

## ORIGINAL ARTICLES

# Efficacy of the eradication of *Helicobacter pylori* infection in patients with chronic urticaria. A placebo-controlled double blind study

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### SUMMARY

*Helicobacter pylori* has been involved in the pathogenesis of chronic idiopathic urticaria (CIU) in patients suffering both CIU and *H. pylori* infection. We selected 49 patients with <sup>13</sup>C urea breath test positive, long-lasting CIU and *H. pylori* infection; 20 remained symptomatic, had positive urease test or *H. pylori* histologic identification in gastric biopsy material and accepted to participate in a placebo-controlled treatment trial. They were randomized for a 7-day, double-blind, placebo-controlled *H. pylori* eradication treatment with amoxicillin, clarithromycin and omeprazol or placebo. *H. pylori* eradication was assessed by a second <sup>13</sup>C urea breath test six weeks after the end of treatment. We observed a significant improvement of more than 70% of CIU; baseline clinical score was seen in 4 of the 9 (44%) patients who eradicated *H. pylori* after active treatment and in 1 of the 7 (12,3%) of those who did not ( $p = 0.19$ ). No clinical differences in CIU characteristics were found between patients with and without improvement. No serious adverse effects were observed in either treatment group. We conclude that the eradication of *H. pylori* may be useful for patients suffering long-lasting CIU and *H. pylori* infection, although these results did not reach statistical significance probably owing to the strict conditions of the recruitment.

**Key words:** *Helicobacter pylori*. Chronic urticaria. Infection. Treatment.

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### INTRODUCTION

*Helicobacter pylori* is the most common chronic bacterial human infection worldwide. It causes some of the most prevalent gastroduodenal diseases such as peptic ulcer disease, gastric cancer and B-cell gastric lymphoma. It has also been associated with other extradigestive conditions such as cardiovascular, immunological or skin diseases (1).

Chronic urticaria is a long-lasting skin disease characterized by pruritic wheals daily or almost daily for more than six weeks. Chronic urticaria is defined as idiopathic (CIU) when all known conditions causing the disease have been ruled out.

In recent years, some studies have suggested that *H. pylori* could be involved in the pathogenesis of CIU. Hence, several studies have shown a higher prevalence of *H. pylori* infection in patients with CIU than in the general population, and occasional remissions of skin lesions have been reported after eradication treatment (2-5). However, other investigations have failed to find a significant improvement after successful eradication (6-8). These differences may be due to pitfalls of design, especially the lack of a control group, in the majority of the studies. The aim of the present study was to investigate the efficacy of *H. pylori* eradication on CIU in patients affected by both conditions, using a prospective, randomized, double-blind placebo-controlled design.

## PATIENTS AND METHODS

### Patients

Patients with chronic urticaria of more than three months' duration were recruited from the outpatient allergy clinic of a general hospital in the setting of a small Mediterranean town. All were entered in a study protocol in which data of the following were collected: physical examination, common tests for physical urticarias, complete blood count, ESR, liver and renal function tests, chest X-rays, abdominal ultrasound study, skin tests to common inhalant and food allergens, stool analysis for parasite ova, serum tests for hepatitis B and C viruses and *Treponema*, thyroid function tests, ANA, anti-thyroglobulin and anti-peroxidase antibodies, C<sub>3</sub>, C<sub>4</sub>, IgG, IgM, IgA and IgE. Patients with negative results were tested for *H. pylori* infection with a <sup>13</sup>C urea breath test (Microvir-*Helicobacter pylori*, Instituto Valenciano de Microbiología, Bétera, Spain). Patients with positive results were then scheduled for endoscopy with corpus and antral mucosa biopsies. The presence of *H. pylori* infection was established by a positive biopsy urease-test (Ballard Medical Products, Draper, Utah) or identification of *H. pylori* by histology study.

### Methods

The patients in whom *H. pylori* infection was confirmed at least by biopsy urease test or histologic identification and who remained symptomatic were randomly assigned to a 7-day double-blind, placebo-controlled treatment. The treatment consisted of amoxicillin 1 g b.i.d; clarithromycin 500 mg b.i.d and omeprazole 20 mg, b.i.d or the corresponding placebos. *H. pylori* eradication was confirmed by a second <sup>13</sup>C urea breath test six weeks after the end of treatment. The study was approved by the Ethics Committee of the Hospital and all patients gave their informed consent.

**Table I**  
**Clinical score**

Score	N <sup>o</sup> wheals	Angioedema	Itching*	Rescue treatment
0	None	None	None	None
1	1 to 6	—	Mild	Antihistamine-H <sub>1</sub>
2	7 to 12	—	Moderate	—
3	> 12	Yes	Severe	Corticosteroid

\* None: no symptoms. Mild: few symptoms, not affecting daily life, Moderate: symptoms affecting daily life. Severe: symptoms clearly modifying daily life and activities.

The effect of eradication on CIU was evaluated by a daily clinical score, including several urticaria symptoms and use of rescue treatment (table 1), measured the week before eradication therapy (baseline) and the sixth week after treatment. Only the disappearance of the urticaria or a decrease of at least 70% in the baseline score were considered as significant.

Descriptive analysis was performed using absolute and relative frequencies for categorical variables and medians and ranges for quantitative variables. Intergroup comparisons were made using the  $\chi^2$  test for categorical variables and the Mann-Whitney *U* test for quantitative variables. The level of statistical significance was set at  $p \leq 0.05$ . All analyses were performed with the statistical software package SPSS 6.1.

### RESULTS

From a total of 106 patients screened, 88 were diagnosed of CIU. The <sup>13</sup>C urea breath test was positive in 49 of these (56%). Twenty-seven patients were excluded: eight because of spontaneous disappearance of wheals, four refused to undergo endoscopy and the remaining fifteen for personal reasons, including reluctance to participate in placebo trials. In two additional patients, both Clo-test and histology failed to confirm *H. pylori* infection. Therefore, only 20 patients were included in the study. Sensitivity of the <sup>13</sup>C urea breath test compared to endoscopic tests was 91%. No patient presented gastrointestinal symptoms or endoscopic lesions.

Nine of the ten patients assigned to active treatment and three of the ten assigned to placebo eradicated *H. pylori* infection. One patient from the placebo group dropped out of the study for accidental reasons. For the final analysis and, given that the probability of spontaneous *H. pylori* eradication in adults is very small (9), we excluded the 3 patients who showed a negative second <sup>13</sup>C urea breath test after being treated with placebo.

CIU improved significantly in 4 of the 9 patients (44.4%) who eradicated *H. pylori* infection after active treatment and in 1 of the 7 (12.3%) who did not ( $p = 0.19$ ). No clinical differences in CIU characteristics were found between patients with and without improvement (table 2). No serious adverse effects were observed in either treatment group.

### DISCUSSION

The reported prevalence of *H. pylori* infection in CIU patients is high, ranging from 24 to 80% depen-

ding on the geographical area and patients' age (2, 7, 8). We found a prevalence of 56%, in agreement with other Spanish authors (4, 6) which is similar to that of the general population.

In the present study, a tendency towards improvement with successful eradication was seen, although these results did not reach statistical significance. As chronic urticaria usually shows an erratic nature and, moreover, may disappear spontaneously in the first 6 months in approximately half the patients (7, 10), very strict conditions in the trial design were established, yielding a small number of recruited patients.

Our results are in the range of previous studies, in which CIU improvement varies from 13% to almost 100% (2-4, 11). In the only other double-blind placebo-controlled study by Schnyder et al (7), only three patients eradicated *H. pylori* and, therefore, result was inconclusive.

In summary, since in some patients remission of a long-lasting urticaria after *H. pylori* eradication was observed without adverse effects, we believe that a trial of *H. pylori* eradication should be offered to patients with CIU and evidence of *H. pylori* infection. The high sensitivity of the <sup>13</sup>C urea breath test makes it the most convenient and cost-effective screening test for *H. pylori* infection in these patients. The results of this study support further investigation into the involvement of *H. pylori* infection in CIU and offer the possibility of an effective treatment for a chronic, symptomatic, quality-of-life-affecting disease.

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## RESUMEN

La infección por *Helicobacter pylori* ha sido implicada en la patogénesis de la urticaria crónica idiopática (UCI), sin embargo los resultados de los diversos estudios publicados son contradictorios. Seleccionamos 49 pacientes con UCI de larga evolución y con una prueba del aliento con urea <sup>13</sup>C positiva. De ellos 20 que estaban con síntomas activos y que presentaron una prueba de la ureasa positiva o identificación histológica de *H. pylori* en el material de la biopsia gástrica aceptaron participar en un estudio ciego con tratamiento activo controlado con

**Table II**  
**Characteristics of nine patients with and without CIU improvement after *H. pylori* eradication**

Characteristic	CIU improvement	CIU not-improved	p
N <sup>o</sup> patients	4 (44,4%)	5 (55,5%)	
Sex (M/F)	2/2 (50%)	0/5 (0%)	0.07
Age (years) *	43.5 (27-55)	42 (42-51)	0.62
Atopy (yes/no)	2/2 (50%)	1/4 (20%)	0.34
Total IgE (IU/mL)*	56 (29-310)	4.5 (17-407)	1.0
CIU duration (months)*	16 (14-120)	72 (6-492)	0.46
Baseline clinical score*	5.9 (1.7-9.5)	3.6 (1.7-10)	0.90

\* Median (range).

placebo. Para ello se aleatorizaron para tratamiento erradicador de *H. pylori* con amoxicilina, claritromicina y omeprazol durante 7 días o para placebo. La erradicación de la infección por *H. pylori* fue valorada por una segunda prueba del aliento con urea <sup>13</sup>C, 6 semanas después de acabado el tratamiento.

Los resultados mostraron una mejoría superior al 70% del baremo clínico basal en 4 de los 9 pacientes (44%) que erradicaron la infección después de realizar el tratamiento activo y en uno de los 7 (12,3%) que no lo hicieron (p=0,19). No encontramos características clínicas diferentes entre los pacientes que mejoraron y los que no. No se registraron reacciones adversas destacables en ninguno de los grupos de tratamiento.

Concluimos que la erradicación de la infección por *H. pylori* puede ser útil en algunos pacientes afectados de UCI de larga evolución con infección por *H. pylori*, aunque los resultados no llegaron a ser estadísticamente significativos debido a las estrictas condiciones del reclutamiento.

**Palabras clave:** *Helicobacter pylori*. Urticaria crónica. Infección. Tratamiento.

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## REFERENCES

1. Realdi G, Dore MP, Fastame L. *Extradigestive manifestation of Helicobacter pylori infection: fact and fiction*. Dig Dis Sci 1999;44:229-36.
2. Bohmeyer J, Heller A, Harting C, Wetenberger-Treumann M, Huchzermeyer H, Otte HG, Stadler R. *Association of chronic urticaria with Helicobacter pylori-induced antrum gastritis*. Hautarzt 1996;47:106-8.
3. Wedi B, Wagner S, Werfel T, Mans MP, Kapp A. *Prevalence of Helicobacter pylori-associated gastritis in chronic urticaria*. Int Arch Allergy Immunol 1998;116:288-94.
4. Rojo-García JM, Muñoz-Perez MA, Escudero J, Camacho F, Hergueta P, Herreras JM. *Helicobacter pylori in rosacea and chronic urticaria*. Acta Derm Venereol 2000;80:156-7.
5. Gala G, Cuevas M, Eiras P, de la Hoz B, Fernández R, Hinojosa M, Boixeda D, Losada E. *Chronic urticaria and Helicobacter pylori*. Ann Allergy Asthma Immunol 2001;86:696-8.
6. Dauden E, Jiménez-Alonso I, García-Diez A. *Helicobacter pylori and idiopathic chronic urticaria*. Int J Dermatol 2000;39:446-52.
7. Schnyder B, Helbling A, Pichler WJ. *Chronic idiopathic urticaria: natural course and association with Helicobacter pylori infection*. Int Arch Allergy Immunol 1999;119:60-3.
8. Erel F, Sener O, Erdil A, Karaayvaz M, Gür G, Çaliskaner Z, Ozangüç N. *Impact of Helicobacter Pylori and Giardia lamblia infections on chronic urticaria*. J Investig Allergol Clin Immunol 2000;10:94-7.
9. Xia HH, Taley NJ. *Natural acquisition and spontaneous elimination of Helicobacter pylori infection: clinical implications*. Am J Gastroenterol 1997;92:1780-7.
10. Champion RH. *Urticaria and angio-oedema: a review of 554 patients*. Br J Dermatol 1969;81:588-97.
11. Valsecchi R, Pigatto P. *Chronic urticaria and Helicobacter pylori*. Acta Derm Venereol 1998;78:440-2.