Idiopathic thrombocytopenia and *Helicobacter pylori* infection: platelet count increase and early eradication therapy

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Dear Sir,

Steroid therapy is the first-line treatment for autoimmune thrombocytopenias requiring immunosuppressive therapy. Splenectomy, thrombopoietin receptor agonists and rituximab are considered treatments for relapsed thrombocytopenias. However, for some years it has been proposed that *Helicobacter pylori (H. pylori)* eradication therapy could be used to treat infected patients with chronic idiopathic thrombocytopenia (ITP). Indeed, in 1998 some Japanese authors reported the case of an elderly patient with chronic ITP who was treated with a proton pump inhibitor because of a concomitant peptic ulcer and who had a significant increase in platelet count[1]. Subsequently, Gasbarrini *et al*.[2] reported significant increases in platelet counts in eight of eleven patients with ITP in whom *H. pylori* infection was successfully eradicated: this increase was accompanied, in six of the eight patients, by the disappearance of antiplatelet antibodies. Since then, *H. pylori* eradication has been variably associated with substantial and persistent improvements of platelet count in patients with ITP. The percentages of partial and complete responses reported in various studies and meta-analyses are around 50% in Japanese and Italian populations and lower in trials in France, Spain and North America[3].

Following these results, ITP is currently one of the two extra-intestinal pathologies for which *H. pylori* eradication is indicated according to the Third Consensus Conference in Maastricht and a search for *H. pylori* is listed among the first-line tests for the diagnosis of ITP in the new guidelines for the diagnosis and treatment of ITP in the recent International Consensus Report[4]. As yet no distinctive clinical characteristics or specific factors predicting the platelet response to infection eradication therapy have been identified; it does, however, seem that ITP of long duration and profound thrombocytopenia (platelet count below 30,000/μL) respond less well to eradication therapy, although this aspect was not systematically investigated in most of the studies so far, in which patients treated usually had moderate thrombocytopenia. In this study we, therefore, evaluated whether the duration of thrombocytopenia prior to treatment could influence the effect of *H. pylori* eradication therapy in patients with ITP. We analysed 46 consecutive patients with ITP (platelet counts below 30,000/μL) who were seen at our Haematology Department between 2001 and the end of 2008 and for whom follow-up data for at least 1 year were available.

The diagnosis of ITP was made by excluding other possible causes of thrombocytopenia such as EDTA-related pseudothrombocytopenia, infections by hepatitis C virus and human immunodeficiency virus, drugs, autoimmune diseases and lymphoproliferative disorders. Bone marrow studies and chromosome mapping was carried out in patients over 60 years old in order to exclude possible myelodysplastic syndromes. Results from 40 of the 46 patients initially enrolled could be evaluated; two cases of pregnancy-related ITP with a follow-up shorter than 1 year were excluded and four cases were lost from follow-up. The patients' median age was 52.2 years (range, 15-87 years). There were 20 males and 20 females, 38 Caucasians and two patients from South America. The median platelet count at the time of the first observation was 9,000/μL (range, 1,000-24,000/μL).

For the 40 patients analysed it was determined whether tests for *H. pylori* infection had been conducted and the mean duration of the

Blood Transfus 2011;9:340-2 DOI 10.2450/2011.0014-10

thrombocytopenia prior to the first observation in our Division. Furthermore, the behaviour of the platelet counts was compared between *H. pylori*-positive patients who received eradication therapy and patients who were *H. pylori*-negative.

Thirty-four of the patients had new-onset ITP, while six patients had a recurrence of thrombocytopenia that had been diagnosed and followed in other centres. Of these six patients, four had recurrences after treatment with steroids and immunoglobulins and two had relapsed after splenectomy.

Investigations for *H. pylori* had been carried out in 22/40 of the patients (55%); 12/22 (54.5%) patients were positive and 10/22 (45.5%) negative. The mean platelet count at the time of the first observation was similar between the *H. pylori*-positive and -negative patients (9,583.3±3,987.6/μL versus 12,000±9,568.4/μL; p=0.74). The 22 patients in whom *H. pylori* was looked for included three with recurrent ITP at the time of first observation; it is interesting to note that all three of these patients were positive for the infection. All the patients had received immunosuppressive therapy (steroids or steroids combined with immunoglobulins), given their marked thrombocytopenia. Eradication therapy in *H. pylori*-positive patients was carried out within 4 months of the first observation and consisted of amoxicillin 1 g twice daily and clarithromycin 500 mg twice daily, both for 7 days, together with omeprazole 20 mg twice a day for 14 days. The efficacy of the eradication therapy was evaluated at least 12 weeks after its completion.

A response was defined as a platelet count of 100,000/μL or more, 1 year after the first observation without the need for further treatment. First-line immunosuppressive therapy led to a complete remission in 11 patients (57.14%); 6/12 (50%) patients were *H. pylori*-positive and 5/10 (50%) were *H. pylori*-negative. The complete remission was maintained for 1 year in 3/6 *H. pylori*-positive patients in whom the infection was eradicated and in 4/5 of those who were *H. pylori* negative. One *H. pylori*-positive patient who was unresponsive to immunosuppressive therapy was resistant to the eradication treatment. There were no statistically significant differences at 1 year between *H. pylori*-positive and -negative patients, with regards to the type of response and age, sex or median platelet count at the time of diagnosis. However, in *H. pylori*-positive patients there was a statistically significant (p=0.01) inverse correlation between the duration of the thrombocytopenia before eradication and the response at 1 year: this was also confirmed in multivariable analysis.

The mean duration of the thrombocytopenia in *H. pylori*-positive patients was longer than that of uninfected patients (52.7±116.1 months versus 2.8±1.9 months), given that all the patients with relapsed thrombocytopenia at the time of the first observation belonged to the infected group. However, even when the cases with recurrent ITP at first observation were excluded, the mean duration of thrombocytopenia was longer in the *H. pylori*-positive patients than in the *H. pylori*-negative ones (4.3±2.1 months versus 2.8±1.9; p=0.04). The results of our study do not show a benefit of eradicating *H. pylori* infection in patients with marked thrombocytopenia, since the percentage of complete remissions was about 27% at 1 year, in line with published data. However, our study did confirm that early eradication therapy, started promptly when the thrombocytopenia was still moderate, was more effective: reducing the bacterial load and blocking the initial platelet destruction independent of the production of auto-antibodies could decrease the formation of cross-reacting antibodies, thus switching off the autoimmune mechanism that perpetuates the thrombocytopenia. Alternatively, increased clearance by the reticulo-endothelial system means that the bacterial antigens are presented to T-lymphocytes which, stimulated, amplify the humoral response against *H. pylori*. Somatic mutations of the antibody repertoire could lead to the formation of a second generation of immunoglobulins able to recognise bacterial antigens bound to the platelets or which cross-react with platelet antigens, increasing platelet destruction. In cases of long-lasting ITP it is possible that, following further somatic mutations, a third class of antibodies develops which lose antigenic specificity against bacterial antigens but maintain reactivity against platelets: in this phase, eradication therapy would be totally ineffective[5]. In conclusion, on the basis of our results, the promptness of investigations for the presence of *H. pylori* infection and eradication treatment in positive cases could explain, alongside the severity

of the thrombocytopenia, possible virulence factors of the different strains of *H. pylori* and particular genetic features of the infected individuals, some of the differences in the published results concerning the efficacy of such eradication treatment.

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Received: 18 November 2010 - Accepted: 16 December 2010
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