Treatment of immune-mediated thrombocytopenia purpura with concurrent intravenous immunoglobulin and platelet transfusion: A retrospective review of 40 patients

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We performed a retrospective review of patients with immune-mediated thrombocytopenia (ITP) treated with prolonged infusions of intravenous immunoglobulin (IVIg) (1 g/kg by continuous infusion over 24 hr) and concurrent platelets (1 pheresis unit every 8 hr), to determine the response rate of this therapy. Patient inclusion criteria included clinically significant thrombocytopenia, with either active bleeding, need for anticoagulation, or a needed surgical procedure. The average pretreatment platelet count was 10,000/μl, which increased to 55,000/μl after 24 hr and 69,000/μl after 48 hr. After 24 hr, 62.7% of patients had a platelet count > 50,000/μl. Bleeding was controlled initially in all patients, and those requiring a procedure experienced no bleeding complications. Over half of the patients (52.5%) required additional treatments for recurrent or refractory ITP. Six of the 21 patients requiring retreatment (29%) received IVIg and platelets again in a similar fashion, with similar results. No side effects of the combined treatment were noted. There is limited literature on the optimal dose and schedule for administration of IVIg and platelets. Our approach for administration of IVIg and platelets concurrently was associated with minimal side effects, resolution of bleeding, ability to safely undergo procedures, and rapid restoration of adequate platelet counts. Am. J. Hematol. 83:122–125, 2008. © 2007 Wiley-Liss, Inc.

Introduction

Immune-mediated thrombocytopenia (ITP) is an autoimmune disorder that occurs spontaneously or secondary to another disease process such as severe infection or autoimmune disease. For individuals that require an increased platelet count in an emergent fashion (such as with life-threatening bleeding), splenectomy is an option. For individuals who need a higher platelet count, but do not need it urgently, intravenous immunoglobulin (IVIg) can be used at a dose of 0.4 grams/kilogram (g/kg) given over 4–6 hr per day for up to 5 days. In January 2000, two individuals at our institution were treated with prolonged infusions of IVIg and platelets for urgent correction of ITP; one of these patients had a suboptimal response to the standard IVIg regimen [1]. The dose of IVIg used was 1.0 g/kg given by continuous infusion over 24 hr with concurrent platelet transfusions at a rate of 1 pheresis unit every 8 hr. Excellent results were seen with this new regimen [1]. Based on these results, our current management of these patients is that if an increase in platelets is needed within 24 hr, or patients have been refractory to standard IVIg dosing, and do not require a splenectomy, prolonged infusion of IVIg and platelets is used. Reasons necessitating a rapid increase in platelets included planned surgery/biopsy/invasive procedure within 24 hr, nonlife threatening bleeding, or the need for anticoagulation. This report describes our experience with this protocol in 40 patients. Our hypothesis was that this novel treatment regimen would improve post-treatment platelet counts in the first 72 hr, control active bleeding, and allow patients to safely undergo needed procedures.

Results

Patient demographics are listed in Table I. Forty patients met entry criteria. The average patient age was 52 years (range 19–87 years). The majority of patients were 20–80 years old, but 12.5% of the patients were older than 80 years at the time of treatment. The male to female ratio was 1:3. For all patients, the average pretreatment platelet count was 10,000/μl, which increased to 55,000/μl at 24 hr and 69,000/μl at 48 hr after treatment (Fig. 1). By 72 hr, the average platelet count had begun to decline, although the platelet count remained at an acceptable level. Over 51% of the patients achieved platelet counts $>$ 50,000/μl by 24 hr. By 24 and 48 hr, respectively, only 7 patients (17.5%) and 4 patients (12.5%) did not achieve platelet counts $>$ 20,000/μl. Bleeding was controlled initially in all patients treated with this regimen regardless of platelet count achieved, and all patients requiring a procedure were able to undergo the procedure without bleeding complications.

Nine of the 40 patients (22.5%) had previously failed treatment with single agent IVIg at standard doses, before receiving IVIg with concurrent platelets. Response rates of these "failure" patients were similar to the nonpretreated rates, with 33 and 78% of "failure" patients obtaining platelet counts of greater than 50,000/μl and 20,000/μl, respectively, at 24 hr. The average platelet count in this population increased from 6,000/μl to 42,000/μl at 24 hr and 94,000/μl at 48 hr. Additionally, 2 of the 40 patients failed prior treatment with WinRho. Both of these latter patients achieved clinical improvement in symptoms, but only one experienced a significant increase in platelet count. The other patient required splenectomy.

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TABLE I. Patient Demographics and Response to IVIg/Platelets

	All patients		Good responders[a]	
	Number (40)	Percentage	Number (19)	Percentage
Male	23	57.5	9	39.1
Female	17	42.5	10	58.8
Age				
<20	1	2.5	1	5.3
20–40	13	32.5	8	42.1
41–60	11	27.5	5	26.3
61–80	10	25.0	4	21.1
>80	5	12.5	1	5.3
Reason for treatment				
Active bleeding	33	82.5	17	89.5
Need for anticoagulation	2	5.0	1	5.3
Required surgery	5	12.5	4	21.1
Underlying medical conditions				
Recent URI	10	25.0	5	26.3
Diabetes mellitus	4	10.0	1	5.3
Hashimoto's thyroiditis	2	5.0	2	10.5
Myasthenia gravis	3	7.5	2	10.5
Prior ITP	4	10.0	1	5.3
CLL	2	5.0		
Other treatment				
Steroids	38	95.0	18	94.7
Splenectomy	14	35.0	5	26.3
Prior to IVIg/Plts	3	7.5		
After IVIG/Plts	11	27.5		
Rituximab	6	15.0	1	5.3
WinRho	3	7.5	1	5.3
Cytoxan	5	12.5	1	5.3
Azathioprine	1	2.5		
Vincristine	3	7.5		
Fludarabine	1	2.5		

[a]Defined as patients with platelet counts > 50,000/μl at 24 hr.

Thirty-eight of the 40 patients (95%) received steroid treatment, which was administered concurrently with the IVIg and platelets. No patient received another treatment for ITP within the 72-hr time frame of initiation of IVIg and platelets. Over half of the patients (52.5%) required additional treatments for recurrent or refractory ITP, and 35% of these patients ultimately underwent splenectomy. Splenectomy was performed outside of the 72-hr time frame of receiving IVIg and platelets, or the postsplenectomy platelet counts were not included in the overall results, avoiding bias from the splenectomy effect.

Six of the 21 patients requiring retreatment (29%) were rechallenged with IVIg and platelets in a similar fashion. The response rate to obtain a platelet count > 50,000/μl was 66% at 24 hr, and 83% at 48 hr. The average retreatment platelet counts at 24 and 48 hr were 53,000/μl and 49,000/μl, respectively, with clinical improvement in bleeding in all patients. Only 2 patients died (5%) during the study, one from a massive intracranial bleed secondary to ITP refractory to multiple treatments including rituximab, vincristine, and splenectomy. The other died from an infectious cause secondary to multiple active medical problems during the same time as ITP was being treated.

Those patients who had a good initial response ("good responders"), defined as an increase in platelet count of greater than 50,000/μl at 24 hr, comprised ~47.5% (19 of 40 patients) of all patients. No specific predictor of response could be identified. There was an equal distribution of age, sex, underlying medical conditions, and no significant difference in initial platelet count in responders and nonresponders. Equal numbers of patients in each group (good initial responders vs. noninitial responders) required retreatment with IVIg and platelets (6 patients in each group).

Finally, several different IVIg products were utilized throughout the study. Patients received the IVIg product that was available at the time when they received IVIg. No adverse reactions to IVIg were identified with any product in any patient, using the prolonged administration. Additionally, no specific IVIg product appeared to produce better results in terms of rate of response, duration of response, or clinical improvement (data not shown).

Discussion

Human immunoglobulin (IVIg) is a pooled blood product collected from 100 to 100,000 donors. It is composed of mostly IgG, but contains smaller amounts of all Ig subtypes. The mechanisms of action of IVIg are complex and beyond the scope of this article. Detailed discussions of the possible mechanisms of action of IVIg have been previously published [2–5].

Recent literature indicates that the specificity of the autoantibody to the platelet receptor may determine whether IVIg will be effective in increasing platelet counts in ITP patients. In a murine model, it appears that IVIg can produce an increase in platelet count in animals that have antibodies specific for the GPIIb-IIIa receptor, but not for the GPIb receptor [6,7]. Whether this effect is also seen in humans is currently unknown, but this may provide an explanation as to why IVIg works in some, but not all patients. Additionally, identifying specific antibody responses could help predict which patients may respond best to IVIg, and help limit exposure to IVIg only to those patients likely to respond.

IVIg dosing for ITP has ranged from 0.4 to 2 g/kg/day [8]. Trials have demonstrated that the dose of 1 g/kg/day for 1–2 days appears to be the optimal dose (when administered as single agent). Typically IVIg is administered over several hours, at rates from 0.03 to 0.13 ml/kg/min [9]. There is limited literature on the most appropriate dose and schedule for administration of IVIg and platelets concurrently, although the dose of 1 g/kg/day appears to be the most effective dose, with higher doses showing no further improvement in platelet response. No large studies have been performed to date looking at the prolonged infusion of IVIg (1 g/kg) over 24 hr. The typical side effects of IVIg administration include allergic-type reactions, fluid overload, thrombotic events, and renal tubular damage. Most of these symptoms can be avoided or reduced with slower infusion rates [9], making a 24-hr infusion ideal for minimizing side effects. Additionally, limited literature has been published on the most effective way to administer platelets with IVIg. Traditional infusions of platelets have been given rapidly over 15–60 min, depending upon the amount of platelets given and transfusion reactions. Although the combination of concurrent IVIg and platelet administration has been used as early as 1984 in leukemic patients refractory to standard platelet transfusions [10], Baumann, et al. published the first article on concurrent IVIg and platelet administration in ITP, reporting the results of 6 patients, and establishing the effectiveness of this combination [11].

A review of the literature discussing the use of IVIg in ITP was performed in which 90 articles matched our search criteria (Immunoglobulins, ITP; with limits including English language, clinical trial, randomized control trial, case reports, and human); the vast majority of articles dealt with childhood ITP and treatment. Very few reports (18 in total) were found dealing with adult ITP treatment with IVIg (with or without platelets) [12–29]. Of those 18 reports, only one

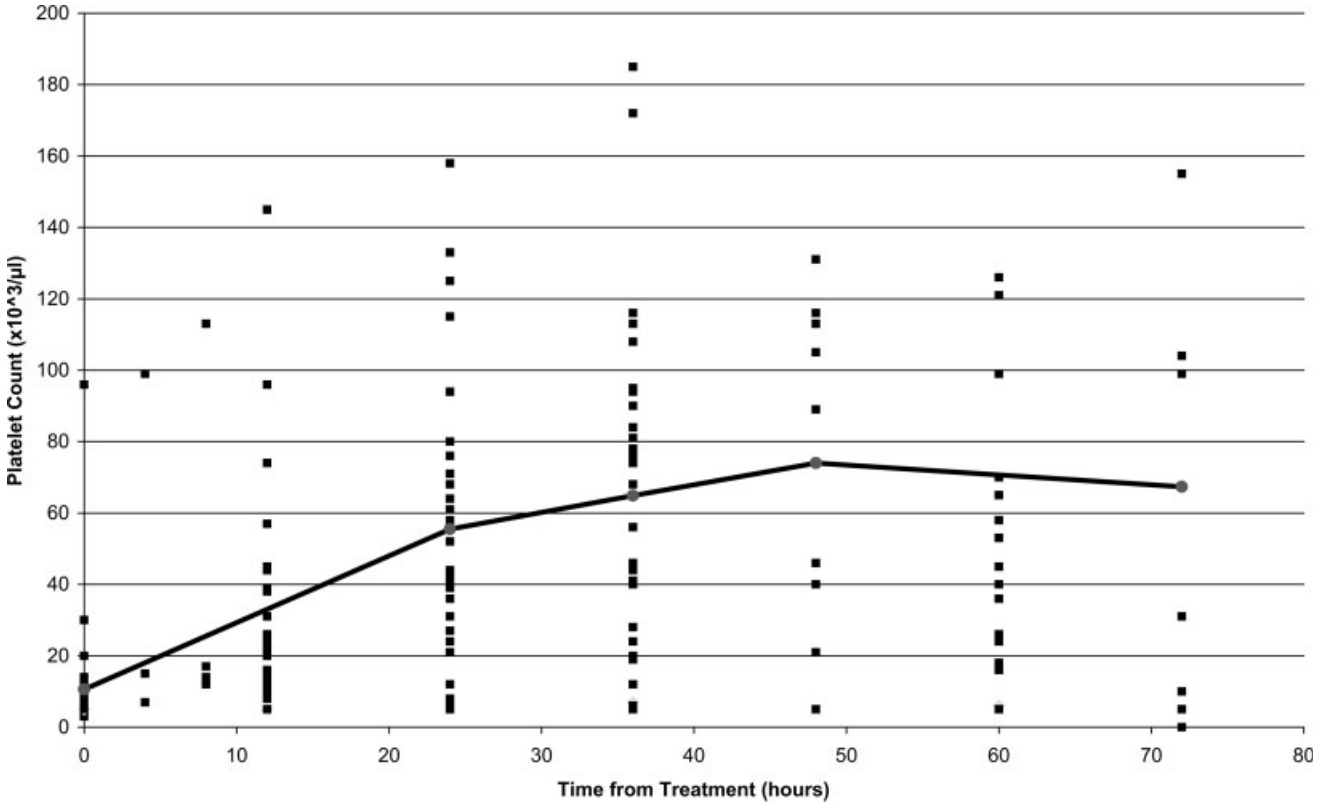

Figure 1. Platelet count over time with concurrent IVIg and platelet administration. The average platelet count (black line) increased to greater than 55,000/μl by 24 hr and greater than 69,000/μl by 48 hr. The average platelet count began to decrease by 72 hr but still remained greater than 50,000/μl. The individual platelet counts are represented by black dots. The patient with an initial platelet count of 96,000/μl was treated due to excessive bleeding on anticoagulation, with a strong indication for continued anticoagulation.

dealt specifically with ability of patients to safely undergo a procedure [17], in which 3 patients were successfully able to undergo coronary artery bypass grafting surgery with administration of IVIg and platelets. This, however, was a retrospective study and the administration of IVIg was not standardized. The other studies did not deal with urgent issues (active bleeding, the need for procedures, or need for active anticoagulation).

Our results demonstrated that concurrent IVIg and platelets are safe and effective at rapidly increasing platelet counts as well as for controlling bleeding symptoms. Our response rates were similar to published rates with IVIg, although response rates of 65–75% have been reported by some [8,30,31]. It should be noted that these response rates were based on both adult and pediatric populations, and ITP in children is typically an acute disease with rapid resolution, compared with adults, where chronic ITP is much more common. Additionally, the duration of time required to obtain platelet counts $>$ 50,000/μl was measured in several days to weeks, versus 24–48 hr in our study. Bierling, however, reported platelet counts $>$ 50,000/μl could be obtained in 1–2 days in patients treated with 0.4 mg/kg/day IVIg given over a 5 days (unpublished data) [8]. This certainly has not been our experience with single agent IVIg. Godeau et al. reported obtaining platelet counts $>$ 50,000/μl with single agent IVIg at day 3–4 in one study [24], and obtaining platelet counts $>$ 80,000/μl in only 28% at 24 hr and 61% at 48 hr with single agent IVIg in another study [13]. Neither of these studies report on the control of bleeding symptoms nor the ability of patients to undergo procedures. Our retreatment results were superior to published data of retreatment with single agent IVIg of 33% [8], although notably, we only had 6 patients who were retreated.

The majority of patients in our study also received concurrent steroid therapy, typically at doses of 1 mg/kg/day. Certainly this additional treatment could have had a significant effect on the reported platelet count. The French AITP study compared IVIg (0.7 g/kg) to high-dose methylprednisolone (HDMP) in which 122 patients were randomized [24]. Results revealed a higher platelet count with IVIg; platelet counts being 40,500/μl and 84,500/μl at 72 hr and 96 hr with IVIg, compared to 34,500/μl and 61,000/μl, respectively, with HDMP. Additionally, treatment with high-dose dexamethasone has been associated with an increase in platelet count [32]. The average increase, however, did not occur until ~3 days from initiation of therapy. Given this information, the addition of steroids to the regimen may be beneficial to improve overall response in patients in need of control of bleeding symptoms or rapid rise in platelet count.

By nature of design, this treatment regimen requires hospital admission. Typically, the patients being treated with this regimen would require hospitalization for other indications (ITP with active bleeding, a needed procedure, etc). Those patients who would typically be treated in the outpatient setting, while this regimen would still likely improve platelet counts, usually would not require such an aggressive approach.

Materials and Methods

We performed an IRB-approved retrospective electronic chart review of adult patients hospitalized from January 2000 to December 2005.

Inclusion criteria included patients older than 18 years, documented ITP with clinically significant thrombocytopenia with either (1) active bleeding, (2) need for anticoagulation, or (3) requirement for a surgical procedure, treatment consisting of IVIg (1 g/kg) given as a continuous infusion over 24 hr, with platelets (1 pheresis unit given every 8 hr), beginning 1 hr after initiation of IVIg, and no treatment for ITP (except for steroids) in the preceding 4 weeks. Outcomes evaluated included 24, 48, and 72 hr posttreatment platelet counts, clinical bleeding response, the ability of patients to safely undergo needed procedures, and requirement for further therapy in the 4 weeks following the treatment. Subsequent treatments, such as steroids, immunosupressives, or rituximab, as well as splenectomy were utilized at the discretion of the treating hematologist.

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