

Possible benefit from treatment of *Helicobacter pylori* in antihistamine-resistant chronic urticaria

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Summary

Background. Some patients with chronic spontaneous urticaria (CU) are resistant to conventional doses of antihistamine (AH) medications. Some research groups have reported an association between CU and *Helicobacter pylori* infection.

Aim. To determine whether *H. pylori* eradication can reverse AH resistance in CU.

Methods. We retrospectively reviewed cases of patients with CU, and recorded their Urticaria Activity Score (UAS) and results of a ¹³C-urea breath test (¹³C-UBT) for *H. pylori* infection. Patients without improvement in CU despite a full 8 weeks of AH treatment at four times the initial dose comprised the resistant CU group, while the patients who did respond comprised the responsive CU group. Patients with resistant CU and a positive ¹³C-UBT ($n = 46$) were offered a 14-day treatment with amoxicillin 1 g twice daily, clarithromycin 500 mg twice daily and omeprazole 20 mg twice daily. The effect of *H. pylori* eradication on CU was evaluated by the UAS, measured at baseline and at 8, 16, and 28 weeks after triple therapy.

Results. Of the 46 patients with resistant CU, 29 (63%) had a positive ¹³C-UBT result. Treatment eradicated *H. pylori* in 18 of the 29 patients (subgroup A), and 11 patients refused the triple therapy (subgroup B). The remaining 17 patients had a negative ¹³C-UBT result, (subgroup C). In subgroup A, baseline UAS reduced from 5.29 ± 0.94 to 3.62 ± 0.96 ($P = 0.03$) at week 8; to 1.43 ± 0.41 ($P < 0.001$) at week 16, and to 1.17 ± 0.32 ($P = 0.04$) at week 28. Five of the patients (27.8%) in this group were completely free of symptoms at week 28, whereas none of the untreated patients achieved complete remission.

Conclusion. Some patients with resistant CU might benefit from *H. pylori* eradication.

Introduction

Urticaria is considered a heterogeneous group of diseases that share a distinct skin reaction pattern, i.e. the development of urticarial skin lesions.¹ Spontaneous chronic urticaria (CU) is defined as weals arising

spontaneously without any external physical stimuli and the disease lasting > 6 weeks.¹

Patients with CU are often dissatisfied with standard therapy, and their quality of life can be impaired.² The most recent guidelines recommend non-sedating H1-antihistamine (AH) as first-line therapy, with an increase in dosage as second-line therapy, and addition of a leucotriene antagonist or switching to another AH as third-line therapy.³ Although guideline-recommended increases of up to four times the original dose result in symptom control in most affected subjects, we have found that a considerable number of patients receive only slight benefit from higher doses of AH, which is also supported by the literature.⁴

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Currently, all other treatments for AH-resistant CU are off label.

It is accepted that autoimmune mechanisms are involved in the pathogenesis of CU, and various pathogenic autoantibodies, either causing a release of histamine, or reacting with IgE epitopes or with the α -chain of Fc ϵ RI receptors, are thought to play a role.^{3,4} Assessment of these autoantibodies in clinical practice is performed by the autologous serum skin test (ASST) and by immunoassay, and a positive ASST correlates with CU exacerbation.⁵

The role of *Helicobacter pylori* infection in CU is still a matter of debate, although an association between CU and *H. pylori* has been found by some research groups.⁶ In a previous study, we found that eradication of *H. pylori* infection by triple therapy significantly reduced Urticarial Activity Score (UAS) in patients with CU, either with positive or negative ASST results, and the ASST status had no bearing on response to eradication therapy.⁷

In this study, we aimed to determine whether AH-resistant CU is associated with *H. pylori* infection and whether eradication of *H. pylori* can reverse the AH resistance.

Methods

As part of the standard practice in our allergy clinic all subjects had been informed about any risks involved with allergological investigations [skin prick test (SPT), ASST] and their written informed consent had been obtained. As these investigations are part of routine diagnostic practice in our clinic, further ethics approval was not required.

Patients

We retrospectively studied cases of adult patients aged > 18 years who were referred to the outpatient allergy clinic from Ashdod region (Ashdod, Israel) between January 2007 and January 2011 with a diagnosis of CU and/or angio-oedema of at least 6 weeks' duration. Patients with other underlying aetiologies (vasculitis, thyroid diseases, systemic lupus erythematosus, food allergy, malignancy) were excluded. In total, 385 patients were assessed, and 289 (88 men, 201 women, mean $\pm$ SD age 42.9 ± 8.7 years, range 18–69) were diagnosed as having spontaneous CU without specific aetiological factors, based on a diagnostic protocol including the stated tests in the EAACI/GA²LEN/EDF/WAO guidelines.³

At study entry, all the patients underwent physical examination, complete blood count, erythrocyte sedimentation rate measurement, liver, renal and thyroid function tests, stool analysis for parasite ova, and tests for antinuclear, antithyroglobulin and antiperoxidase antibodies, C3, C4, and IgE. Patients were excluded from the study if they were on chronic steroid treatment, were receiving any immunosuppressive medication, or had physical urticaria, cholinergic urticaria or exercise-induced urticaria (according to their medical history). To exclude physical types of urticaria, testing was carried out for dermographism, cold and heat provocation, and pressure (0.2 – 1.5 kg/cm² for 10 and 20 min) as well as a threshold test using ice cubes and warm water. All patients with CU were treated according to the current guidelines on the management of urticaria,³ including an offer to test them for *H. pylori* with a view to eradicating the infection if found.³

For CU severity assessment, patient-reported measurement of daily intensity of pruritus [range 0 (none) to 3 (severe)] and number of weals [range 0 (none) to 3 (> 50 weals/24 h or large confluent areas of weals)] were summed to create a daily UAS (range 0–6 points/day). Daily UAS results were summed over a week to create the UAS7 and a mean UAS7 (UAS:7; range 0–6 points) was used to determine differences in UAS scores.³

Antihistamine treatment and response assessment

Nonsedating H1 antihistamines were used by all patients as first-line treatment. Fexofenadine hydrochloride 180 mg four times daily (Telfast®; Sanofi-Aventis, Netanya, Israel), desloratadine 5 mg four times daily (Aerius®; Schering-Plough Hasharon Israel) or cetirizine 10 mg four times daily (Zylergy®; Dexcel Pharma Technologies Ltd, Jerusalem, Israel) are our drugs of choice for treating patients with CU. AH treatment was considered effective if the patient reported the total or near-total disappearance of weals, angio-oedema and pruritus.

Patients with significant improvement in CU using conventional doses of these AH medications were considered 'responsive' and designated as the control group. Patients with CU who did not respond sufficiently to the approved dose were given doses up to four times the original dose. No H2 blockers, corticosteroids or immunomodulatory medications were prescribed before the increase in AH medications. Any patients with persisting pruritus and recurrent weals (with or without angio-oedema) despite a full 8-week treatment period of the fourfold dose were considered as having AH treatment failure and were classified as the 'resistant' CU group.

Of the 289 patients with CU, 245 patients responded to the medication and 46 (15.9%) did not, even with four times the original AH dose. The demographic characteristics of the study groups are presented in Table 1.

Assessment of *Helicobacter pylori* Infection

The ^{13}C -urea breath test (^{13}C -UBT) for *H. pylori* was performed on all 289 patients with CU. Proton pump inhibitors, H2 antagonists or antibiotics were not permitted for 15 days before the ^{13}C -UBT was performed. Trained nurses in regional laboratories performed the ^{13}C -UBT sampling, and the samples were analysed by a mass spectrometer (AP2003; Analytical Precision, Edinburgh, UK) at the Central Laboratory, Leumit Health Services, Israel.

The patients were given 75 mg urea labelled with ^{13}C in 200 mL of orange juice, and breath samples were collected at time 0 (before C^{13} intake) and 30 min later. The cut-off $\text{C}^{12}:\text{C}^{13}$ ratio at time 30/0 min was 3.5 according to the referral laboratories and the manufacturer's instructions.

Triple therapy

Triple therapy against *H. pylori* was offered to all 29 patients with positive UBT, after they were given an explanation of the rationale and possible adverse

reactions of triple therapy. These patients received twice-daily doses of amoxicillin 1 g, clarithromycin 500 mg and omeprazole 20 mg for 14 days. The effect of this *H. pylori* eradication treatment on CU was evaluated by UAS, measured at study entry (baseline), and at 8, 16 and 28 weeks after triple therapy.

Statistical analysis

The χ^2 and the Fisher exact test (two-tailed) were used as appropriate for the comparison of categorical variables between groups. Student *t*-test (two-tailed) was used to examine continuous variables, which are expressed as mean $\pm$ SD. $P < 0.05$ was considered significant. All statistical analyses were performed using Statistica software (version 6; StatSoft Inc., Chicago, IL, USA).

Results

There were no differences between the responsive and resistant groups in urticarial weal distribution, but baseline UAS was higher in the resistant group (5.28 ± 0.81) than in the responsive group (3.32 ± 1.25 ; $P < 0.001$).

Of the 46 resistant patients with CU evaluated by the ^{13}C UBT for the presence of active *H. pylori* infection, 29 had a positive result. None of them had symptoms of

Table 1 Demographic and laboratory data of study groups.

Characteristics	Resistant CU, <i>n</i> = 46	Responsive CU, <i>n</i> = 245	<i>P</i>
Gender, M : F, <i>n</i> (%)	7 : 39 (15.2 : 84.8)	162 (66.1%)	0.33
Age, years*	42.4 ± 7.9	43.5 ± 9.1	0.44
BMI, kg/m ²	26.9 ± 4.8	27.2 ± 4.5	0.68
Positive ^{13}C UBT	29 (63%)	74 (30.2%)	< 0.01
Angio-oedema	27 (58.7%)	49 (20%)	< 0.001
Concomitant physical urticaria†	11 (23.9%)	21 (12.2%)	0.01
Baseline UAS*	5.28 ± 0.81	3.32 ± 1.25	< 0.001
Positive ASST, <i>n</i> (%)	34 (73.9)	79 (45.4) #	< 0.001
Total IgE, U/mL	114.7 ± 42.1	109.5 ± 52.4	0.52
TSH, µg/dL	2.81 ± 0.94	2.64 ± 0.86	0.23
C-reactive protein (mg/L)	8.62 ± 3.91	2.49 ± 1.34	< 0.001
ESR, mm/h	13.9 ± 11.3	15.3 ± 12.1	0.47
Blood cells, per mm ³			
White blood cells	7.1 ± 3.8	7.9 ± 4.3	0.24
Lymphocytes	2.4 ± 0.9	2.7 ± 1.1	0.08
Eosinophils	0.39 ± 0.15	0.41 ± 0.21	0.54
Basophils	0.04 ± 0.07	0.16 ± 0.13	< 0.001
Platelets	$27.3 \pm 138 \times 10^9$	$291 \pm 129 \times 10^9$	0.39

ASST, Autologous serum skin test; BMI, body mass index; CU, chronic urticaria; ESR, erythrocyte sedimentation rate; TSH, thyroid-stimulating hormone; UAS, Urticaria Activity Score; UBT, urea breath test; WBC, white blood cell count. *Under treatment with standard doses of antihistamine medications. †defined as symptomatic dermographism/dermographic urticaria and delayed pressure urticaria. ‡ASST was performed in 174 of the 245 responsive patients.

active peptic disease, therefore, upper gastrointestinal endoscopy was not performed. There were no significant differences in clinical or laboratory characteristics between UBT-positive and UBT-negative patients with resistant CU.

Only 18 of the 29 patients agreed to the treatment. *H. pylori* eradication was successful in all 18 (100%) patients, as confirmed by repeat UBT in 8 weeks after HP eradication, and these patients were defined as subgroup A. The 11 patients with positive UBT who refused the therapy were classified as subgroup B, and the 17 patients with a negative UBT were classified as subgroup C.

At week 8 (after initiation of triple therapy), baseline UAS had reduced from 5.29 ± 0.94 to 3.62 ± 0.96 ($P < 0.03$) in subgroup A; the same degree of UAS reduction was noted in both untreated subgroups B (4.38 ± 0.99 ; $P = 0.21$) and C (4.32 ± 1.05 ; $P = 0.09$). At week 16 there was an additional decrease in UAS in all three subgroups (with and without treatment), but the treatment group (subgroup A) had the most marked improvement (1.43 ± 0.41 ; $P < 0.001$) (Table 2). There was an additional reduction in UAS at week 28 in all three subgroups, with subgroup A again having the largest decrease (1.17 ± 0.32 ; $P = 0.04$) (Table 2).

At week 16, there was one patient (5.8%) who was completely symptom-free without AH treatment (this patient was in subgroup A). At week 28, there were eight patients with resistant CU in complete remission: five (27.8%) in subgroup A and three (17.6%) in

subgroup C. None of the subjects in subgroup B achieved complete remission during the study period.

Discussion

Our study shows that patients with CU experience certain clinical improvement of UAS over time. However, improvement was different between responsive and resistant patients (Table 2), and between the different subgroups of resistant patients (Table 2). Therefore, we speculate that the additional improvement in UAS in the treated patients with positive breath test (subgroup A) at weeks 16 and 28 was associated with the eradication of *H. pylori*, although the result does not exclude spontaneous remission of CU, unrelated to the triple therapy.

The role of *H. pylori* in skin diseases is still a controversial subject. The best evidence comes from a number of studies, in which CU was found to improve clinically in many patients with *H. pylori* infection once the bacterium was eradicated.^{7–10} However, recent critical appraisal of previous trials, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, found that the evidence for benefit of *H. pylori* eradication in patients with CU was weak and conflicting.¹¹ For this reason, a decision to proceed with *H. pylori* eradication should be considered carefully with regard to the risk–benefit ratio and to patient beliefs and preferences.¹¹

The pathogenetic mechanisms by which *H. pylori* may induce urticaria are still unclear, and several

Table 2 Influence of triple therapy on Urticaria Activity Score (UAS) and clinical remission rate on antihistamine (AH)-resistant chronic urticaria (CU).

	AH-resistant subgroup			Responsive CU group, <i>n</i> = 245	<i>P</i> 1	<i>P</i> 2	<i>P</i> 3	<i>P</i> 4
	A, <i>n</i> = 18	B, <i>n</i> = 11	C, <i>n</i> = 17					
UAS at baseline*	5.29 ± 0.94	5.33 ± 0.86	5.14 ± 0.75	3.32 ± 1.25	0.91	< 0.001	< 0.001	< 0.001
UAS at week 8	3.62 ± 0.96 §	4.38 ± 0.99	4.32 ± 1.05	1.14 ± 0.62 §	0.05	< 0.001	< 0.001	< 0.001
Symptom-free at week 8, <i>n</i> (%)†	0	0	0	96 (39.2)	0.99	< 0.001	< 0.001	< 0.001
UAS at week 16	1.43 ± 0.41	2.48 ± 0.86	1.91 ± 0.79	1.21 ± 0.39	0.002	0.03	< 0.001	< 0.001
Symptom-free at week 16, <i>n</i> (%)†	0	0	0	132 (58.9)	0.99	< 0.001	< 0.001	< 0.001
Symptom-free at week 16, <i>n</i> (%)‡	1 (5.8)	0	0	83 (33.9)	0.99	< 0.01	0.07	0.02
UAS at 28 weeks	1.37 ± 0.32	2.64 ± 1.15	1.84 ± 0.98	1.34 ± 0.55	< 0.01	0.61	0.06	< 0.001
Symptom-free at week 28, <i>n</i> (%)‡	5 (27.8)	0	3 (17.6%)	102 (41.6)	0.15	0.63	0.04	0.21

Subgroup A: resistant CU, positive C¹³UBT, treated for *H. pylori* infection, *H. pylori* eradicated; subgroup B: resistant CU, positive C¹³UBT, not treated for *H. pylori* infection; subgroup C: resistant CU, negative C¹³UBT; control group: CU responsive to AH drugs. *P*1: between subgroups A and B; *P*2: between subgroup A and responsive CU group (control); *P*3: between subgroup B and control; *P*4: between subgroup C and control. *UAS at presentation (before initiation of triple therapy); †completely symptom-free with standard dose AH; ‡completely symptom-free without AH treatment; §significant difference between baseline and week 8; ¶significant difference between weeks 8 and 18.

hypotheses regarding the link between bacterium and disease have been put forward. The immunomodulatory role of *H. pylori* infection in CU has been the subject of intensive study. IgG and IgA antibodies to the 19-kDa *H. pylori*-associated lipoprotein were found to play a role in the pathogenesis of CU.¹² In another study, when IgA-, IgG- and IgE-mediated immune responses against *H. pylori* antigens were analysed, some bacterial immunoresponsive proteins were identified in patients with CU.¹³ *H. pylori* can cause excessive consumption of complement by specific antibodies produced against the bacterium, contributing to the pathogenesis of CU.¹⁴ Generally, *H. pylori* causes some kind of immunomodulation in infected people, and different strains of *H. pylori* may elicit different pathogenic responses.¹⁵ Moreover, in some cases, specific IgE antibodies to *H. pylori* antigens have been described, both in patients with active CU¹⁶ and in patients with complete remission after *H. pylori* eradication.¹⁷ In *H. pylori*-infected patients with CU, significant increases in gastric eosinophil infiltration and in production of gastric juice eosinophil cationic protein (ECP) were described,¹⁸ and *H. pylori* eradication resulted in a significant decrease in both.¹⁸

CU is associated with a systemic inflammatory response, whereas the acute-phase response is characterized by increased levels of circulating interleukin-6, which varies in tandem with C-reactive protein (CRP) changes, and may be related to the urticarial activity.¹⁹ We recently reported that patients with resistant CU have higher levels of CRP and proinflammatory cytokines along with signs of platelet activation, compared with patients whose CU is well controlled with conventional doses of AH medication.²⁰ *H. pylori* triggers an intense leucocyte infiltration of the gastric submucosa, an action that is mediated by proinflammatory cytokines.²¹ At this point, we can only speculate that *H. pylori* eradication reduces the clinical severity of the disease by attenuating the proinflammatory state in resistant CU. Alternatively, treatment and eradication of *H. pylori* may improve the absorption and the bioavailability of AH medications.²²

This study has several limitations, mainly related to its retrospective nature with a small number of patients with resistant CU. Recording bias is another possible limitation. We also did not investigate possible mechanisms of *H. pylori* eradication in the pathophysiology of AH resistance in CU.

Nevertheless, it seems possible that eradication of *H. pylori* can have a beneficial effect on patients with CU resistant to AH medication. Future prospective

studies should clarify whether this type of treatment schedule has an effect on the remission rate of such patients.

What's already known about this topic?

- An association between CU and *H. pylori* infection has been found by several research groups.
- Some patients with CU are resistant to AH drugs.

What does this study add?

- To our knowledge, this is the first study investigating an association of AH-resistant CU with *H. pylori* infection.
- Some patients with resistant CU will possibly benefit from *H. pylori* eradication.

References

- 1 Zuberbier T, Asero R, Bindslev-Jensen C *et al*. EAACI/GA²LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy* 2009; **64**: 1417–26.
- 2 Staubach P, Eckhardt-Henn A, Dechene M *et al*. Quality of life in patients with chronic urticaria is differentially impaired and determined by psychiatric comorbidity. *Br J Dermatol* 2006; **154**: 294–8.
- 3 Zuberbier T, Asero R, Bindslev-Jensen C *et al*. EAACI/GA²LEN/EDF/WAO guideline: management of urticaria. *Allergy* 2009; **64**: 1427–43.
- 4 Staevska M, Popov T, Kralimarkova T *et al*. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. *J Allergy Clin Immunol* 2010; **125**: 676–82.
- 5 Tong LJ, Balakrishnan G, Kochan JP *et al*. Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol* 1997; **99**: 461–5.
- 6 Hizal M, Tuzun B, Wolf R, Tuzun Y. The relationship between *Helicobacter pylori* IgG antibody and autologous serum test in chronic urticaria. *Int J Dermatol* 2000; **39**: 443–5.
- 7 Magen E, Mishal J, Schlesinger M, Scharf S. Eradication of *Helicobacter pylori* infection equally improves chronic urticaria with positive and negative autologous serum skin test. *Helicobacter* 2007; **12**: 567–71.
- 8 Gaig P, Garcia-Ortega P, Enrique E *et al*. Efficacy of the eradication of *Helicobacter pylori* infection in patients with

- chronic urticaria. A placebo-controlled double blind study. *Allergol Immunopathol (Madr)* 2002; **30**: 255–8.
- 9 Fukuda S, Shimoyama T, Umegaki N *et al*. Effect of *Helicobacter pylori* eradication in the treatment of Japanese patients with chronic idiopathic urticaria. *J Gastroenterol* 2004; **39**: 827–30.
- 10 Akashi R, Ishiguro N, Shimizu S, Kawashima M. Clinical study of the relationship between *Helicobacter pylori* and chronic urticaria and prurigo chronica multiformis: effectiveness of eradication therapy for *Helicobacter pylori*. *J Dermatol* 2011; **38**: 761–6.
- 11 Shakouri A, Compalati E, Lang DM, Khan DA. Effectiveness of *Helicobacter pylori* eradication in chronic urticaria: evidence-based analysis using the Grading of Recommendations Assessment, Development, and Evaluation system. *Curr Opin Allergy Clin Immunol* 2010; **10**: 362–9.
- 12 Bakos N, Fekete B, Prohaszka Z *et al*. High prevalence of IgG and IgA antibodies to 19-kDa *Helicobacter pylori*-associated lipoprotein in chronic urticaria. *Allergy* 2003; **58**: 663–7.
- 13 Mini R, Figura N, D'Ambrosio C *et al*. *Helicobacter pylori* immunoproteomes in case reports of rosacea and chronic urticaria. *Proteomics* 2005; **5**: 777–87.
- 14 Farkas H, Gyeney L, Majthényi P *et al*. Angioedema due to acquired C1-esterase inhibitor deficiency in a patient with *Helicobacter pylori* infection. *Z Gastroenterol* 1999; **37**: 513–18.
- 15 Tokunaga Y, Shirahase H, Yamamoto E *et al*. Semiquantitative evaluation for diagnosis of *Helicobacter pylori* infection in relation to histological changes. *Am J Gastroenterol* 1998; **93**: 26–9.
- 16 Gala OG, Cuevas AM, Erias MP *et al*. Chronic urticaria and *Helicobacter pylori*. *Ann Allergy Asthma Immunol* 2001; **86**: 696–8.
- 17 Shiotani A, Okada K, Yanaoka K *et al*. Beneficial effect of *Helicobacter pylori* eradication in dermatologic diseases. *Helicobacter* 2001; **6**: 60–5.
- 18 Ojetti V, De Armuzzi A, Luca A *et al*. *Helicobacter pylori* infection affects eosinophilic cationic protein in the gastric juice of patients with idiopathic chronic urticaria. *Int Arch Allergy Immunol* 2001; **125**: 66–72.
- 19 Kasperska-Zajac A, Sztylec J, Machura E, Jop G. Plasma IL-6 concentration correlates with clinical disease activity and serum C-reactive protein concentration in chronic urticaria patients. *Clin Exp Allergy* 2011; **41**: 1386–91.
- 20 Magen E, Mishal J, Zeldin Y, Schlesinger M. Clinical and laboratory features of antihistamine-resistant chronic idiopathic urticaria. *Allergy Asthma Proc* 2011; **32**: 460–6.
- 21 Tüzün Y, Keskin S, Kote E. The role of *Helicobacter pylori* infection in skin diseases: facts and controversies. *Clin Dermatol* 2010; **28**: 478–82.
- 22 Lahner E, Annibale B, Delle Fave G. Systematic review. *Helicobacter pylori* infection and impaired drug absorption. *Aliment Pharmacol Ther* 2009; **29**: 379–86.