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# Anti-D and Intravenous Immunoglobulin Treatments in Chronic Idiopathic Thrombocytopenic Purpura

Çağatay ÜNSAL\*, Emel GÜRKAN\*, Birol GÜVENÇ\*, Fikri BAŞLAMIŞLI\*,  
Abdullah CANATAROĞLU\*\*

\* Division of Haematology, Department of Internal Medicine, Çukurova University Medical Faculty,  
\*\* Division of Rheumatology-Immunology, Department of Internal Medicine, Çukurova University Medical Faculty,  
Adana, TURKEY

## ABSTRACT

The aim of this prospective study was to evaluate the data from 29 patients diagnosed as chronic refractory idiopathic thrombocytopenic purpura (ITP) treated with anti-D immunoglobulin and intravenous immunoglobulin G (IVIg). We used anti-D and IVIg in 11 and 18 patients respectively in whom the previous treatments including corticosteroids and splenectomy had been unsuccessful. The complete response rates were significantly higher in IVIg arm (55.5% to 18.1%) with a duration of 8 weeks. The overall efficacy of IVIg in the chronic ITP is similar to previous data, however we found lower platelet responses in patients treated with anti-D that can be attributed to the lower success in the splenectomized patients.

**Key Words:** Anti-D, Intravenous immunoglobulin, Idiopathic thrombocytopenic purpura.

## ÖZET

### Kronik İdiyopatik Trombositopenik Purpurada Anti-D ve İntravenöz İmmünglobulin Tedavisi

Bu prospektif çalışmada anti-D immünglobulin ve intravenöz immünglobulin (IVIg) tedavisi alan 29 hastanın verisi incelenmiştir. Daha önceki kortikosteroid ve splenektomi yaklaşımları başarısız olan 11 hastada anti-D, 18 hastada ise IVIg kullanıldı. IVIg kolunda tam yanıt oranları yüksek iken (%55'e karşı %18.1), süre 8 hafta idi. Genel olarak kronik idiyopatik trombositopenik purpurada IVIg başarısı daha önceki verilerle benzer iken, anti-D immünglobulin alan grupta trombosit yanıtını daha düşük bulduk.

**Anahtar Kelimeler:** Anti-D, İntravenöz immünglobulin, İdiyopatik trombositopenik purpura.

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## INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease of children and adults characterized by low platelet counts secondary to accelerated platelet destruction and no other significant hematologic abnormalities<sup>[1]</sup>. Although ITP is generally a benign disease, there is an increased risk of morbidity and mortality in certain patients<sup>[2]</sup>. Refractory patients comprise about 25% to 30% of patients with ITP and are defined as those in whom treatment with standard-dose corticosteroids and splenectomy fails and who require further therapy because of unsafe platelet counts or clinical bleeding<sup>[3]</sup>. Death as a result of hemorrhage from ITP may occur in 5% of refractory adults who fail to respond to therapy and have persistently low platelet counts and bleeding signs and symptoms<sup>[4]</sup>. In patients who have severe bleeding or require surgery, a rapid increase in the platelet count can usually be achieved with gammaglobulin or methylprednisolone therapy<sup>[3]</sup>. Intravenous immunoglobulin G (IVIG) or corticosteroid administration to raise the platelet count temporarily is used for the acute treatment of patients with emergency conditions or before surgery. IVIG is effective especially in patients who are refractory to corticosteroid and/or splenectomy. However, increased cost and potential for acute side effects are among the major drawbacks of IVIG therapy<sup>[5]</sup>. Anti-D, an IgG fraction containing a high proportion of antibodies to the Rho (D) antigen of red blood cells (RBCs) is used in recent years as an alternative to IVIG therapy. Salama et al performed the first infusions of anti-D immunoglobulin in a series of ITP patients reported between 1983 and 1986<sup>[6,7]</sup>. These studies showed that treatment with anti-D immunoglobulin consistently resulted in platelet increases in ITP patients. Tarantino et al reported that in children with acute ITP anti-D was as effective as IVIG in which a single dose 50 µg/kg anti-D was used compared to 0.8 to 1 g/kg IVIG<sup>[8]</sup>. Although the mechanism of effect has not been entirely clarified,

antibody-coating of RBC is unequivocally required for efficacy, because Rh negative patients consistently failed to respond<sup>[9-11]</sup>. Splenectomized patients responded less well than patients with an intact spleen<sup>[5]</sup>. In this study our main objective is to compare the clinical efficacy of anti-D treatment with IVIG in respect to cost and adverse effects in ITP patients who require immediate elevations of platelet counts to safe levels.

## MATERIALS and METHODS

Twenty-nine patients, 7 male and 22 female, diagnosed as chronic ITP during the period from February 1998 to July 2000 were included in the study. Median age was 25.4 (15-68) years for male and 42.8 (18-68) years for female.

The clinical diagnosis of ITP was made according to the presence of the following criteria: platelet count less than 150.000/mm<sup>3</sup>, a normal bone marrow cytology with normal or increased number of megakaryocytes and absence of any other cause of thrombocytopenia. Thrombocytopenia, lasting more than 6 months was accepted as chronic ITP. Patients with associated systemic diseases were excluded and merely the patients with platelet count below 50.000/mm<sup>3</sup> were treated. The patients with platelet count > 150.000/mm<sup>3</sup> or within 50-150.000/mm<sup>3</sup> after treatment were defined as a complete response or a partial response respectively, and no response to treatment if platelet count was below 50.000/mm<sup>3</sup>. Eight of 29 patients were splenectomized. Antinuclear antibody tests were found to be negative at the initiation of treatment. Coulter Counter was used for the initial complete blood count and consecutive follow-up count, the results were confirmed by blood smear. Platelet, hemoglobin, leukocyte, reticulocyte count, direct Coombs' test and biochemical tests including aspartate aminotransferase, lactate dehydrogenase (LDH) and bilirubin levels were determined on days 1 (pretreatment), 3, 7, 30 and 60. All patients were hospitalized during treatment. Anti-D was infused to 11 patients with Rh

positive blood type as a single dose of 50 µg/kg over 3 to 5 minutes. Other patients were treated with IVIG infusion, a dose of 2 g/kg over 3 to 5 consecutive days. The anti-D preparation used in the study was WinRho SD (Nabi) and the preparations of IVIG included Gammimune (Bayer) and Sandoglobulin (Sandoz). Analysis of variance (ANOVA; repeated measures of analysis of variance) were used to evaluate the differences in response rates within and among groups using SPSS 9.0. Correlation between direct Coombs test and treatment regimen is studied with chi-square method. The level of significance was set at 0.05 for p values.

### RESULTS

The mean platelet count of all patients before treatment was 10.000/mm<sup>3</sup> (1-20.000/mm<sup>3</sup>). The complete response rates (platelet count > 150.000/mm<sup>3</sup>) to anti-D and IVIG treatments were 18.1% and 55.5%, and the partial response rates (platelet count between 50-150.000/mm<sup>3</sup>) were 27.2% and 5.5%, respectively (Table 1). Patients were followed-up for 8 weeks. There was no significant correlation of splenectomized patients response rates from nonsplenectomized. We observed 12 patients with rise over 50.000/mm<sup>3</sup> in platelet count on first day posttreatment and 4 patients on the third day posttreatment. Minor adverse effects including headache (6.9%), mild fever and chills (10.3%) were observed in anti-D infused patients, identified by the review of former cases, however, no side effects requiring interruption of the infusion were seen during anti-D or IVIG therapy. There were no signs of hemolysis with no significant difference in hemoglobin, bilirubin, and LDH levels (p > 0.05), before and after treatment. Mean ba-

seline hemoglobin level in patients treated with anti-D and IVIG infusions were 12.6 g/dL and 12.5 g/dL and posttreatment levels were 12.7 g/dL and 12.3 g/dL respectively. There was no correlation between baseline hemoglobin levels and platelet response, also baseline platelet count and duration of ITP had not a remarkable effect on response. Duration of response after both anti-D and IVIG treatments lasted over 60 days in responders (Figure 1).

### DISCUSSION

This randomized study was designed to compare the therapeutic role of anti-D and IVIG in the chronic refractory ITP in adults. Overall efficacy of IVIG at the conventional doses of 2 g/kg was similar to the data of previous studies on the population with chronic ITP<sup>[8]</sup>. The reported long-term complete remission rates due to IVIG treatment were quite low, we recorded platelet responses after IVIG infusions lasting 8 weeks. IVIG

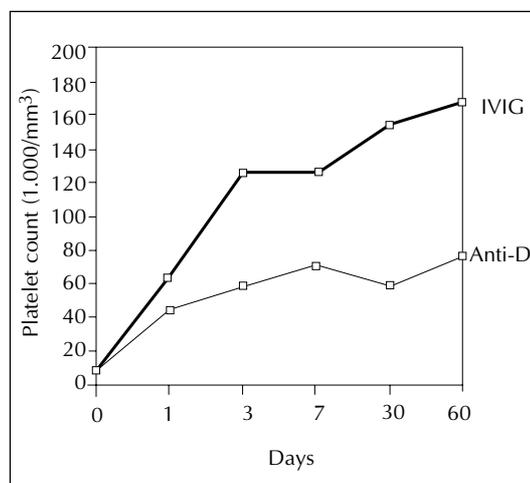


Figure 1. Platelet counts after treatment.

Table 1. Platelet increments in the follow up (x 1000/mm<sup>3</sup>)

	Posttreatment day 1	+3	+7	+30	+60
Anti-D	35	50	61	50	67
IVIG	54	117	117	146	160

treatment was shown to be effective in 64% of patients with a peak platelet count of greater than  $100.000/\text{mm}^3$  and 83% of patients with  $50.000/\text{mm}^3$ , in the present study we demonstrated an increase in platelet count over  $50.000/\text{mm}^3$  in 61% of patients<sup>[9-11]</sup>. The results were consistent with the earlier reports with a minor difference which may be originated from the splenectomized patients. However, platelet response to anti-D infusion was lower than the historical data. Scaradavau et al demonstrated an increase in the platelet count greater than  $20.000/\text{mm}^3$  in 72% of cases and  $50.000/\text{mm}^3$  in 45% of cases with a duration response of 21 days in 50% of responders<sup>[8,12]</sup>. In another study, anti-D was shown to be effective to elevate platelet count in 79% to 90% of patients<sup>[13]</sup>. We found a mean of  $67.000/\text{mm}^3$  increase which reached the peak level at day 60 and the duration of effect was continued more than three weeks.

Treatment of ITP includes conventional modalities, such as steroids, IVIG and splenectomy<sup>[14,15]</sup>. Patients with severe thrombocytopenia require a treatment that should ideally be rapidly, reliably and durably effective. It should be inexpensive and simple to administer. Currently, the mainstays of pharmacologic management for acute ITP are IVIG and corticosteroids. IVIGs has advantages over steroids such as a more rapid increase in platelet count and absence of the adverse effects of steroid use. Infusions of IVIG result in substantial platelet increases in more than 70% to 80% of patients with ITP. Mechanism of action of IVIG in ITP appears to be the Fc receptor blockade<sup>[16]</sup>. The optimal dose of IVIG is controversial, particularly for adults. Mostly used treatment regimen consist original doses of 0.4 g/kg body weight (bw) daily for 5 consecutive days or the dose of 1 g/kg bw for 2 days<sup>[16]</sup>. We have used the original dose of 0.4 g/kg bw daily for 4 consecutive days. The ability of IVIG infusions to increase the platelet count in patients with acute ITP was first reported by Imbach et al in 1981 who observed platelet res-

ponses in children receiving 0.4 g/kg bw daily for 5 days IVIG infusions are used for initial treatment of patients with severe thrombocytopenia and also when surgery is planned, in order to reduce the risk of peri- and postoperative bleeding<sup>[4,17]</sup>. However IVIG is disadvantageous as a first-line therapy because of high cost. It was demonstrated previously that anti-D which has a similar mechanism of action with IVIG in ITP raises platelet counts effectively and is also less expensive<sup>[18]</sup>. Generally, 50 µg/kg of anti-D is sufficient<sup>[5]</sup>. The primary goal of treatment for patients with chronic, refractory ITP is to prevent major bleeding, not to cure the disease. Although CR and PR rates were better in IVIG group, our data has shown that anti-D use was effective as IVIGs in raising platelet counts to safe levels (i.e.  $\geq 30.000/\mu\text{L}$ ). We have seen less adverse effects with anti-D compared to IVIG infusions. We have observed that anti-D raised the platelet counts as more slowly than as did IVIG and the length of hospital stay was shorter for patients receiving anti-D. In some reports, treatment with anti-D resulted in a slower rise in platelet count than with steroids or IVIG<sup>[19]</sup>. However other studies have shown that an increased dose of anti-D raised platelet counts as quickly as IVIG<sup>[18]</sup>. In anti-D group three of the four splenectomized patients responded partially to the treatment which was even within safe levels. This suggests that the effect of anti-D may not be limited to the Fc receptor blockade.

We have found no correlation with Coombs positivity and response to therapy. A pilot clinical trial of anti-D treatment in 3 Rh-positive patients by Bussel et al found no correlation between parameters of hemolysis and platelet increases<sup>[11]</sup>.

Fifteen cases of hemoglobinemia and/or hemoglobinuria that occurred following anti-D treatment were reported to the FDA between May 1996 and April 1999<sup>[20]</sup>. The mean dose of anti-D was 50 µg/kg for 12 patients whose hemoglobin level was greater than or

**Table 2. Clinical features, response rates and cost of therapy**

	Anti-D (n= 11)	IVIG (n= 18)
Age (median, range)	28 (15-61)	45.1 (21-68)
Sex (f/m)	8/3	14/4
Partial response	3 (27.2%)	1 (5.5%)
Complete response	2 (18.1%)	10 (55.5%)
Cost of therapy per course	6840\$	1850\$
Cost per hospitalization	126\$	72\$

equal to 10 g/dL with a median dose of 50 µg/kg. The other 3 patients who had a hemoglobin of less than 10 g/dL received a mean dose of 58 µg/kg, with a median dose of 52 µg/kg. Although we have used similar doses of anti-D in our patients we did not observe any adverse effects concerning hemoglobinemia/hemoglobinuria.

Our analysis demonstrated that single-dose anti-D, at 50 µg/kg for the treatment of severe thrombocytopenia is as effective as IVIG treatment and is tolerated without severe hemolysis or anemia. In addition this type of treatment modality seems preferential in underdeveloped and developing countries like Turkey because of low cost (Table 2).

There are few published reports on the cost of treatment of ITP with IVIG and anti-D. The cost of anti-D treatment has been reported to be 10% of the cost of IVIG treatment<sup>[9]</sup>. Oksenhendler et al estimated that the cost of anti-D therapy was significantly less than IVIG<sup>[10]</sup>. The unit cost of treatment with IVIG or anti-D has two components; the drug costs and the labor and supplies cost associated with infusion<sup>[21]</sup>. In a retrospective observational study performed by Simpson et al, anti-D treatment had at least as good an effect as IVIG in terms of frequency and magnitude of response, sustainability, peak platelet increase<sup>[21]</sup>. Furthermore, it's worth mentioning that the infusion process is much shorter and the associated costs are lower. In conclusion anti-D is as effective as IVIG for the treatment of complicated severe

thrombocytopenia in adult patients with ITP. In appropriate cases i.e. Rh-positive patients with severe thrombocytopenia the use of anti-D saves both money and time. Anti-D has the advantages of IVIG like high efficacy rate, few side effects without the obvious disadvantages (long infusion time, postinfusion headache, high cost). We suggest anti-D use for the treatment of severe hemorrhage in ITP patients, prior to surgical procedures and with the aim of deferring splenectomy. Anti-D may be a good maintenance therapeutic option in chronic refractory patients also.

## REFERENCES

1. Scaradavou A, Bussel JB. Clinical experience with anti-D in the treatment of idiopathic thrombocytopenic purpura. *Semin Hematol* 1998;35:52-7.
2. Tarantino MD, Goldsmith G. Treatment of acute immune thrombocytopenic purpura. *Semin Hematol* 1998;35:28-35.
3. McMillan R. Therapy for adults with refractory chronic immune thrombocytopenic purpura. *Ann Intern Med* 1997;126:307-14.
4. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood* 1996;88:3-40.
5. Scaradavou A, Woo B, Woloski BMR, et al. Intravenous anti-D treatment of immune thrombocytopenic purpura: experience in 272 patients. *Blood* 1997;89:2689-700.
6. Salama A, Mueller-Eckhardt C, Kiefel V. Effect of intravenous immunoglobulin in immune thrombocytopenia. Competitive inhibition of reticuloendothelial system function in sequestration of autologous red blood cells. *Lancet* 1983;2:193-5.
7. Salama A, Kiefel V, Mueller-Eckhardt C. Effect of IgG anti-Rho (D) in adult patients with chronic auto-

- immune thrombocytopenia. *Am J Hematol* 1986;22:241-50.
8. Tarantino MD, Madden RM, Fennewald DL, et al. Treatment of childhood acute immune thrombocytopenic purpura with anti-D immune globulin or pooled immune globulin. *J Pediatr* 1999; 134:21-6.
  9. Bussel JB, Graziano JN, Kimberly RP, et al. Intravenous anti-D treatment of immune thrombocytopenic purpura: analysis of efficacy, toxicity and mechanism of effect. *Blood* 1991;77:1884-93.
  10. Oksenhendler E, Bierling P, Brossard Y, et al. Anti-RH immunoglobulin therapy for human immunodeficiency virus-related immune thrombocytopenic purpura. *Blood* 1988;71:1499-502.
  11. Bussel JB, Graziano JN, Kimberly RP, et al. Anti-D Ig for treatment of immune thrombocytopenic purpura. *Blood* 1991;78:2157 (letter).
  12. Ruivard M, Caulier MT, Vantelon JM, Tournilhac O, Schaffer A, Godau B, Bierling P. The response to high-dose intravenous immunoglobulin or steroids is not predictive of outcome after splenectomy in adults with autoimmune thrombocytopenic purpura. *Br J Haematol* 1999;105:1130-2.
  13. Godeau B, Caulier MT, Decuypere L, Rose C, Schaeffer A, Bierling P. Intravenous immunoglobulin for adults with autoimmune thrombocytopenic purpura: results of randomized trial comparing 0.5 and 1g/kg b.w. *Br J Haematol* 1999;107:716-9.
  14. Proctor SJ, Crossley AP, Calvert JE. Autoimmune (idiopathic) thrombocytopenic purpura. *Lancet* 1997;350:68.
  15. Bussel JB, Pham LC. Intravenous treatment with gammaglobulin in adults with immune thrombocytopenic purpura: reviews of the literature. *Vox Sang* 1987;52:206-11.
  16. Clarkson SB, Bussel JB, Kimberly RP, et al. Treatment of refractory immune thrombocytopenic purpura with an anti-Fc gamma receptor antibody. *N Engl J Med* 1986;314:1236-9.
  17. Imbach P, d'Apuzzo V, Hirt A, et al. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. *Lancet* 1981;1:1228-30.
  18. Chu YW, Korb J, Sakamoto KM. Idiopathic thrombocytopenic purpura. *Pediatrics in Review* 2000;21: 1-13.
  19. Blanchette V, Imbach P, Andrew M, et al. Randomized trial of intravenous immunoglobulin G, intravenous anti-D, oral prednisone in childhood acute immune thrombocytopenic purpura. *Lancet* 1994;334:703-7.
  20. Gaines AR. Acute onset hemoglobinemia and/or hemoglobinuria and sequelae following Rho (D) immune globulin intravenous administration in immune thrombocytopenic purpura patients. *Blood* 2000;95:2523-9.
  21. Simpson KN, Coughlin CM, Eron J, et al. Idiopathic thrombocytopenia purpura: treatment patterns and analysis of cost associated with intravenous immunoglobulin and anti-D therapy. *Semin Hematol* 1998;35:58-64.

#### Address for Correspondence:

Çağatay ÜNSAL, MD

Division of Haematology

Department of Internal Medicine

Çukurova University Medical Faculty

Adana, TURKEY