The association between platelet autoantibody specificity and response to intravenous immunoglobulin G in the treatment of patients with immune thrombocytopenia

We retrospectively investigated the association between platelet autoantibody specificity and response to intravenous immunoglobulin G (IVIG) in 17 patients with immune thrombocytopenia (ITP). Platelet-associated antibodies against glycoprotein (GP) IIb/IIIa, GPIb/IX, and GPIa/IIa were detected in 13, 10, and 8 patients, respectively. A response occurred in 7 of 7 patients without anti-GPIb/IX, but in only 3 of 10 patients with anti-GPIb/IX ($p<0.01$). There was no difference in the response rates in patients with or without anti-GPIIb/IIIa or anti-GPIa/IIa. We conclude that ITP patients with anti-GPIb/IX may be less responsive to IVIG.

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Intravenous immunoglobulin G (IVIG) is an effective treatment for immune thrombocytopenia (ITP) but has significant limitations. In a randomized trial comparing IVIG and high dose methylprednisolone, 76% of patients treated with IVIG achieved a platelet count of ≥50×10⁹/L within the first 4 days. Unfortunately, responses were usually transient, with a median time to treatment failure of only 41.5 days.[1] Moreover, IVIG is a costly treatment and may potentially cause serious complications such as thrombosis.[2] It is not yet possible to predict reliably on clinical grounds which patients will benefit from IVIG. While the mechanism of action of IVIG remains incompletely understood, one prevailing hypothesis is that IVIG blocks Fcγ receptors on macrophages and thus prevents the uptake of autoantibody-coated platelets by reticuloendothelial cells.[3] Platelet surface glycoproteins (GP) IIb/IIIa and Ib/IX are the two most common target antigens in ITP.[4] A study by Nieswandt *et al.* using a murine model of ITP strongly suggested that the identity of the target antigen recognized by antiplatelet antibodies determines the mechanism of platelet destruction. In contrast to anti-GPIIb/IIIa, F(ab)$_2$ fragments of anti-GPIbα induced thrombocytopenia with the same intensity as intact antibodies. These data support an Fc-independent mechanism of platelet destruction by anti-GPIbα.[5] Based on these findings, a recent study by Webster *et al.* tested the hypothesis that IVIG may not be equally effective in preventing ITP caused by anti-GPIIb/IIIa versus anti-GPIbα in mice. They found that pre-treatment with IVIG prevented ITP in all of the anti-GPIIb/IIIa (JON1, JON2, JON3)-treated mice. Conversely, IVIG failed to prevent ITP in all anti-GPIbα (p0p3, p0p5, p0p9, p0p11)-treated mice, except for the p0p4 ones.[6] These data are intriguing and may have potential clinical implications.

The aim of this study was to investigate whether platelet autoantibody specificity is associated with response to IVIG treatment in patients with ITP. After obtaining approval from our Institutional Review Board, we retrospectively reviewed the clinical history of ITP patients who had platelet autoantibody tests performed and had received IVIG for the treatment of thrombocytopenia between 2000 and 2006. ITP was diagnosed by clinical criteria. Since it became available to our institution as a referral test in 2000, platelet autoantibody testing is being performed ever more frequently when a diagnosis of ITP is suspected. All platelet autoantibody tests were performed by the Blood Center of Wisconsin (Milwaukee, WI, USA) using the PakAuto assay (GTI, Brookfield, WI, USA). This commercially available GP-specific solid phase enzyme-immunoassay is designed primarily to detect autoantibodies reactive with platelet GPIIb/IIIa, GPIb/IX, or GPIa/IIa. The sensitivity, specificity, positive, and negative predictive values were reported to be 53%, 72%, 90%, and 24%, respectively.[7] A test is considered positive when an autoantibody is detected in the patient's eluate (platelet-associated). IVIG was generally given at a dose of 1 g/kg/day intravenously for 2 days, each infusion over a period of 4 to 6 hours. A

Table 1. Patients' demographics, clinical findings, and response to intravenous immunoglobulin G.

Patient	*Age (years)*	*Sex*	*Disease duration (months)*	*Platelet count (×10⁹/L)*	*Presence of antibody to* GPIIb/IIIa	GPIb/IX	GPIa/IIa	*Response to IVIG*	*Concomitant hematologic disorders*	*Current therapy*	*Previous therapy*
1	57	F	2.5	53	N	N	N	Y	None	Pred	Pred
2	30	F	16	2	N	N	N	Y	None	None	Pred
3	84	F	5	32	N	N	N	Y	None	Pred	Pred; dex
4	79	M	180	36	Y	Y	Y	N	None	None	Dex; anti-D
5	20	F	25	22	Y	Y	Y	Y	None	Pred	Pred
6	71	M	0	1	Y	Y	Y	Y	CLL	Pred	Pred
7	18	F	5	68	Y	Y	Y	N	None	Pred	Pred
8	50	M	0	6	Y	Y	Y	Y	None	None	None
9	79	M	0	2	Y	Y	Y	N	CLL	None	None
10	69	M	1.5	1	Y	Y	Y	N	None	Pred	Pred; splen
11	38	M	162	5	Y	Y	Y	N	None	Pred	Pred; splen; dana; dex
12	68	M	12	7	Y	Y	N	N	NHL	Pred	Pred
13	30	M	6.5	33	Y	N	N	Y	None	Pred	Anti-D; pred
14	83	M	336	62	Y	N	N	Y	None	None	Pred
15	58	F	20.5	36	Y	N	N	Y	None	None	Pred; splen
16	82	F	2	9	Y	N	N	Y	MDS	Pred	Pred
17	34	M	0.5	26	N	Y	N	N	None	Pred	Pred

F: female; M: male; N: no; Y: yes; CLL: chronic lymphocytic leukemia; NHL: non-Hodgkin's lymphoma; MDS: myelodysplastic syndrome; Pred: prednisone; Vinc: vincristine; Dex: dexamethasone; Dana: danazol; Splen: splenectomy.

response to IVIG was defined as a post-treatment platelet count of ≥50×10⁹/L with a minimum increment of 30×10⁹/L.

We found 17 patients who had received IVIG and had had platelet autoantibody tests performed (Table 1). Their median age was 58 years (range, 20-83) and ten (59%) were males. ITP was considered idiopathic in 13 patients. In the remaining four patients, the following hematologic conditions were present: chronic lymphocytic leukemia (n=2), myelodysplastic syndrome (n=1), and non-Hodgkin's lymphoma (n=1). Antibodies reactive with GPIIb/IIIa, GPIb/IX, and GPIa/IIa were detected in 13, 10, and 8 patients, respectively. In three patients, none of these antibodies was detected. Among the 14 patients with antibodies, nine (64%) had antibodies against more than one glycoprotein. The median pre-treatment platelet count was 22×10⁹/L (range, 1-68). Overall, ten (59%) patients responded to IVIG. We analyzed IVIG response rate according to platelet autoantibody specificity. A response occurred in seven out of seven patients without anti-GPIb/IX, but in only three out of ten patients with anti-GPIb/IX (p<0.01). Responses occurred similarly in patients with (3 out of 8) or without (7 out of 9) anti-GPIa/IIa (p=0.15) and in patients with (7 out of 13) or without (3 out of 4) anti-GPIIb/IIIa (p=0.60). We did not find any of the clinical features including sex, age, platelet count at the time of treatment, and number of prior therapies to be predictive of IVIG response (*data not shown*). Except for occasional mild infusion reactions, no patient developed any complication from IVIG therapy.

Because of the small number of patients investigated and the retrospective nature of our study, our data should be interpreted with caution. Additional studies in a larger patient population are necessary to confirm our findings. Our study, like previous prospective and retrospective studies evaluating the use of IVIG, did not show that any of the other patients' clinical features or ITP treatment history were helpful in predicting a response to IVIG.[1,8-10] Despite the limitations of our study, our results are quite interesting and support the murine model findings by Webster *et al*. that ITP mediated by anti-GPIbα may be less responsive to IVIG treatment.[6] If confirmed by other studies, platelet autoantibody specificity may become a useful predictor of IVIG response in the treatment of patients with ITP. In the light of earlier studies that showed response to IVIG predicted response to splenectomy in adults and children, investigations into the relationship between platelet autoantibody specificity and response to splenectomy or anti-D would also be of interest.[8-10]

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