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Efficacy of *Helicobacter pylori* eradication in raising platelet count in adult patients with idiopathic thrombocytopenic purpura

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Background and Objectives. There are data consistent with an association between idiopathic thrombocytopenic purpura (ITP) and *Helicobacter pylori* (HP) infection. In addition, a significant increase of platelet count following HP eradication has been reported in a proportion of ITP patients. We describe here our experience on the efficacy of anti-HP treatment in ITP patients.

Design and Methods. Between December 1998 and May 2001 sixteen adult patients with ITP and documented HP infection were treated with standard antibiotic therapy for HP eradication (amoxicillin and clarithromycin plus pantoprazole combination). Of these patients, 7 had untreated ITP with mild/moderate thrombocytopenia (median platelet count 70×10^9/L, range 41-91), 5 had relapsed following a previous steroid treatment (median platelet count 39×10^9/L, range 30-90) and 4 were refractory to steroids (median platelet count 18.5×10^9/L, range 9-30).

Results. An improvement of platelet count was observed in 11/15 patients (73.3%) who achieved HP eradication. The difference between the mean platelet count ± SD before and after HP eradication was statistically significant ($51.6\pm28.2\times10^9$/L vs. $143.3\pm131.1\times10^9$/L; p=0.01). Complete or partial responses were obtained in 11/16 treated patients (68.7%). This result still persisted after a median follow-up of 11.7 months.

Interpretation and Conclusions. Our data confirm the efficacy of *Helicobacter pylori* eradication in increasing platelet count in adult ITP patients.

Key words: idiopathic thrombocytopenic purpura, *Helicobacter pylori*, thrombocytopenia.

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Helicobacter pylori (HP), has been considered for years as only the etiologic agent of gastritis, peptic ulcer, gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphomas. More recently, HP has been found to be associated with a number of autoimmune disorders, such as rheumatoid arthritis, autoimmune thyroiditis,[1-3] and adult idiopathic thrombocytopenic purpura (ITP).[4,5] Many interpretations have been suggested, but the underlying pathogenetic mechanisms are still unclear.[6,7] We evaluated the efficacy of HP-eradicating treatment in untreated ITP patients and in patients with poor or no response to conventional ITP therapy.

Design and Methods

Between December 1998 and May 2001 we investigated the presence of gastric HP infection in 35 adult ITP patients consecutively admitted to our Institution. ITP was diagnosed on the basis of the presence of isolated thrombocytopenia (platelets $<100\times10^9$/L) and megakaryocytic bone marrow hyperplasia. Other causes of thrombocytopenia (drugs, pseudothrombocytopenia, hepatitis C virus infection, human immunodeficiency virus infection, autoimmune disorders, etc.) were excluded. We documented HP infection by the urea breath test in 25/35 patients (71.4%). In 12 of them (48.0%) HP infection was also confirmed by histologic examination of gastric biopsies. Nine patients (36%) showed a stable remission after standard steroid treatment (prednisone 1 mg/kg daily for 3 weeks, then gradually lowered during the following 4 weeks until withdrawal). The remaining 16 patients (64%; median age 55 years, range 33-78) received standard antibiotic therapy for HP eradication (amoxicillin 1 g twice a day and clarithromycin 250 mg three times a day for 7 days plus pantoprazole 20 mg twice a day for 20 days). The duration of follow-up time between ITP diagnosis and antibiotic therapy was 16.4 months (range 3-40). Patients were divided into three groups: group 1: (n=7) pre-

viously untreated patients (with mild/moderate thrombocytopenia; median platelet count 70×10^9/L, range 41-91); group 2: (n=5) relapsed patients (after 1 or more cycles of steroids; median platelet count 39×10^9/L, range 30-90); group 3: (n=4) refractory patients (resistant to different treatments, including steroids, splenectomy, high dose intravenous immunoglobulins, danazole or cyclosporine and severely symptomatic; median platelet count 18.5×10^9/L, range 9-30).

Antibiotic therapy was started in group 2 patients at least 1 month after the withdrawal of steroids; by contrast, we administered the antibiotics to group 3 patients during their steroid therapy (prednisone 25 mg daily); this latter was withdrawn at the end of the HP treatment. HP eradication was assessed by the urea breath test two months after antibiotic therapy. The platelet count was monitored monthly during the first year and every 3 months thereafter. Response to treatment was defined as complete (CR) if the platelet count was above 150×10^9/L and partial (PR) if platelet count was between 50 and 150×10^9/L. All other patients were considered as non-responders (NR).

Results

HP eradication was achieved in 15/16 (93.7%) patients. Table 1 shows the main clinical features of patients at diagnosis and their response to antibiotic treatment. All seven patients of group 1 no longer had evidence of HP at a gastric level. As far as platelet count is concerned, one of these patients (#2) achieved CR and 4 (#3, 4, 5, and 7) reached PR. Two patients (#1 and 6) were non-responders. In group 2, HP eradication was obtained in 4/5 cases (80%). Among these, 2 patients (#8 and 12) achieved CR, 1 patient (#11) PR and 1 patient (#9) did not respond to treatment. One of the 5 patients (#10) was still positive for HP and had no improvement in platelet count. In group 3 all the 4 patients became negative for HP: 1 patient (#15) achieved a CR, 2 patients (n.13 and 16) showed a PR and 1 patient (#14) did not respond. This last patient did, however, have an improvement of platelet count and did not require further platelet transfusions. At present all patients are free from immunosuppressive treatment. Overall, 11/16 HP positive patients (68.7%) have achieved a significant response to antibiotic therapy (4 CR, 7 PR) and this result persists after a median follow-up of 11.7 months (range 6-28 months). The difference between the mean platelet count±SD before and after HP therapy is statistically significant ($51.6\pm28.2\times10^9$/L vs. $143.3\pm131.1\times10^9$/L; p=0.01).

Table 1. Response to eradicating therapy in 16 patients with idiopathic thrombocytopenic purpura (ITP) and *Helicobacter pylori* infection.

			Platelet count ($\times10^9$/L)			
Patients	*Age/Sex*	*HP eradicated*	*At diagnosis*	*Before HP therapy (6 mo.)*	*After HP therapy*	*Platelet response*
Group 1						
1. BE	55/F	Yes	67	90	110	NR
2. CL	56/F	Yes	42	70	153	CR
3. MF	62/M	Yes	56	55	107	PR
4. SM	43/M	Yes	81	91	130	PR
5. TE	61/F	Yes	42	41	140	PR
6. TG	67/F	Yes	57	67	85	NR
7. VP	70/M	Yes	77	88	140	PR
Median (range)			57 (42-81)	70 (41-91)	130 (85-153)	
Group 2						
8 MG	78/M	Yes	10	34	271	CR
9. PS	55/M	Yes	7	30	15	NR
10. CG	53/F	No	53	55	51	NR
11. CP	33/F	Yes	50	39	100	PR
12. GP	38/F	Yes	60	90	184	CR
Median (range)			50 (7-60)	39 (30-90)	100 (15-271)	
Group 3						
13. BL	64/F	Yes	5	30	104	PR
14. CM	35/F	Yes	22	17	48	NR
15. DVN	64/F	Yes	11	9	581	CR
16. MA	55/F	Yes	5	20	75	PR
Median (range)			8 (5-22)	18.5 (9-30)	89.5 (48-581)	
Total median (range)			46 (5-81)	48 (9-91)*	108.5 (15-581)*	

Group 1 included patients with mild/moderate ITP and no bleeding, who had never required immunosuppressive therapy; group 2 included ITP patients who had relapsed after steroid therapy; group 3 included patients with refractory ITP. HP, Helicobacter pylori; F, female; M, male; CR, complete response; PR, partial response; NR, no response.
**The difference between the mean platelet count before and after H. pylori therapy was statistically significant (p=0.01).*

Discussion

Idiopathic thrombocytopenic purpura is an autoimmune disease caused by autoantibodies against platelets.[8] Steroids are considered the most effective therapy for symptomatic ITP in adults and for those with a platelet count of 30×10^9/L or less. Despite this approach, most patients relapse when steroids are withdrawn and only 10-30% of them maintain a durable remission.[9] Recently, a number of studies[4,5] reported a frequent association between HP infection and thrombocytopenia and in most of them a variable increase of platelet count was observed after HP eradication.[4,5,10,12] However, these results have not been confirmed by other studies and are still debated.[7,12]

In our 16 HP-positive ITP patients, HP was eradicated in all patients but one following antibiotic therapy. These results are in agreement with those

previously reported by Gasbarrini *et al*.[5] HP eradication led to a substantial increase of platelet count in 11/16 patients, and the difference was statistically significant. All these patients showed a stable platelet count with no need of further therapy after a median follow-up of 11.7 months. The remaining 5/16 patients showed little or no response to treatment and 1 of them was still HP positive at the end of treatment. A sustained platelet increase following HP eradication was observed in all three groups of patients, i.e. untreated, relapsed and refractory patients. Eradication therapy was particularly effective in the group of patients who had never been treated with immunosuppressive therapy (group 1). The entity of platelet count improvement in this group of patients is too high to be considered as random. In addition, the response to treatment of the patients with refractory, severe ITP requiring continuous immunosuppressive therapy (group 3) appears quite impressive since HP-eradication dramatically improved their quality of life, liberating them from immunosuppressive therapy and transfusions. Our data provide further support to the evidence of a pathogenetic role of HP infection in ITP and a therapeutic role of HP eradication in a good proportion of ITP patients. Consequently, the assessment of HP gastric infection may become crucial in ITP patients at diagnosis, since it can drive the therapeutic approach towards a less immunosuppressive, but equally effective treatment.

Contributions and Acknowledgments

DV takes primary responsibility for the paper; DV and GP designed the study; all the authors contributed to data analysis and interpretation, and to the preparation of the final manuscript. MF created Table 1. DV was the principal investigator of the study.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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Peer Review Outcomes

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Douglas Cines, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Professor Cines and the Editors. Manuscript received June 26, 2002; accepted September 27, 2002.

What is already known on this topic

The relationship between infection with *H. pylori* and the development of ITP has become an exciting and controversial area of investigation with implications both for understanding pathogenesis and effective patient management.

What this study adds

There have been stark differences reported both as to the prevalence of *H. pylor*i in ITP patients and the responsiveness of ITP to successful eradication of infection. Variation in host populations, criteria for infection, definition of response and potentially differences in genetic strain may account for these discrepancies.

Potential implications for clinical practice

This study sets the stage for much needed placebo-control trials as well for more detailed mechanistic investigation into the relationship between the host response to *H. pylori* infection and the development of platelet-reactive autoantibodies.

Douglas Cines, Associate Editor (Philadelphia, USA)