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R. Sajid

*Aga Khan University*

Salman Adil

*Aga Khan University, salman.adil@aku.edu*

Z. Fadoo

*Aga Khan University*

S. Sabir

*Aga Khan University*

Mohammad Khurshid

*Aga Khan University, mohammad.khurshid@aku.edu*

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# Use of Intravenous anti-D in patients with refractory and relapsed Immune Thrombocytopenic Purpura

R. Sajid, S. N. Adil, Z. Fadoo, S. Sabir, M. Khurshid  
Department of Pathology, The Aga Khan University, Karachi.

## Abstract

**Objective:** To determine the response to IV anti-D and its comparison with splenectomy as second line therapy in refractory and relapsed cases of ITP, in the Aga Khan University Hospital, Karachi.

**Methods:** A total of 23 patients with chronic ITP were treated with either anti-D or splenectomy as second line treatment. The patients were assessed for time to achieve a response to second line treatment, duration of response and adverse events.

**Results:** There were 12 patients in the anti-D group and 11 in the splenectomy group. The mean platelet count at presentation was 9,000/cumm. The mean age was 8.9 years and 13.0 years and the male to female ratio was 1:1 and 1:1.2 in anti-D and splenectomy group respectively. 54.5% of the patient in the anti-D group responded compared to 81.8% in the splenectomy group. Median time to achieve a response was 7 days in the anti-D group and 1 day in the splenectomy group. Mean time to relapse was 87.8 days in the anti-D group and 55.4 days in the splenectomy group. No adverse events were recorded for any of the infusions of anti-D and none of the patients had more than 0.5 gm /dl fall in the hemoglobin level following anti-D infusion.

**Conclusion:** It was thus concluded that Anti-D is a relatively safe, convenient and effective therapy for chronic ITP and can be used as a splenectomy sparing agent when treatment is clinically indicated (JPMA 53:537;2003).

## Introduction

Immune thrombocytopenic purpura (ITP) is an acquired disease of children and adults defined by a low platelet count in the absence of other clinically apparent causes of thrombocytopenia.<sup>1</sup> It is principally a disorder of increased platelet destruction caused by antiplatelet antibodies.

In 1983 Salama et al reported platelet responses in three of six Rh (D) positive patients treated with 400 to 2500 ug of anti-D (2). Anti-D is a plasma derived immunoglobulin prepared from donors selected for a high titer of Rho (D) antibody. The investigators suggested that the rise in platelet count is due to competitive inhibition of the macrophage binding of platelets by preferential sequestration of immunoglobulin coated red blood cells.<sup>2</sup>

Important observations from published reports include evidence of a dose response relationship, reproducibility of responses, and efficacy of anti-D in Rh (D) positive but not in Rh (D) negative subjects. Similarly splenectomized patients had minimal or no responses.<sup>3</sup> The lower cost of anti-D plus the ease of administration make anti-D therapy an attractive option as splenectomy sparing therapy and as maintenance therapy in patients with chronic ITP.<sup>4</sup>

## Patients and Methods

This was a case series study which was carried out from January 2000 to October 2002.

This study was conducted upon diagnosed patients

with Immune Thrombocytopenic Purpura. All patients of ITP received Anti-D were included in one group and patients who underwent splenectomy were included in the second group. Patients with established diagnosis of ITP were included in the study. All patients who had persistently low platelet counts for at least six months, were blood group Rh positive (anti-D group) had not undergone splenectomy and were not receiving other forms of therapy were included in the study. Post splenectomy patients and patients with blood group other than Rh positive were excluded.

Patients were eligible for inclusion if they had a diagnosis of acute or chronic ITP, had not undergone splenectomy, their blood group was Rh positive (anti-D group). All 23 patients included in the study fulfilled the criteria mentioned above. All patients were analyzed for demographic features including age, sex, age at the time of diagnosis, clinical features at presentation, response to initial treatment, rise in platelet counts following second line treatment (IV anti-D) and persistence of response for 3 months. Response was defined as an increase in platelet count to >50,000/cumm or doubling of pretreatment platelet counts. Any adverse events with anti-D or splenectomy were also recorded.

Anti-D (WinRho) was given at a dose of 50mg/kg. The anti-D preparation was diluted in physiologic normal saline and infused intravenously during a 15-30 minute period on an outpatient basis. Patients were followed at weekly intervals and any adverse events were recorded. Complete blood count was performed at each outpatient

visit. Platelet counts were performed on EDTA specimens by means of automated coulter STKS counter and correlated with microscopic examination of peripheral blood film.

All the data was analyzed using SPSS program (statistical package for social sciences) version 10.0 by Kaplan Maier analysis.

### Results

A total of 23 patients with chronic ITP were treated with either anti-D or splenectomy as second line treatment. There were 12 patients in the anti-D group and 11 in the splenectomy group. The mean platelet count at presentation was 9,000/cumm. The minimum follow-up after second line treatment was 3 months. The mean age was 8.9 years and 13.0 years in the anti-D and splenectomy groups respectively. The male to female ratio was 1:1 and 1:1.2 in the anti-D and splenectomy groups respectively.

Petechaie and Epistaxis were found to be the most common symptoms at presentation, seen in 65% and 26.1% of the patients respectively.

Out of 23 patients, 21 patients were initially treated with steroids. One patient received IVIG and one patient had intravenous anti-D as first line treatment. The patient who received IV anti-D as first line treatment achieved complete remission and did not require any further therapy. Out of the remaining 22 cases, 8/22 (36.3%) relapsed after tapering of steroids and 14/22 (63.6%) were refractory to steroids.

Anti-D was given in 11 patients as second line treatment and 11 patients underwent splenectomy as second line treatment. 54.5% of the patients in the anti-D group had a response compared to 81.8% of the patients in the splenectomy group.

### Adverse Events

No adverse events were recorded for a total of 14 infusions of iv anti-D. None of the patients had more than 0.5 gm/dL fall in haemoglobin following anti-D infusion. All patients had pre-treatment Hb levels of more than 10 gm/dL. In all cases the anaemia resolved spontaneously and without specific therapy.

**Table 1. Comparison of Anti-D and splenectomy for duration of response.**

	Anti-D	Splenectomy
Median time to response	7days	1.0 day
Mean time to relapse	87.8 days	55.4 days

### Follow up of Patients who responded to Anti-D

Median time to achieve a response and mean time to relapse is shown in table 1 and Kaplan Maier analysis is shown in Figures 1 and 2.

**Table 2. Results with anti-D in various studies.**

Author (reference)	No. of patients	Response rates (%)	Duration of response
Andrew M (5)	25	72	5 weeks (1-24)
Michael D (6)	14	70	Not defined
Scaradavou A (7)	272	72	3 weeks in >50% of patients
Present study	12	58	12 weeks

**Figure 1 : Kaplan Maier survival function for anti-D and splenectomy**

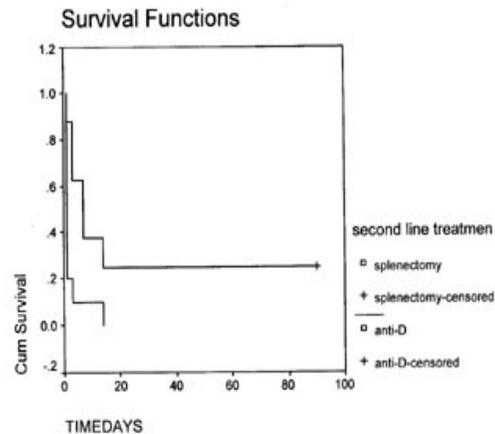


Figure 1. Kaplan Maier survival function for anti-D and splenectomy.

**Figure 2: Kaplan Maier survival function for time to relapse for anti D and splenectomy**

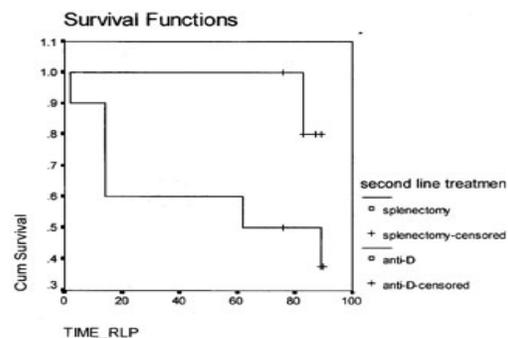


Figure 2. Kaplan Maier survival function for time to relapse for anti-D and splenectomy.

Three out of 6 patients who initially responded to

anti-D relapsed. Two patients after splenectomy and one after a second dose of anti-D.

### **Follow up of patients who were resistant to anti-D**

Five out of 11 patients were non responders to an initial infusion of anti-D. Three underwent splenectomy. One received a second infusion of IV anti-D and remained in complete remission till last follow up. One patient was lost to follow up.

### **Discussion**

Patients with ITP may require therapy to increase the platelet counts for a variety of reasons and a number of therapies are available to achieve that effect. However most of these therapies are helpful on short term basis and many have unacceptable side effects and high costs. Anti-D appears to be promising since cost is low and side effects are minor and rare. It can be given on outpatient basis saving admission costs and considerable morbidity associated with other second line therapies.

In our study the responses were rapid, had with minimal toxicity a reasonable duration of effect.

However in comparison to splenectomy the response rates were significantly lower and durable responses were seen in only 50% of the patients as compared to more than 70% in the splenectomy arm.

Most of the available literature recommends anti-D as splenectomy sparing therapy and our recommendation would remain such too. The comparison of response rates

and the duration of responses with international studies are summarized in table 2.

### **Conclusion**

It is concluded that anti-D is a relatively safe, convenient and effective therapy for chronic ITP and can be used as a splenectomy sparing agent when treatment is clinically indicated. A 50 µg /kg dose of anti-D yields more than 50% response rates with median duration of effect of 12 weeks.

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