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Effect of *Helicobacter pylori* eradication therapy in rosacea patients

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ABSTRACT

Objective: the causal relation between rosacea and *Helicobacter pylori* infection is discussed. We evaluated the clinical evolution of rosacea after infection eradication.

Patients and methods: we have prospectively studied 44 patients diagnosed with rosacea. *Helicobacter pylori* infection was determined, and infected patients were treated with eradication therapy. The evolution of dermatological symptoms in a subgroup of 29 infected patients in whom eradication had been achieved was followed during 16.8 (± 17.8) months. Median age was 50.6 (± 14.1) years for 22 women (75.9%) and 7 men (24.1%). Clinical response according to gender and clinical subtype of rosacea was evaluated.

Results: complete improvement was observed in 10 patients (34.5%; 95% CI: 18.6-54.3%), relevant improvement in 9 (31.1%; 95% CI: 16-51%), poor improvement in 5 (17.2%; 95% CI: 6.5-36.4%), and absence of improvement in 5 cases (17.2%; 95% CI: 6.5-36.4%). No significant differences in dermatological evolution according to sex were observed. Regarding subtype of rosacea there was a relevant improvement in 83.3% (95% CI: 64.1-93.8%) of cases with papulopustular type as opposed to 36.5% (95% CI: 20-56.1%) of cases with erythematous predominance, p = 0.02.

Conclusions: based on these results, the relation between *Helicobacter pylori* and rosacea is supported, and infection should be investigated in these patients because an appreciable percentage of patients diagnosed with rosacea and *Helicobacter pylori* infection can benefit from eradication therapy, mainly in the papulopustular subtype.

Key words: Acne rosacea. Eradication therapy. *Helicobacter pylori*.

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INTRODUCTION

Since *Helicobacter pylori (H. pylori)* identification in 1983 (1), an increasing amount of knowledge has accumulated, with this agent having been directly involved in the pathogenesis of several gastroduodenal pathologies. This bacterium has also been associated with certain extradigestive conditions, including chronic urticaria, rosacea, Sjögren's syndrome, Schönlein-Henoch purpura, and ischemic heart disease, among others.

Rosacea is a chronic and relapsing inflammatory dermatosis that is characterized by the presence of persistent or transient central facial erythema and visible capillaries, often associated with papules and pustules, and which may finally develop cutaneous tuberosities (phymas). Due to the fact that rosacea mainly affects the facial region, many patients feel that their professional and social life is affected (2,3). This disease is more prevalent in females; however, male patients tend to present with more severe cases (4). The most frequent symptom in these patients is the presence of a central facial erythema lasting for at least three months; some authors have proposed that the presence of this type of erythema alone should be considered enough to establish a diagnosis of rosacea (3). This type of patients often exhibit symptoms such as periocular skin affectation, edema, plaque, dryness, ocular manifestations, and peripheral locations.

Different subtypes of rosacea have been established. In erythematotelangiectatic-type rosacea, facial redness

episodes may be prolonged (more than ten minutes), which may help differentiate it from the physiologic redness that may occasionally be seen in healthy people. Although the central facial area is the region most frequently affected, redness may also involve the periphery of the facial region, neck, ears and even the upper part of the chest (5). These episodes of redness may be spontaneous or secondary to specific stimuli, like emotional stress, hot drinks (6), alcohol (7), spices (8), exercise, cold or warm weather, and hot water baths (3). Redness is frequently associated with a burning sensation and itching; however, sweating and tachycardia are not frequently associated. Papulopustular rosacea or "classical rosacea" is characterized by the presence of persistent or episodic inflammatory changes in the central facial area, consisting of small papules that may evolve into pustules with accompanying edema. Periocular skin is generally affected. A prior history of facial redness is common, but to a lesser extent than in patients affected by the erythematotelangiectatic subtype. Most patients are middle-aged women (9), and the condition is not so frequently triggered by external stimuli (10). In phyma-type rosacea a marked thickening of the skin develops in association with superficial nodularity, which may be found in the nose (rhinophyma), ears (otophyma), chin (gnatophyma), forehead (metophyma) or eyelids (blepharophyma) (11). In ocular rosacea, the most frequent ocular manifestations are blepharitis and conjunctivitis. Iritis, scleritis and keratitis represent the most severe complications (12,13). Ocular manifestations may precede cutaneous manifestations by years (14).

The underlying etiology of rosacea remains unknown. During these last few years, several studies have suggested a potential relationship between *H. pylori* and rosacea, as it has been shown that the prevalence of *H. pylori* infection is higher in patients affected by this condiction when compared to the general population (15). Moreover, it has been described that rosacea symptoms may improve after *H. pylori* eradication (16).

In the present manuscript we aim to describe the clinical outcome of 44 unselected patients diagnosed with rosacea in whom the prevalence of *H. pylori* infection could be assessed, and whose dermatologic symptoms were followed up long-term after *H. pylori* eradication.

PATIENTS AND METHODS

Between March 1996 and December 2001 we prospectively evaluated in the Gastroenterology Outpatient Clinic a total of 44 unselected patients referred from the Dermatology Department in our hospital with the diagnosis of rosacea with or without gastrointestinal symptoms. Before referral to our service the only treatment used for their rosacea was oral antihistaminics, so these patients were not multitreated or refractory to other previous treatments.

A clinical history and full physical examination were obtained for all patients. After that, patients were invited to participate in the present study, which was conducted according to Declaration of Helsinki principles. All those who accepted to participate underwent a C^{13}-urea breath test for *H. pylori,* and values superior to 5 Delta Units were considered a positive result. *H. pylori* serologic tests (IgG antibodies using ELISA) were performed, and a value of 15 Units or higher was considered a positive result. In addition, patients included in this study were also invited to undergo an upper gastrointestinal endoscopy with biopsy following their signed informed consent. These biopsies were processed for histologic analysis (with hematoxilin-eosin and Giemsa) and for microbiologic culture (incubation for 7 days in microaerophilic conditions). In a follow-up visit, patients infected by *H. pylori* were treated with eradication therapy even when no gastrointestinal symptoms were present.

A patient was diagnosed as infected by *H. pylori* when at least two diagnostic tests (breath test, serology, histology or culture) were positive, while it was considered that a patient was not infected when all diagnostic tests were negative for *H. pylori*.

Eradication therapy for *H. pylori* infection included the oral administration of a proton-pump inhibitor (omeprazole 20 mg or pantoprazole 40 mg) associated with clarithromycin (500 mg) and amoxicillin (1 g) twice daily for one week.

Given the high reliability of breath testing for the verification of *H. pylori* eradication (17), a new test was performed two months later. In those cases with a persistent positive breath test, a second eradication treatment (quadruple therapy) was indicated, consisting of the association of pantoprazole (40 mg twice a day) with tetracycline (500 mg q.i.d.), metronidazole (500 mg t.i.d.) and colloidal bismuth subcitrate (120 mg q.i.d.) for ten days; eradication of infection was confirmed at two months following eradication therapy completion.

Patients underwent clinical monitoring with serial C^{13}-urea breath tests during follow-up visits.

The statistical analyses conducted in the present study were performed by means of the SPSS 10.0 statistical software package, with continuous variables being presented as mean, standard deviation and range, and discrete variables being presented as percentage and 95% confidence interval (95% CI). Statistical tests employed in the analysis were Student's t-test, Levene's test for the assessment of variance homogeneity, and Fisher´s exact test.

The mean age of patients included in the study was 50.4 (± 14.6) years (range: 24-78 years); thirty-four of them were females (77.3%) and ten were males (22.7%).

No significant medical history for gastrointestinal disease could be found in 90.9% of patients; one single patient had a prior history of gastric ulcer (2.3%), 3 additional patients reported prior duodenal ulcers (6.8%), and 2 of them also reported gastrointestinal bleeding.

At the time of the initial visit 17 patients were asymptomatic regarding gastrointestinal complaints (38.6%), while 23 patients presented with epigastric abdominal pain or heartburn (52.3%), and 4 patients presented with nausea and vomiting (9.1%).

Regarding rosacea subtypes in this cohort of patients, 17 patients (38.6%) were classified as predominantly having erythematous rosacea, and 27 patients had papulopustular rosacea (61.4%).

An upper gastrointestinal endoscopy was performed in 37 patients, while 7 patients refused to undergo this endoscopic examination. Endoscopic findings are displayed on table I.

Table I. Findings in oral endoscopy

Endoscopic diagnosis	*n (%)*
Duodenal ulcer	2 (5.4%)
Erosive duodenitis	2 (5.4%)
Chronic gastritis	7 (18.9%)
AIGM*	1 (2.7%)
Normal	25 (67.6%)
Total	*37 (100%)*

*AIGM: acute injury of gastric mucosa.

RESULTS

H. pylori infection was found in 37 of all 44 patients evaluated (84.1%), while 7 patients had no findings supporting *H. pylori* infection (15.9%). The group of 37 patients infected by *H. pylori* were offered eradication therapy, with 35 of them accepting it. *H. pylori* eradication was obtained in 25 patients with first-line treatment (71.4%), while 8 patients required second-line therapy (22.9%), and there were 2 patients (5.7%) that could not be eradicated after two eradication treatments.

Therefore, eradication was obtained in 33 patients, whereas the rest (patients not infected, not treated or without successful eradication) returned to the Dermatology Dept. and were treated with different therapies (antihistaminics, oral and/or topical antibiotic therapy, laser therapy, other) according to each individual case. Therefore, we cannot consider these patients for any comparison, since they did not follow a unique and protocolized treatment.

Among the group of 33 patients in whom *H. pylori* eradication was achieved, adequate follow-up could be obtained in 29 patients, while 4 patients were lost to follow-up due to patient withdrawal in one case –who did not return to revision and was not possible to locate– and residence change and loss of possibility of contact in the other 3 cases. Not knowing the clinical evolution of these 4 patients, they were not finally evaluated as with "intention to treat", and were excluded from the final analysis. Mean follow-up in the cohort of 29 patients with adequate monitorization was 16.8 (± 17.8) months; during this period, these patients were not treated with oral and/or topical antibiotics, laser therapy or any other type of therapy, except basic measures such as dietary advice, hydration or, eventually, antihistaminics.

Patient demographics in this cohort of 29 patients were not significantly different from the original group. Mean age was 50.6 (± 14.1) years (range: 24-78 years), 22 females (75.9%) and 7 males (24.1%). In this analyzed group, 11 patients (37.9%) presented with the erythematous type, and 18 (62.1%) presented with the papulopustular type.

Skin lesions were surveyed. Both the physical exploration and the patient's subjective perception were assessed. It was considered reasonable to wait a minimum of three months after eradication therapy to assess dermatological response. Ten patients showed a complete regression of symptoms and signs associated with rosacea (34.5%; 95% CI: 18.6-54.3%), with a mean follow up of 26.5 (± 20.2) months. Nine patients (31.1%; 95% CI: 16-51%) had a significant improvement in frequency and intensity of symptoms, with a mean follow-up of 8.2 (± 6.4) months. Five patients (17.2%; 95% CI: 6.5-36.4%) experienced a minor improvement in their rosacea symptoms; however, a significant reduction in the number of active episodes was noted. Mean follow-up in this group of patients was 11.5 (± 6.6) months. Finally, 5 additional patients (17.2%; 95% CI: 6.5-36.4%) showed no improvement in their cutaneous lesions during a follow-up of 15.6 (± 24.8) months. In conclusion, 19 patients showed a "good dermatological response" (total or important improvement of symptoms) *versus* 10 patients who had a "poor dermatological response" (scant improvement or no improvement).

No statistically significant differences could be identified in terms of clinical response (“good response/poor response”) of cutaneous lesions according to sex differences: males (3/7 = 42.9%; 95% CI: 25.3-62.2%)/females (16/22 = 72.7%; 95% CI: 52.8-86.7%) (p = 0.19). On the other hand, statistically significant differences in terms of patient clinical evolution were observed depending on type of rosacea (Table II), as 15 of 18 patients with papulopustular-type rosacea (83.3%; 95% CI: 64.1-93.8%) had a good response to therapy *versus* 4 of 11 patients with erythematous rosacea (36.4%; 95% CI: 20-56.1%), p = 0.02.

DISCUSSION

The etiology of rosacea remains unknown with several etiologic mechanisms posited, like degeneration of the dermal matrix, vascular etiology, and ingestion of chemical or infectious agents (3). Among them, infection by *Demodex folliculorum* (18), a bacteria that is relatively

Table II. Dermatological response after eradication based on subtype of rosacea

Rosacea subtype	*Good response*	
	Cases	*Percentage*
Papulopustular	15/18	83.3% (CI95%: 64.1-93.8%)
Erythematous	4/11	36.4% (CI95%: 20-56.1%)

p = 0.02.

common in the skin of humans, has been suggested. This hypothesis is driven by the fact that this microorganism is frequently isolated in the areas of the skin affected by rosacea (3), and also because an immunological response against *Demodex* may be detected in patients affected by rosacea (19,20). However, the prevalence of this microorganism in healthy adults reaches 100%, and because of this fact, its association with rosacea does not imply an etiopathogenic relationship (21,22).

The interest of a potential association between rosacea and *H. pylori* relies on the frequent and well-established association between rosacea and certain digestive diseases, such as gastritis, hypochloridria or a number of jejunal mucosal abnormalities (23). Among symptoms associated with rosacea, it should be noted that dyspepsia, constipation, diarrhea, and abdominal discomfort have been described. Moreover, it is typical that rosacea presents with a seasonal periodicity like peptic ulcer disease (4), and likewise it has been known for years that some antibiotics used in the eradication, as clarithromycin and metronidazole (24), can be useful to a certain extent in the management of some rosacea patients. In 1994, Rebora et al. (25) described the association between *H. pylori* and rosacea. Since then, several studies have shown an elevated prevalence of *H. pylori* infection in patients with rosacea (15, 26-28), even when compared with age- and sex-matched control patients (29). In contrast, other authors could not show a higher prevalence of infection in these patients (4,30-34).

In the present study, the prevalence of infection was 84.1% (37/44 patients), which represents a significantly higher prevalence ($p < 0.01$) *versus* the general healthy population of Madrid, which has been estimated to be around 53% by Martín de Argila et al. (35), a study that was performed using serology. Moreover, 61.4% of patients presented with digestive symptoms at the time of their initial visit, which confirms the previously known association between rosacea and gastrointestinal symptomatology. Sharma et al. (32) compared a group of 45 rosacea patients with a control group, finding that 66.7% of patients had digestive symptoms, a percentage similar to that reported in the present study. However, the prevalence of infection in this study reached only 26.7% and was assessed by means of serology, while in our group the presence of *H. pylori* was confirmed by at least two positive diagnostic tests.

It has also been described that *H. pylori* eradication may improve rosacea symptoms or even help clear cutaneous lesions (3,4); however, other authors have not been able to demonstrate improvements in these lesions (34).

In the present study, 34.5% of patients had a complete improvement of cutaneous lesions, while only 17.2% experienced no improvement at all. This improvement (complete or at least important) was more frequently found in the group with papulopustular rosacea (83.3%) than in patients with erythematous rosacea (36.4%), with differences reaching statistical significance. There have been few studies in the literature that have considered rosacea types. In a study published in 1999, Son et al. (33) found no significant differences in the outcome of rosacea after eradication depending on the type of rosacea. Contrarily, Suarez et al. (36) in 1999 demonstrated improved cutaneous symptomatology in 64% of papulopustular rosacea patients and only 14.3% of erythematous patients, which represents similar results to those described in the present study. Differences in the clinical evolution of the different types of rosacea may explain the discrepancies observed among the various studies published in the literature that have not taken into account the clinical subtype of rosacea. Regarding this point, it is important to outline the results obtained by Diaz et al. (37), who recently suggested that rosacea severity may be closely related to this bacterial infection. This may justify our results supporting a higher utility of eradication in papulopustular rosacea patients, who frequently make up for more severe cases.

In another study by Utas et al. (4), although no significant difference was found in the prevalence of *H. pylori* infection between rosacea and a control group, there was a significant improvement in the clinical symptoms of rosacea patients, but unfortunately rosacea types were not considered. Bamford et al. (38) conducted a double-blind study in which they divided rosacea patients in two treatment groups (eradication and placebo), and found a significant improvement of erythema in patients actively treated as compared to the control group, and a diminution in papules and pustules in both groups of patients.

Our results support a causal relationship between *H. pylori* and rosacea, mainly in the papulopustular type. According to this information it would be interesting to determine the presence of this infection in these patients, and to assess the possibility of eradication, which might be beneficial in a valuable percentage of patients. Up to date, according to the most recent consensus conferences (39), there was not sufficient evidence to recommend eradication in rosacea patients. Nevertheless, we believe that further investigation is mandatory in this field, as a confirmation of our results would necessary require larger, multicenter, controlled studies comparing the efficacy of eradication according to rosacea subtype, and taking into account the type of infecting bacteria, as some studies have suggested a higher prevalence of CagA-positive *H. pylori* in rosacea patients (3).

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