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Effects of lansoprazole plus amoxycillin on the cure of Helicobacter pylori infections in Japanese peptic ulcer patients

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Summary

Aim: The effect of lansoprazole plus amoxycillin on curing Helicobacter pylroi and peptic ulcer recurrence was evaluated.
Method: Subjects were 68 patients with gastric ulcers and 51 with duodenal ulcers, all were H. pylori-positive. The participants were assigned at random to the lansoprazole alone group (lansoprazole 30 mg o.m. for 6 or 8 weeks) or the lansoprazole plus amoxycillin group (lansoprazole alone regimen plus amoxycillin at 500 mg q.d.s. concomitantly for the first 2 weeks). Healed patients were not given maintenance treatment with acid secretion inhibitors. The cure rate for H. pylori infection and ulcer recurrence rate after 1 year were investigated.
Result: The cure rate for H. pylori infection was 4.2% in patients receiving lansoprazole alone and 38.5% in patients receiving lansoprazole plus amoxycillin ($p < 0.01$) for gastric ulcers and 0% in patinets receiving lansoprazole alone and 61.9% in patients receiving lansoprazole plus amoxycillin ($p < 0.001$) for duodenal ulcers. The recurrence rate was 42.3% in patinets receiving lansoprazole alone and 28.6% in patients receiving lansoprazole plus amoxycillin for gastric ulcers and 66.7% for patinets receiving lansoprazole alone and 11.1% for patients receiving lansoprazole plus amoxycillin ($p < 0.001$) for duodenal ulcers. None of the patients with gastric or duodenal ulcers cured of H. pylori infections had recurrences.
Conclusion: Concomitant use of lansoprazole and amoxycillin increased the curative effects on H. pylori infections. However, the cure rates with the regimen remained inadequate.

Key words: Helicobacter pylori, lansoprazole, peptic ulcer, recurrence prevention

Introduction

Since it was first reported by Warren and Marshall in Australia in 1983[1], Helicobacter pylori has been found to be closely related not only to gastritis but also to gastric and duodenal ulcers, gastric cancers and gastric lymphomas. Treatment to eradicate H. pylori is effective in preventing recurrences of peptic ulcers[2-4], and the NIH Consensus Conference issued a recommendation in February 1994 calling for concomitant treatment with an acid secretion inhibitor and antibiotic for patients with peptic ulcers in both initial and recurrent cases[5]. For H. pylori eradication, triple therapy consisting of a bismuth preparation, metronidazole or tinidazole, and tetracycline or amoxycillin was used initially, but this treatment was plagued with problems of many adverse reactions and low compliance. Thereafter, concomitant therapy consisting of a proton pump inhibitor, one type of acid secretion inhibitor and an antibiotic was used because it had few adverse reactions. Reports to data on concomitant therapy with PPI and antibiotics have almost all involved omeprazole together with amoxycillin or clarithromycin, and high cure rates required high doses of both omeprazole and amoxycillin[6].

Lansoprazole is a benzimidazole-type proton pump inhibitor, which has been found to have more a potent gastric acid secretion inhibitory action at a dose of 30 mg than omeprazole at 20 mg[7]. It is also known to have a more potent antibacterial activity against H. pylori than omeprazole[8]. Therefore, in the present study, we performed a randomized controlled study in a group given 30 mg of lansoprazole alone and a group given 30 mg of lansoprazole and 2 g of amoxycillin concomitantly to study the effects of lansoprazole on eradication treatment. Unlike other parts of the world, Japan has a higher frequency of gastric ulcers than of duodenal ulcers[9], and differences by ulcer site and preventive effects on post-treatment recurrences in Japanese peptic ulcer patients were also studied.

Materials and Methods

Sixty-eight patients with gastric ulcers and 51 with duodenal ulcers, found to be H. pylori-positive using the rapid urease test, participated in the randomized controlled study. These ulcers were all found endoscopically to have diameters of at least 5 mm. Patients who had undergone gastrectomies beforehand, those with an allergy to penicillins, those with serious complications, those who had used adrenocortical steroids or non-steroidal anti-inflammatory

drugs within 1 month, and those who took anticoagulants were excluded. The patients were told the objective of the study beforehand, and informed consent was obtained from all of the patients.

The patients were all assigned at random to either the lansoprazole alone group (n = 56) or the lansoprazole plus amoxycillin group (n = 63). Patients in the lansoprazole alone group were administered 30 mg of lansoprazole o.m. for 8 weeks in the case of gastric ulcer patients and for 6 weeks for duodenal ulcer patients. In the lansoprazole plus amoxycillin group, amoxycillin at a dose of 500 mg q.d.s. was administered for the first 2 weeks concomitantly with the same lansoprazole regimen as in the lansoprazole alone group. On completion of lansoprazole administration, endoscopy was performed and ulcer healing was confirmed. Patients with healed ulcers, both gastric or duodenal, were not given maintenance therapy using acid secretion inhibitors, and their progress were monitored for 1 year after treatment. Endoscopy was performed every 3 months during follow-up, during which the presence of ulcer recurrences and H. pylori were noted. When abdominal symptoms appeared and ulcer recurrences were suspected, endoscopy was performed as required.

H. pylori was evaluated by the CLO test (Delta West, Australia), a rapid urease test. In the CLO test, the presence of H. pylori was evaluated by colour changes after 2 h using biopsy specimens collected from three sites during endoscopy: greater curvature of the antrum, greater curvature of the corpus and margin of the ulcer. Cure of the H. pylori infection was evaluated by observing the progress for 1 year after completion of therapy, those patients who remained negative with the CLO test during the observation period were considered as cured. Patients who changed from negative to positive during follow-up were all evaluated as having not been cured of H. pylori infection.

For the statistical analysis of the demographic and clinical characteristics between the two groups, the Student's t-test and the chi-square test or Fisher's exact test were used. The chi-square test and Fisher's exact test were also used for comparison of the results between the two groups. Differences were considered significant at risk rates of less than 5%.

Results

The gastric ulcer patients were divided into 33 patients receiving lansoprazole alone and 35 patients receiving lansoprazole

plus amoxycillin, and the duodenal ulcer patients into 23 patients receiving lansoprazole alone and 28 patients receiving lansoprazole plus amoxycillin. The demographic and clinical characteristics of gastric ulcer or duodenal patients in the lansoprazole alone group and the lansoprazole plus amoxycillin group were compared, but no significant differences were seen between the two groups (Table 1 and 2).

The 8-week healing rate for gastric ulcers was 90.9% in the lansoprazole alone group and 85.7% for the lansoprazole plus amoxycillin group; no significant difference was seen between the two groups (Table 3). The 6-week healing rate for duodenal ulcers was 95.7% in the lansoprazole alone group and 100% in the lansoprazole plus amoxycillin group; there was no significant difference between the groups (Table 3). No adverse reactions were found in patinets receiving lansoprazole alone, but in patinets receiving lansoprazole plus amoxycillin, two patients had diarrhea, one had a rash and one liver dysfunction. The incidence of adverse reactions was 1.3%.

The study could be followed for up to 1 year after completion of therapy in 54 patients in the gastric ulcer group (26 in the lansoprazole alone group, 28 in the lansoprazole plus amoxycillin group) and 45 patients in the duodenal ulcer group (18 in the lansoprazole alone group, 27 in the lansoprazole plus amoxycillin group). Eight patients did not complete the follow-up period, two were given an H_2-receptor antagonist during the follow-up period, and H. pylori was eradicated in one patient by triple therapy during the follow-up period. The recurrence rate up to 1 year after completion of treatment was 42.3% in patients receiving lansoprazole alone and 28.6% in patients receiving lansoprazole plus amoxycillin (p = N.S.) for gastric ulcers. For duodenal ulcers, it was 66.7% for the lansoprazole alone group and 11.1% for the lansoprazole plus amoxycillin group ($p = 0.001$). There was no difference between the two groups for gastric ulcers, but the lansoprazole plus amoxycillin group had a low recurrence rate for duodenal ulcers (Table 3).

H. pylori could be evaluated up to 1 year after treatment in 50 gastric ulcer patients and 39 duodenal ulcer patients. H. pylori could not be evaluated after 1 year in 10 patients. The H. pylori infection cure rate was 4.2% in patients receiving lansoprazole alone and 38.5% in patients receiving lansoprazole plus amoxycillin for gastric ulcer ($p < 0.01$) and 0% in patients receiving lansoprazole alone and 61.9% in patients receiving lansoprazole plus amoxycillin for duodenal ulcer ($p < 0.001$). The cure rate was significantly

higher in the lansoprazole plus amoxycillin group than in the lansoprazole alone group for both gastric and duodenal ulcers (Table 3). The H. pylori infection cure rate in the lansoprazole plus amoxycillin group did not show any significant difference between gastric and duodenal ulcers.

When the recurrence rate after 1 year was correlated with the status of H. pylori infections, the recurrence rate was 46.2% for gastric ulcers and 57.7% for duodenal ulcers in patients without H. pylori infection cures, but no recurrences were seen in any of the patients with gastric or duodenal ulcers who were cured of H. pylori infections (Table 4)(Figures. 1 and 2).

Discussion

Peptic ulcers have been treated with drugs which inhibit acid secretion such as H_2-receptor antagonists and proton pump inhibitors. These agents not only showed good peptic ulcer healing rates but also suppressed ulcer recurrences when used in maintenance therapy. However, when maintenance therapy using acid inhibitory agents was stopped, the ulcers recurred at a high rate, and it was considered that the natural history of peptic ulcers, i.e., repeated recurrences, had not changed[10]. Recently, H. pylori was discovered and a relation between H. pylori and peptic ulcers was found. Many reports have been published on attempts to cure H. pylori infections and ulcer recurrence rates in duodenal ulcer patients, and it was evident that curing H. pylori infection markedly inhibited ulcer recurrences[2-4,11]. There have been fewer reports on such results for gastric ulcers than for duodenal ulcers, but it has also been found that recurrence rates in gastric ulcer patients cured of H. pylori infections were definitely lower than those in patients who were not cured[12-14].

Among the countries of the world, Japan is exceptional in having a higher frequency of gastric ulcers than of duodenal ulcers[9]. The ratio of duodenal ulcers to gastric ulcers in Japan is 0.6:1, while it is 2.7:1 in the USA[15], 2.4:1 in Ireland[16] and 17.1:1 in India[17]. The reason for this is not clear, but it might be related to the high incidence of atrophic gastritis in the Japanese, and H. pylori infection conditions or environmental factors are affected by this. In the present study on Japanese patients with peptic ulcers, recurrences of both gastric and duodenal ulcers were almost completely inhibited when H. pylori infections were cured. Therefore, no differences due to ulcer site were seen in the relation between ulcer recurrences and H. pylori.

Many studies have been performed on the treatment of H. pylori infections, but no drugs or treatment methods which provide a reliable cure have been established. Because of the high incidence of adverse reactions and poor compliance for triple therapy, a new method of treatment using an acid secretion inhibitor and an antibiotic concomitantly has been developed. Proton pump inhibitors have been found to show potent antibacterial activity against H. pylori. With proton pump inhibitors monotherapy, H. pylori infections cannot be cured, but when they are used concomitantly with an antibiotic, the therapeutic effects of the antibiotic are enhanced. The mean cure rate for H. pylori infections when using a proton pump inhibitor plus amoxycillin regimen was 60%, but the cure rate is affected by the dose and number of administrations of the proton pump inhibitor, and the dose and time of administration of the antibiotic[18]. The H. pylori infection cure rate has been raised to 85% by high doses of a proton pump inhibitor twice a day and high dose of amoxycillin[6,19,20].

The mechanism of action of proton pump inhibitor against H. pylori might involve direct action on H. pylori or an inhibitory action on urease activity or ATPase of H. pylori[6,8,21]. The reason for the concomitant effects of proton pump inhibitor and an antibiotic is that the low acid condition in the stomach caused by the action of the proton pump inhibitor prevents inactivation of the antibiotic by acid, strengthens the antibacterial action, promotes localized action of the proton pump inhibitor and eliminates H. pylori by proliferation of gastric flora. These actions promote curing of H. pylori infections[6].

Lansoprazole used in the present study is a proton pump inhibitor with a benzimidazole skeleton. Lansoprazole at a dose of 30 mg o.m. healed 93% of the gastric ulcers in 8 weeks and 98% of the duodenal ulcers in 6 weeks. In a study of the 24-h intragastric pH, lansoprazole at 30 mg was found to have a more potent acid secretion inhibitory action than omeprazole at 20 mg[22]. Lansoprazole has also been reported to have a lower MIC for H. pylori than omeprazole[23]. In the present randomized controlled study, the cure rate of H. pylori infections by 30 mg of lansoprazole alone was 2.4%, but when concomitant treatment was performed using 30 mg of lansoprazole and 2 g of amoxycillin, the cure rate of H. pylori infections increased to 48.9%. The concomitant use of lansoprazole increased the curative effects on H. pylori infections, but the cure rate was not sufficient using this regimen. To obtain an effective eradication rate by concomitant use of a proton pump inhibitor and an antibiotic, it is necessary to increase the dose of the

proton pump inhibitor and administer it twice a day. Consideration should be given to the Italian regimen by which a proton pump inhibitor was administered with two antibiotics concomitantly[24] or quadruple therapy with four drugs concomitantly[25].

In a study of the effects of the ulcer site on treatment to cure H. pylori infections, Culter et al. reported that the cure rate was low in gastric ulcer patients given triple therapy[26]. Labenz et al.[27] found that a proton pump inhibitors and an antibiotic used concomitantly were very effective in gastric ulcer patients. In the present study, the cure rates showed no significant difference between gastric and duodenal ulcers, and there was no difference according to the ulcer site.

In the evaluation of H. pylori eradication, there are still problems which have not been solved, but a cure is defined as a case which is H. pylori-negative when more than 1 month has passed since the completion of therapy[28]. Methods for detection of H. pylori include cultures, microscopy and the urea breath test. The rapid urease test is not used alone because of problems related to sensitivity. However, when the follow-up period was increased to 1 year after completion of treatment, as in the present study, evaluation of cures using only the rapid urease test appeared possible. In cases where the H. pylori infection could not be cured, the rapid urease test was negative1-3 months after treatment and then changed to positive 6-12 months after treatment.

In conclusion, the concomitant use of lansoprazole and amoxycillin increased the curative effects on H. pylori infections, but with the regimen used in this study, the cure rates remained inadequate. If H. pylori infection is cured, ulcer recurrence is markedly suppressed in gastric ulcers or duodenal ulcers.

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Figure Legends

Figure 1. Non-relapse rates in gastric ulcer patients. The gastric ulcer patients in whom H. pylori was cured have no ulcer recurrence in a year after treatment of H. pylori.

Figure 2. Non-relapse rates in duodenal ulcer patients. The duodenal ulcer patients in whom H. pylori was cured have no ulcer recurrence in a year after treatment of H. pylori.

Table 1. Demographic and clinical characteristics of the gastric ulcer patients

	LPZ (n=33)	LPZ+AMPC (n=35)	P
Sex			
Male	22	24	
Female	11	11	N.S.
Age			
20≧	0	0	
21-40	7	5	
41-60	19	20	N.S.
61≦	7	10	
Smoking			
No	12	15	N.S.
Yes	16	17	
Ulcer history			
No	11	10	N.S.
Yes	22	25	
Complication			
No	29	29	N.S.
Yes	4	6	
Compliance			
Good	28	32	N.S.
Fair	5	3	
Number of ulcer			
Single	28	26	N.S.
Multiple	5	9	
Size of ulcer			
Small	2	2	
Medium	29	27	N.S.
Large	2	6	

There was no significant difference between the groups.

LPZ:lansoprazole AMPC:amoxicillin

(N.S. = not significant)

Table 2. Demographic and clinical characteristics of the duodenal ulcer patients

	LPZ (n=23)	LPZ+AMPC (n=28)	P
Sex			
Male	13	17	
Female	10	11	N.S.
Age			
20≧	0	0	
21-40	8	12	
41-60	9	10	
61≦	6	6	N.S.
Smoking			
No	14	13	
Yes	7	15	N.S.
Ulcer history			
No	7	6	
Yes	16	22	N.S.
Complication			
No	19	23	
Yes	4	5	N.S.
Compliance			
Good	19	25	
Fair	4	3	N.S.
Number of ulcer			
Single	17	25	
Multiple	6	3	N.S.
Size of ulcer			
Small	4	4	
Medium	18	23	
Large	1	1	N.S.

There was no significant difference between the groups.

LPZ:lansoprazole AMPC:amoxicillin

(N.S. = not significant)

Table 3. Comparison of healing rates, relapse rates, and *H.pylori* cure rates in gastric and duodenal ulcer patients in two treatment groups

	Healing rate		Relapse rate		Cure rate	
Gastric ulcer						
LPZ	90.9%(30/33)	N.S.	42.3%(11/26)	N.S.	4.2%(1/24)	P<0.01
LPZ+AMPC	85.7%(30/35)		28.6%(8/28)		38.5%(10/26)	
Duodenal ulcer						
LPZ	95.7%(22/23)	N.S.	66.7%(12/18)	P<0.001	0%(0/18)	P<0.001
LPZ+AMPC	100%(28/28)		11.1%(3/27)		61.9%(13/21)	

The *H.pylori* cure rates in patients who recieved lansoprazole plus amoxicillin were significantly higher than in patients who recieved lansoprrazole alone.
LPZ:lansoprazole AMPC:amoxicillin
(N.S.= not significant)

Table 4. Comparison of relapse rates in patients with and without *H.pylori* infection cures

	Relapse rate (after 6 month)	Relapse rate (after one year)
Gastric ulcer		
HP +	33.3%(13/39)	46.2%(18/39)
HP -	0%(0/11)	0%(0/11)
Duodenal ulcer		
HP +	46.2%(12/26)	57.7%(15/26)
HP -	0%(0/13)	0%(0/13)

No recurrence were seen in any of the patients with gastric or duodenal ulcer who were cured of H.pylori infections.

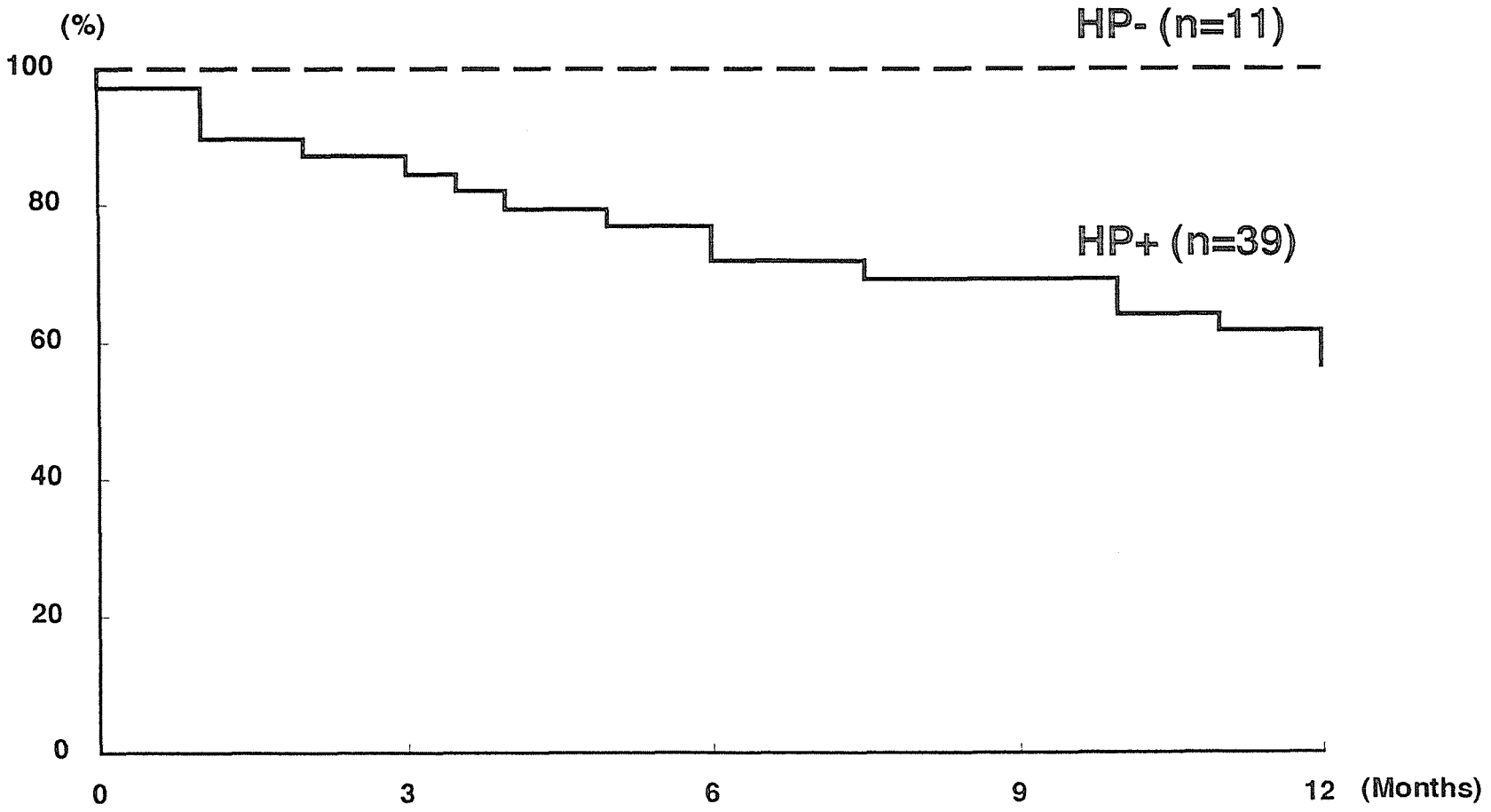

Figure 1. Non-relapse rates in gastric ulcer patients. The gastric ulcer patients in whom *H. pylori* was cured have no ulcer recurrence in a year after treatment of *H. pylori*.

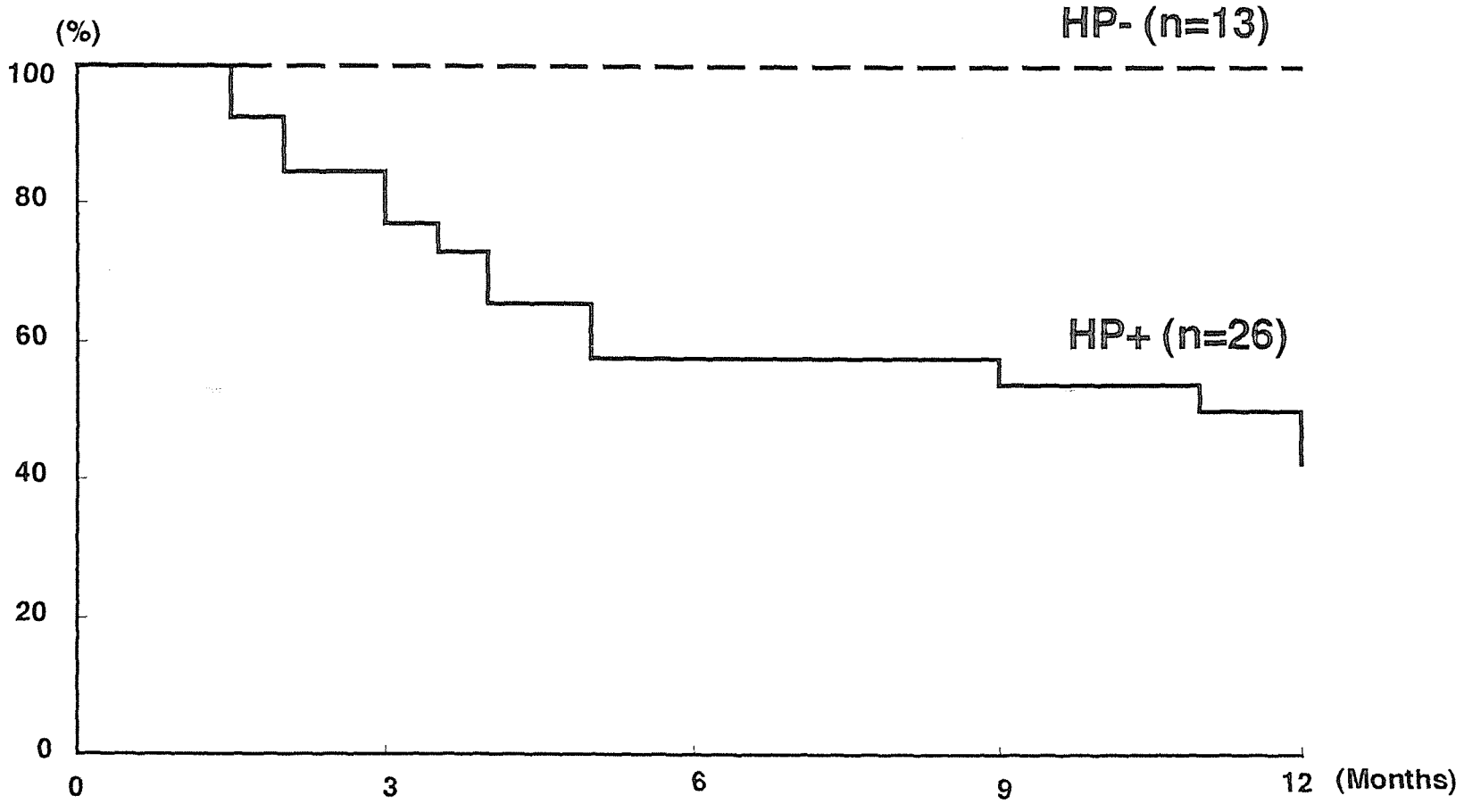

Figure 2. Non-relapse rates in duodenal ulcer patients. The duodenal ulcer patients in whom *H. pylori* was cured have no ulcer recurrence in a year after treatment of *H. pylori*.