

INFLUENCE OF *HELICOBACTER PYLORI* INFECTION ON THE RESPONSE TO ANTIHISTAMINES TREATMENT IN CHRONIC IDIOPATHIC URTICARIA PATIENTS

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ABSTRACT

Urticaria is a common and complex disease, with a profound negative impact on the socio-economic quality of life, involving direct and indirect increased costs. According to studies, the prevalence of urticaria exceeds 20%.

The authors have proposed to assess the impact of *Helicobacter pylori* infection on the response to antihistamine treatment in patients with chronic idiopathic urticaria.

Helicobacter pylori eradication was associated with increased efficacy of the antihistamines treatment in CIU patients. Eradication of *Helicobacter pylori* infection can lead to improvement of symptoms, even if it has no direct role in the etiology of chronic idiopathic urticaria.

Key words: *Helicobacter Pylori*, antihistamine treatment, urticaria

INTRODUCTION

Urticaria is a common and complex disease, with a profound negative impact on the socio-economic quality of life, involving direct and indirect increased costs. According to studies, the prevalence of urticaria exceeds 20%.

This condition has been described since the times of Hippocrates, the current name dating from the 18th century, after the skin reaction that ensued after contact with the stinging nettle (*Urtica dioica*) (1).

In terms of evolution interval, urticaria is divided into: acute urticaria, lasting less than 6 weeks and chronic urticaria, with an evolution interval longer than 6 weeks.

Chronic urticaria can be divided into: physical urticaria, urticaria secondary to a medical condition and chronic idiopathic urticaria, the latter, with a prevalence of 35-65%.

Chronic urticaria commonly affects adults and its course is variable, estimating that 50% of patients will have a duration of disease progression over one year, on average 3-5 years, while about

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20% of patients will continue to have hives for 10 years or longer (2).

Over time, several scoring systems have been proposed to evaluate disease activity in urticaria patients. The latest version of the Guidelines suggests using UAS (Urticaria Activity Score), which is based on the assessment of key symptoms of urticaria: the number of wheals and pruritus intensity (table 1). UAS was proposed as initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the Global Allergy and Asthma European Network (GA(2)LEN), the European Dermatology Forum (EDF) and the World Allergy Organization (WAO) (3).

Daily UAS is the sum of the hives score (0-3) and pruritus score (0-3), registered in 24 hours.

Using UAS allows both doctor and patient to assess urticarial activity and response to treatment, offering the advantage of comparing results of studies performed in different centers.

TABLE 1. Assessment of disease activity in urticaria patients

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 h)	Mild (present but not annoying or troublesome)
2	Moderate (20-50 wheals/24 h)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (>50 wheals/24 h or large confluent areas of wheals)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

Sum of score (UAS): 0–6

The aim of urticaria treatment is to identify and to eliminate the underlying cause/trigger where possible and the remission/relief of symptoms.

The new generation of anti-H₁ antihistamines remain the mainstay of treatment for chronic urticaria.

In many cases, conventional dose of antihistamines is ineffective, so that in these situations, it may increase the dose of antihistamine up to 4 fold the conventional dose, as recommended by the European Academy of Allergology and Clinical Immunology (3). According to studies, 75% of cases of chronic urticaria require higher than conventional antihistamine doses (4). Even in these situations,

sometimes antihistamine therapy remains ineffective, requiring therapeutic alternatives: switching to a different anti-H₁ antihistamine, adding a first-generation H₁-antihistamine to a new-generation one, adding an anti-H₂ antihistamine or a leukotriene antagonist, short courses of corticosteroids, with variable results.

If the etiology of acute urticaria is often detected, in most cases of chronic urticaria, it is not possible to identify the cause.

Bacterial, viral, parasitic and fungal infections have been suspected as triggers for chronic urticaria. Their frequency and relevance vary between different geographical regions and different types of patients. They may be a cause, an aggravating factor or an unassociated bystander (3).

Research conducted over the years have brought up a possible role of *Helicobacter pylori* (HP) in chronic urticaria. *Helicobacter pylori* is one of the most common pathogens affecting humans, infecting approximately 50% of the world's population (5). Early research on *Helicobacter pylori* focused on gastric complications caused by this bacillus, then the studies have been oriented on the skin implications of this bacteria.

Chronic idiopathic urticaria is a common skin condition that often generate frustration for both patient and doctor because of its treatment often disappointing. A possible association between *Helicobacter pylori* infection and chronic urticaria has been proposed (6-11), hypothesis supported by the increased prevalence of *Helicobacter pylori* infection in patients with chronic urticaria and the remission of chronic urticaria after eradication of *Helicobacter pylori* infection, as reported some clinical trials.

OBJECTIVE

The authors have proposed to assess the impact of *Helicobacter pylori* infection on the response to antihistamine treatment in patients with chronic idiopathic urticaria.

MATERIAL. METHODS

We conducted a prospective study, which included 67 patients aged 18 and over, with chronic idiopathic urticaria (CIU). The study was made between December 2008 and December 2012 within the Dermatology Clinic of “Victor Babes” Hospital, Bucharest. This study was approved by Ethics Committee of the Hospital and all the patients gave

their consent for their inclusion in the research protocol.

At study entry, all patients were evaluated clinical and paraclinical, performing complete blood count, inflammatory tests (ESR, C-reactive protein, fibrinogen), liver tests (including HBS antigen and VHC antibodies), kidney and thyroid tests. We also performed screening tests to detect anti-*Helicobacter pylori* antibodies (immunochromatographic method), anti-thyroglobulin, anti-peroxidase, anti-nuclear antibodies and to assess the C3, C4, IgE serum level. Coproparasitologic tests and intradermal skin testing to autologous serum (ASST) completed the investigations.

Exclusion criteria

We excluded from study patients with urticaria vasculitis, chronic urticaria patients with known etiology: physical urticaria, cholinergic urticaria, hives caused by food allergy, medications, connective tissue and thyroid diseases, malignancies, patients who were receiving corticosteroids, immunosuppressive therapy and patients with ASST (+). We also excluded pregnant and lactating women.

Patients were divided into 3 groups depending on the presence/absence of anti-HP antibodies and the treatment protocol:

Group A included 23 HP-negative patients, UAS = 5.17 ± 0.63 , who received H1-antihistamines treatment;

Group B included 24 HP-positive patients, UAS = 5.26 ± 0.73 , who received H1-antihistamines treatment;

Group C included 20 HP-positive patients, UAS = 5.47 ± 0.36 , who received H1-antihistamines treatment and anti-HP therapy.

H1-antihistamine therapy consisted of levocetirizine 5mg in association with desloratadine 5mg, given at 12 hours. For *Helicobacter pylori* eradication, patients received twice-daily doses of omeprazole 20 mg, amoxicillin 1g and clarithromycin 500 mg for 14 days.

All groups were similar in terms of demographic characteristics and biological profile.

All the patients were evaluated at baseline, at 1, 3 and 6 months after therapy initiation, to assess Urticaria Activity Score (UAS) and anti-HP antibodies. The favorable therapeutic response was assessed by reduction of more than 50% in UAS from baseline (UAS₀).

Statistical analysis

The data were presented by mean value \pm standard derivation and analysis of the results was per-

formed using SPSS software, version 11.5, accepting that $p < 0.05$ is statistically significant.

RESULTS

Biochemical features of patients with chronic idiopathic urticaria monitored in this study are presented in the table 2.

TABLE 2. Demographic and laboratory characteristics of patients included in the study

	Lot A	Lot B	Lot C
Age (years)	52 \pm 9	48 \pm 4	50 \pm 7
Sex (M:F)	1:1.56	1:1.40	1:1.23
Area rural:urban	1:0.77	1:1.19	1:1.34
BMI (kg/m ²)	22.4 \pm 3.1	23.2 \pm 3.4	22.9 \pm 0.9
ASST	negative	negative	negative
Anti-HP antibodies	negative	positive	positive
Blood glucose (mg/dl)	79 \pm 15	82 \pm 11	86 \pm 9
Serum urea (mg/dl)	26 \pm 9	29 \pm 10	25 \pm 4
Serum creatinine (mg/dl)	0.72 \pm 0.11	0.77 \pm 0.12	0.82 \pm 0.09
AST (U/L)	16 \pm 5	13 \pm 7	17 \pm 8
ALT (U/L)	19 \pm 5	14 \pm 3	18 \pm 5
Bilirubin (mg/dl)	0.26 \pm 0.23	0.14 \pm 0.05	0.17 \pm 0.12
GGT (U/L)	12 \pm 7	17 \pm 11	12 \pm 3
Alkaline phosphatase (U/L)	81 \pm 25	97 \pm 17	103 \pm 24
Hemoglobin (g/dl)	13.5 \pm 0.9	14.1 \pm .4	13.7 \pm 0.8
RBC (cells/uL)	4.36 \pm 0.15	4.47 \pm 0.09	4.26 \pm 0.14
Platelets (cells/uL)	226 \pm 62	218 \pm 75	235 \pm 86
White blood cells (cells/uL)	6.1 \pm 1.2	6.3 \pm 0.9	5.9 \pm 0.4
Cholesterol (mg/dl)	156 \pm 18	166 \pm 23	148 \pm 17
Triglycerides (mg/dl)	88 \pm 26	79 \pm 12	81 \pm 26

BMI: body mass index, ASST: intradermal skin testing to autologous serum, AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transpeptidase; RBC: red blood cells.

The evolution of patients was assessed by reference to the values obtained before treatment:

For group A: After one month of surveillance, UAS decreased to 3.12 ± 0.98 ($p < 0.05$) and 9 patients had a reduction of more than 50% in UAS. After 3 months, UAS was 2.01 ± 1.66 , $p < 0.05$ and 19 patients had a reduction of more than 50% in UAS. After 6 months of monitoring, UAS was 0.16 ± 0.42 , $p < 0.05$ and all the patients had a reduction of more than 50% in UAS.

For group B: After 1 month of surveillance, UAS decreased to 4.62 ± 1.42 , $p > 0.05$ and 5 patients had a reduction of more than 50% in UAS. After 3 months, UAS was 3.76 ± 1.37 , $p > 0.05$ and 14 patients had a reduction of more than 50% in UAS.

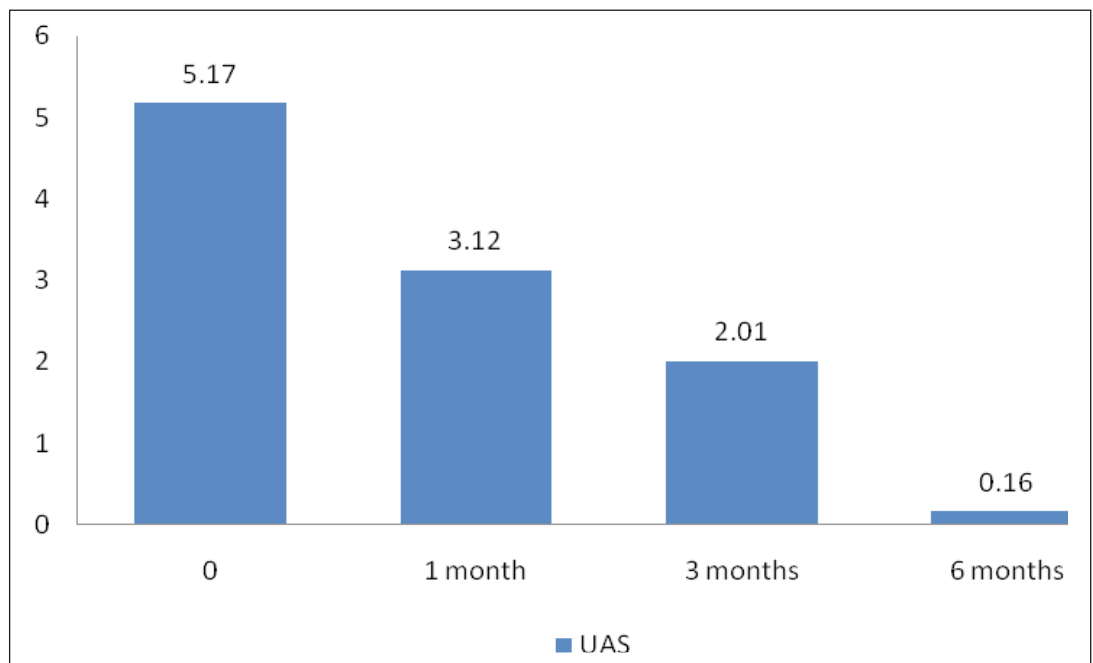


FIGURE 1. UAS variation within 6 months for group A

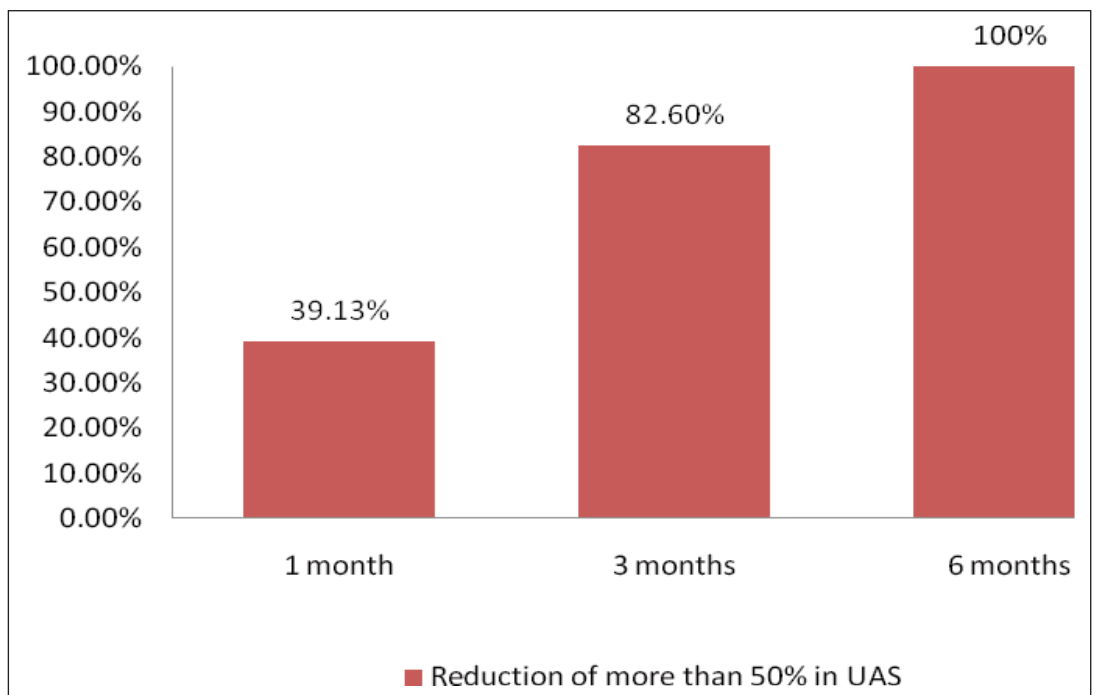


FIGURE 2. Reduction of more than 50% in UAS within 6 months for group A

After 6 months of surveillance, UAS was 1.18 ± 1.1 , $p < 0.05$ and only 19 patients had a reduction of more than 50% in UAS.

For group C: After a month of surveillance, UAS was 4.32 ± 1.65 , $p > 0.05$ and 8 patients had a reduction of more than 50% in UAS. After 3 months, UAS was 3.18 ± 1.21 , $p > 0.05$ and 17 patients had a

reduction of more than 50% in UAS. After 6 months, UAS was 0.62 ± 0.78 , $p < 0.05$ and 20 patients had a reduction of more than 50% in UAS.

By reference to baseline UAS, there was a statistically significant reduction of clinical symptoms in group A patients in all the moments of assessment. Remission of urticaria is much slower in groups B and C (Table 3).

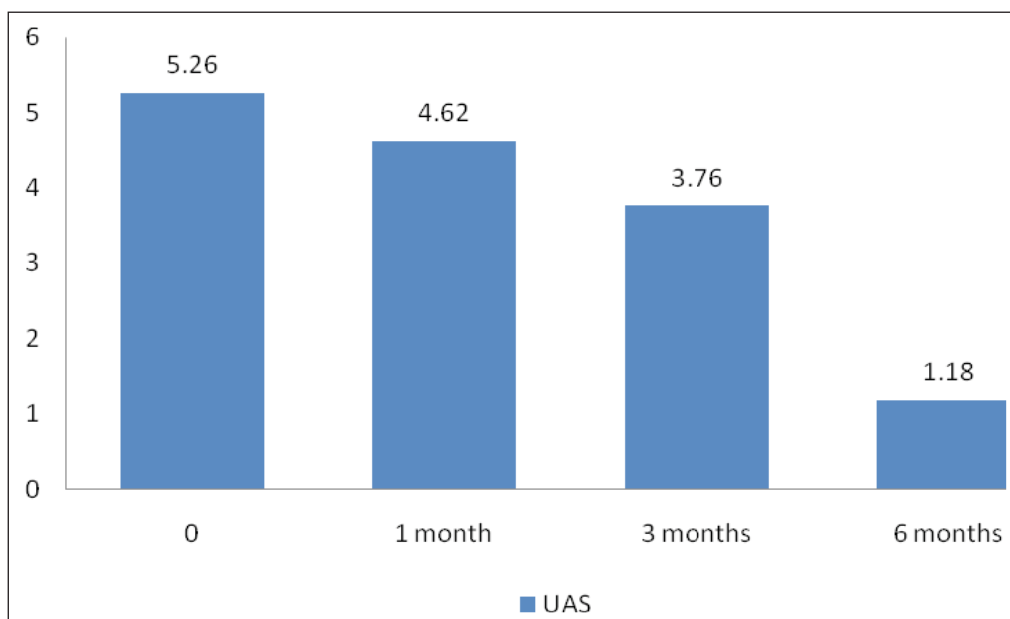


FIGURE 3. UAS variation within 6 months for group B

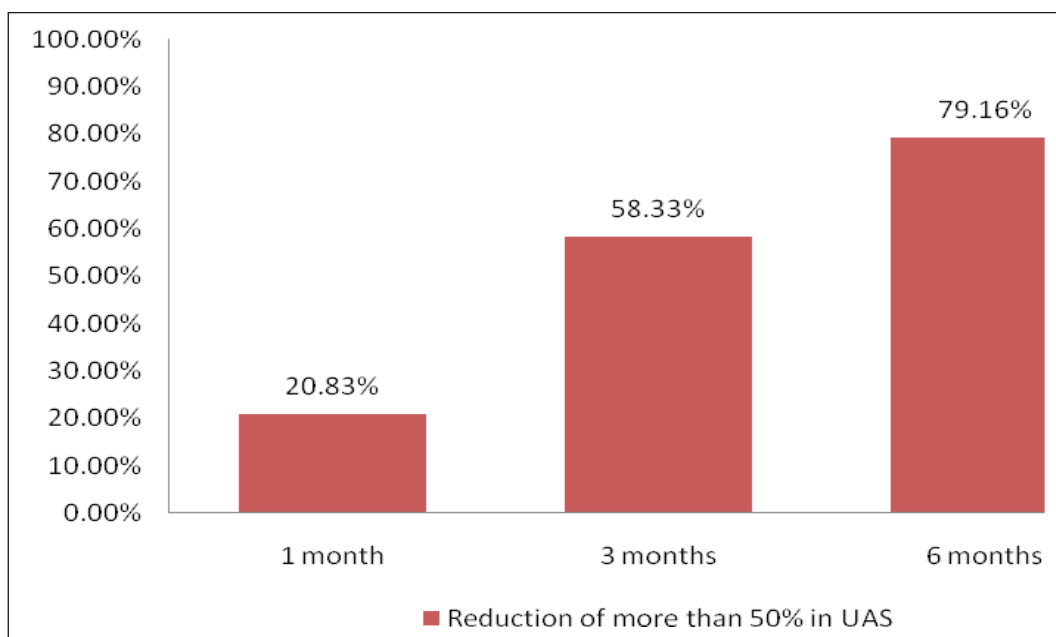


FIGURE 4. Reduction of more than 50% in UAS within 6 months for group B

TABLE 3. UAS variation within 6 months in the studied groups

UAS	Group A (n=23)	p	Group B (n=24)	p	Group C (n=20)	p
UAS ₀	5.17±0.63	-	5.26±0.73	-	5.47±0.36	-
UAS ₁	3.12±0.98	<0.05	4.62±1.42	>0.05	4.32±1.65	>0.05
UAS ₃	2.01±1.66	<0.05	3.76±1.37	>0.05	3.18±1.21	>0.05
UAS ₆	0.16±0.42	<0.05	1.18±1.1	<0.05	0.62±0.78	<0.05

UAS₀ = baseline UAS; UAS₁ = UAS at 1 month after therapy initiation, UAS₃ = UAS at 3 months after therapy initiation; UAS₆ = UAS at 6 months after therapy initiation.

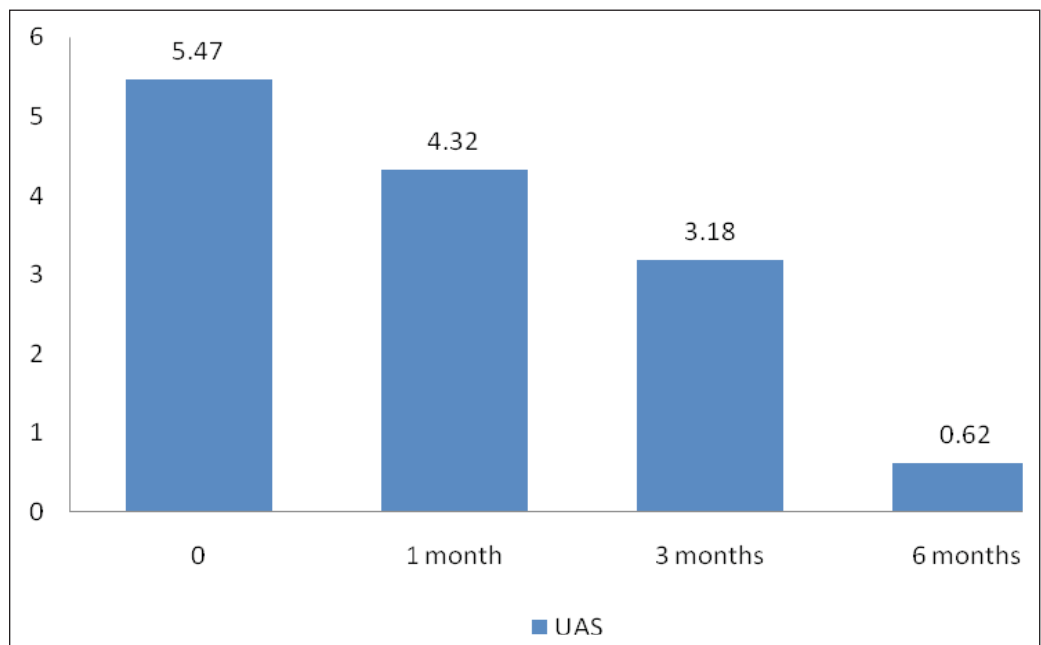


FIGURE 5. UAS variation within 6 months for group C

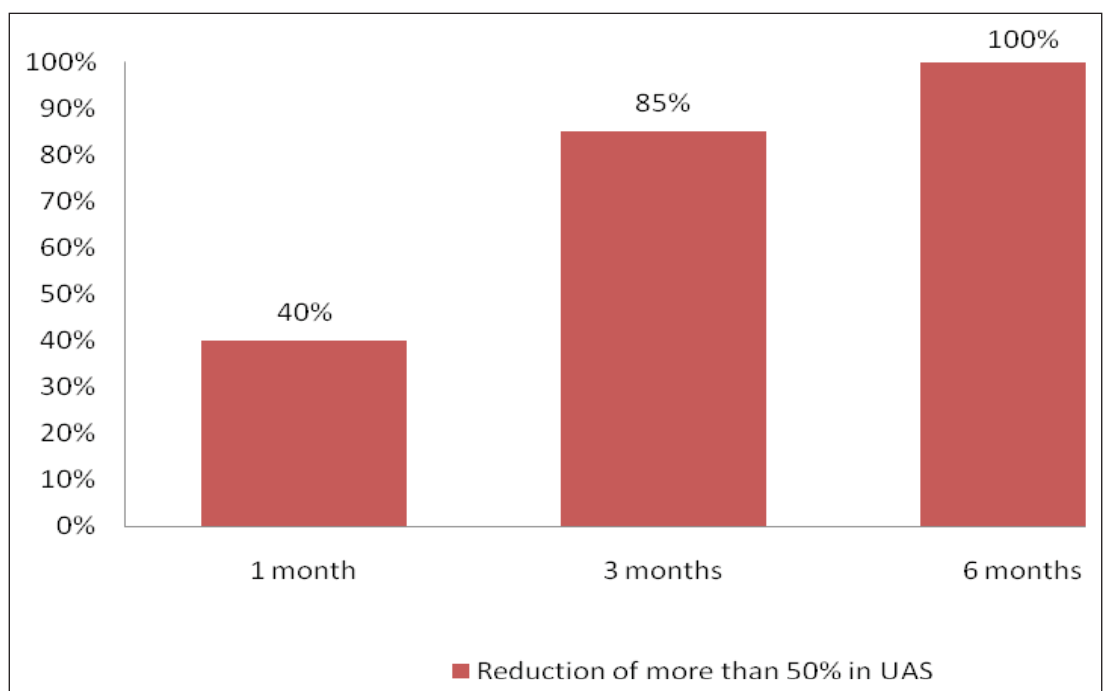


FIGURE 6. Reduction of more than 50% in UAS within 6 months for group C

DISCUSSION

It is critically important to understand that urticaria is a clinical reactive pattern and not simply "a disease" much like the fever is a symptom rather than being a disease, making the management of chronic urticaria in many cases, to be extremely difficult (12). The authors found that *Helicobacter pylori* infection affects the symptoms and H1-antihistamines therapeutic response in chronic idiopathic

urticaria (Figures 3-6). In addition, the eradication of *Helicobacter pylori* infection led to increased treatment efficacy in chronic idiopathic urticaria patients, expressed by substantially reduction of UAS in group C compared with group B (Table 3).

The *Helicobacter pylori* eradication was associated with clinical remission of urticaria, resulting in UAS reduction, even in if in our previous study, the infection has not been shown that has a direct role in the etiology of chronic idiopathic urticaria (13).

Despite numerous studies, the role of *Helicobacter pylori* in chronic urticaria is still a challenge for researchers. The pathogenic mechanisms by which *Helicobacter pylori* can induce or maintain urticaria, are not fully understood. There are several hypotheses about the role of *Helicobacter pylori* in chronic urticaria.

According to some hypotheses, an autoimmune mechanism in which molecular mimicry between *Helicobacter pylori* lipopolysaccharide (LPS) and Lewis group antigen, can occur in autoimmune type-B gastritis (14,15). Thus, positive autologous serum skin tests in patients with chronic urticaria, have been associated with *Helicobacter pylori* infection (16). In some patients with chronic urticaria, but not all, autologous serum skin tests became negative after eradication of *Helicobacter pylori* infection.

In some cases, specific IgE antibodies have been described for *Helicobacter pylori* antigens, both in patients with chronic urticaria and in patients with complete remission after eradication of *Helicobacter pylori* infection (17).

In addition, it was demonstrated that *Helicobacter pylori* can increase serum and tissue levels of nitrous oxide (NO), a free radical which plays an important role in various physiological processes in the skin, including vasodilatation, inflammation and immunomodulation (18).

Helicobacter pylori induces a strong inflammatory response in the gastric mucosa and results in the expression of a wide spectrum of cytokines, chemokines and eicosanoids such as interleukin-8 (IL-8), prostaglandin E2 (PGE2) and leukotriene B4 (LTB4).

Released from the epithelial cells, these potent proinflammatory mediators promote inflammation and tissue damage locally as well as induce migration and activation of neutrophils, macrophages, lymphocytes and plasma cells to the site of infection (19).

In *Helicobacter Pylori* infected patients with chronic urticaria significant increases in gastric eosinophil infiltration and in production of gastric juice eosinophil cationic protein production (ECP) were described and *Helicobacter pylori* eradication resulted in a significant decrease in both (20).

Another proposed mechanism is the increased gastric vascular permeability, during infection, resulting in increased exposure of the host to food allergens (21).

In support of this hypothesis, duodenal ulcer patients have a higher incidence of allergic manifestations compared with control groups (22).

On the other hand, the severity of urticarial symptoms can be related to *Helicobacter pylori* density and the intensity of inflammatory infiltration observed in the gastric biopsy (23).

Helicobacter pylori infection disturbs epithelial barrier functions and induces epithelial cell damage.

Helicobacter pylori modulates also the endocrine and physiological functions of the stomach. Studies have shown that serum pepsinogen (PG) I, sPGII and gastrin (G)-17 levels are high in the presence of *Helicobacter pylori* infection related to non-atrophic chronic gastritis, knowing the relationship between gastrin, mast cells and skin. In addition, it was demonstrated that their serum levels significantly decreased after eradication of *Helicobacter pylori* infection (19).

CONCLUSIONS

Helicobacter pylori eradication was associated with increased efficacy of the antihistamines treatment in CIU patients. Eradication of *Helicobacter pylori* infection can lead to improvement of symptoms, even if it has no direct role in the etiology of chronic idiopathic urticaria.

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