significant differences in baseline characteristics between the two treatment groups (Table 1).

4.2. Efficacy for Reflux Symptoms

The improvement in reflux symptoms after 4-weeks of treatment is shown in Table 2. In the ilaprazole group, the total FSSG score significantly decreased from 24.10 ± 3.30 to 5.12 ± 1.34 ($p < 0.0001$). Similarly, in the omeprazole group the total FSSG score was significantly decreased from 24.45 ± 3.05 to 5.26 ± 1.43 ($p < 0.0001$). There was no significant difference between groups with respect to the FSSG scores after 4 weeks of treatment (P = 0.5685).

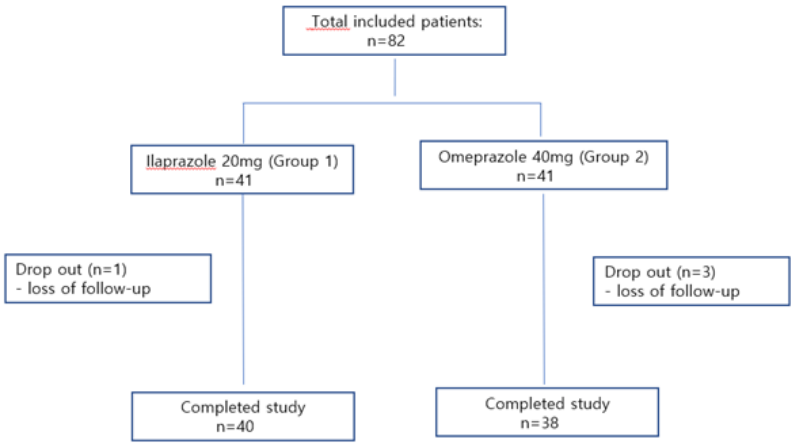

Figure 1: Enrollment flow diagram: distribution of patients into treatment groups.

Table 1: Baseline characteristics of the patients (n= 78).

Characteristics	Group 1	Group 2	P-value*
Number	40	38	
Mean age, years ±SD	62.8 ± 8.0	63.2 ± 8.6	0.5888
Sex			0.7487
male, n(%)	14 (35 %)	12 (31.6 %)	
female, n(%)	26 (65 %)	26 (68.4 %)	
BMI	23.5± 2.5	23.7± 2.2	0.4594
DM	4 (10.0 %)	3 (7.9 %)	1.0
HBP	15 (37.5 %)	18 (47.4 %)	0.3779
Alcohol	10 (25.0 %)	9 (23.7 %)	0.8924
Smoking	2 (5.0 %)	1 (2.6 %)	1.0

Values are presented as mean ± standard deviation or n (%)
P- values were calculated using Wilcoxon rank sum test or Chi-square test.

Table 2: Symptom improvement between Ilaprazole group and Omeprazole group.

	Pre-treatment	Post-treatment	P value
Total FSSG score			
Ilaprazole group (n=40)	24.10± 3.30	5.12± 1.34	<0.0001
Omeprazole group (n=38)	24.45± 3.05	5.26 ± 1.43	<0.0001

Values are presented as mean ± standard deviation or n (%)

P- values were calculated using Wilcoxon rank sum test.

Table 3: GERD related symptom improvement between Ilaprazole and Omeprazole group.

	Ilaprazole group (n = 40)	Omeprazole group (n = 38)	P-value
Heartburn			
Pre-treatment	2.98 ± 0.16	3.00 ± 0	
Post-treatment	0 ± 0	0 ± 0	< 0.0001
Retrosternal burning sensation			
Pre-treatment	2.10± 0.74	2.08± 0.85	
Post-treatment	0 ± 0	0.08 ± 0.49	< 0.0001
Acid regurgitation			
Pre-treatment	2.48± 0.60	2.68± 0.47	
Post-treatment	0.08± 0.27	0.08± 0.27	< 0.0001

Values are presented as mean ± standard deviation or n (%)

P- values were calculated using Wilcoxon rank sum test or Chi-square test.

Analysis of individual symptoms demonstrated that heartburn decreased from 2.98 ± 0.16 to 0 ± 0 in the ilaprazole group and from 3.0 ± 0 to 0 ± 0 in the omeprazole group. Acid regurgitation decreased from 2.48 ± 0.60 to 0.08 ± 0.27 versus 2.68 ± 0.47 to 0.08 ± 0.27. Retrosternal burning sensation decreased from 2.10 ± 0.740 to 0 ± 0 versus 2.08 ± 0.85 to 0.08 ± 0.49 in each group ($P < 0.0001$). However, no significant differences were observed between two groups ($P = 0.3426, 0.9915, 0.1183$)

4.3. Safety Analysis

No drug-related events or clinically significant abnormalities in laboratory test results were observed in either treatment group.

5. Discussion

Non-erosive reflux disease (NERD) is the most prevalent phenotype of gastroesophageal reflux disease (GERD) and accounts for a substantial proportion of patients presenting with reflux symptoms. Although endoscopic mucosal injury is absent, patients with NERD frequently experience considerable impairment in quality of life, highlighting the importance of effective symptom control. Proton pump inhibitors (PPIs) remain the mainstay of treatment; however, data regarding the efficacy of newer PPIs in patients with NERD remain relatively limited [16, 17].

In the present study, once-daily treatment with ilaprazole 20 mg or omeprazole 40 mg for 4 weeks resulted in marked improvement in reflux symptoms. Both treatment groups demonstrated marked reductions in total FSSG scores, from 24.10 ± 3.30 to 5.12 ± 1.34 in the ilaprazole group and from 24.45 ± 3.05 to 5.26 ± 1.43 in the omeprazole group, with no statistically significant difference between the groups. These findings suggest that ilaprazole provides symptom relief comparable to that of omeprazole in patients with NERD.

The observed efficacy of ilaprazole in patients with NERD is consistent with previous clinical evidence. Song et al. reported that ilaprazole significantly improved reflux symptoms and histologic inflammatory changes in patients with NERD [18]. Although that study was limited by its single-arm design and relatively small sample size, it supports the growing evidence that ilaprazole can be an effective therapeutic option specifically in NERD. Since ilaprazole is less affected by CYP2C19 polymorphisms, it can provide more stable and predictable acid inhibition across different patient groups. This pharmacokinetic advantage is especially important in East Asian populations, where CYP2C19 polymorphisms are highly prevalent, and may contribute to more consistent symptom control in NERD compared with traditional PPIs [19]. Furthermore, comparative pharmacodynamic studies have also shown that ilaprazole maintains intragastric pH above 4 for longer durations than omeprazole [21], supporting its potential advantage in acid suppression.

Both treatments were well tolerated throughout the study period. No drug-related adverse events or clinically significant laboratory abnormalities were observed in either treatment group. These findings suggest that ilaprazole has a favourable short-term safety profile comparable to that of omeprazole in patients with NERD.

This study has several limitations. First, the single-centre design and relatively small sample size may limit the generalizability of the findings. Therefore, these findings should be interpreted as preliminary clinical evidence, and further large-scale studies are warranted to draw more definitive conclusions. Second, the treatment duration was limited to 4-weeks, preventing the evaluation of

long-term symptom control and recurrence. Finally, objective reflux monitoring, such as ambulatory pH monitoring or impedance testing was not performed. Therefore, reflux hypersensitivity and functional heartburn could not be completely excluded, and some participants may not have represented true acid-related NERD.

In conclusion, once-daily treatment with ilaprazole 20 mg or omeprazole 40 mg for 4 weeks significantly improved reflux symptoms in patients with non-erosive reflux disease (NERD). Ilaprazole showed efficacy and short-term safety profiles comparable to those observed with omeprazole, supporting its potential role as an alternative therapeutic option for symptom control in patients with NERD.

6. Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

7. Acknowledgements

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