Comparison between IV immune globulin (IVIG) and anti-D globulin for treatment of immune thrombocytopenia: a randomized open-label study

Aziz Eghbali\textsuperscript{a}, Peyman Azadmanesh\textsuperscript{a}, Bahador Bagheri\textsuperscript{b*}, Hasan Taherahmadi\textsuperscript{a}, Bahman Sadeghi Sedeh\textsuperscript{c}

\textsuperscript{a}Department of Pediatrics, Arak University of Medical Sciences, Arak, Iran
\textsuperscript{b}Department of Pharmacology, Semnan University of Medical Sciences, Semnan, Iran
\textsuperscript{c}Department of Social Medicine, Arak University of Medical Sciences, Arak, Iran

Keywords
ITP, Children, anti-D, IVIG

ABSTRACT

To compare the effect of IV immune globulin (IVIG) and anti-D globulin (anti-D) for treatment of immune thrombocytopenia (ITP) in children. A randomized, open-label, single-center clinical trial was carried out in Amir-Kabir Hospital (Arak, Iran). The study was performed on 60 children with acute and chronic ITP, aged from 1 to 15 years. Patients were randomly assigned (1:1) to 50 µg/kg anti-D or 1 g/kg IVIG. Platelet counting was performed at baseline and at 3, 7, and 14 days after treatment termination. Safety assessment was performed in all patients. Anti-D caused a quicker response on the 3rd day of treatment ($P < 0.001$). Both drugs caused a significant rise in number of platelets on the 7th and the 14th day of treatment. Compared to IVIG, except a significant drop in hemoglobin concentration ($P < 0.001$), anti-D had lower rate of side effects including fever ($P < 0.05$), allergy ($P < 0.01$), and headache ($P < 0.001$). Our results showed that anti-D was associated with rapid rise of platelets compared to IVIG. In addition, anti-D treatment had acceptable safety profile.

INTRODUCTION

Immune thrombocytopenia (ITP) formerly known as immune thrombocytopenic purpura is an immune reaction against platelets. ITP is usually defined as platelet count less than $100 \times 10^9/L$ in the absence of other causes or disorders that are associated with thrombocytopenia [1,2]. In children, the usual age range is 1–4 years. The most dangerous complication is intracranial hemorrhage which is estimated to occur in 0.2–1% of children with ITP [3]. ITP usually happens following viral infections suggesting role of infection in the pathogenesis of ITP. HIV, Epstein-Barr virus, and MMR vaccines are best documented examples that are associated with ITP [4]. Autoantibodies are frequently active against platelet glycoprotein including GPIb/IX and GPIIb/IIIa. Antibody-coated platelets are removed by reticuloendothelial system via Fc\textsubscript{y} receptors which are abundantly present in the spleen and liver [4,5]. ITP patients are characterized by sudden petechiae which is commonly seen in the gums and mucosa [3]. Corticosteroids are usually considered as the first line of treatment in ITP; however, during tapering or after discontinuation, sustained response will be reduced [6]. Patients without sustained response to corticosteroids need other drugs. IV immune globulin (IVIG) and anti-D globulin (anti-Rho) are other first-line pharmacological treatments [7]. Rituximab, thrombopoietin agonists (e.g., romiplostim and eltrombopag), and splenectomy are considered as the second line of treatment in chronic ITP [8]. IVIG is derived from human plasma in pools of 3000–10 000 plus donors [7]. Although helpful, it is an
expensive drug, and it may cause aseptic meningitis and anaphylaxis. Anti-D is much cheaper than IVIG and growing evidence suggests at least noninferior efficacy to IVIG [8]. In contrast to IVIG, a small number of studies have evaluated efficacy and safety of anti-D in ITP. According to the last guidelines, anti-D is the only first-line treatment with major changes to the previous guidelines [9]. In the current guidelines, the first-line treatments are corticosteroids, IVIG, and anti-D. There is no clear difference between IVIG and anti-D, but they are different in safety profile and cost. The aim of this study was to undertake a comparison on efficacy and safety of IVIG and anti-D in Iranian children with ITP. We have chosen a randomized control trial method to show differences in safety or efficacy between IVIG and anti-D.

**METHODS**

**Study design**

This single-center, randomized, open-label, parallel-group, active-controlled study was conducted in Amir-Kabir Hospital, Arak, Iran. Children 1–15 years of age who had acute or chronic ITP were included in the study. Diagnosis of primary ITP was based on normal health status, absences of liver and spleen enlargement, negative serology tests against hepatitis B and C and HIV, and also negative result of bone marrow aspiration. Sixty participants were randomized 1: 1–50 μg/kg anti-D (Rhophylac®, CSL Behring, Germany) infused for 15 min or 1 g/kg IVIG (Intratect®, Biotest Pharma, Germany) infused for 8 h. Patients were excluded if they had received anti-D or IVIG within last 3 weeks, hemoglobin concentration less than 10 g/dL, renal failure, total bilirubin more than 2 mg/dL, positive Coombs test, infectious disease, cardiovascular diseases, malignancies, and any other autoimmune disease associated with ITP, like lupus or antiphospholipid syndrome, hemolytic autoimmune anemia (Evans syndrome), and primary immunodeficiency-associated ITP, such as autoimmune lymphoproliferative syndrome and common variable immunodeficiency. Patients were discontinued from the study for these reasons: safety, lost to follow-up, and voluntary discontinuation. The project was approved by local Ethics Committee and written informed consent was obtained from parents of children before participating in this trial. The study was conducted in accord with the European Directive 2001/20/EC. The registration number of this trial corresponds to the Iranian Registry of Clinical Trials was IRCT2012102811289N1.

**Efficacy assessment**

Platelet counting was performed at baseline and at 3, 7, and 14 days of the treatment.

**Safety assessment**

Untoward effects, cell blood count, physical examination, and vital signs were monitored at baseline and at 3, 7, and 14 days of the treatment by physician. For assessment of adverse effects of drugs, patients were monitored for allergy, headache, hemolytic anemia, aseptic meningitis, and fever. Common symptoms of allergy like pruritus, fever, skin rash, swelling, and severe symptoms including dyspnea, palpitation, confusion, and rapid pulse were evaluated.

**Data analysis**

Data are shown in mean ± SD. Analyses were carried out using one-way repeated-measures ANOVA with a Holm–Sidak post hoc test. P < 0.05 was considered as statistical significance. Analysis was carried out using SPSS software version 18.0, Chicago, IL, USA.

**RESULTS**

**Baseline characteristics**

Of the 69 patients who were included nine patients did not enter the randomized treatment. A total of 60 patients were studied between May 2014 and June 2015. Forty-seven subjects had acute ITP and 13 subjects had chronic ITP. Patients with chronic form had received 2 mg/kg prednisolone for 2 weeks. Patients flow through the study is presented in Figure 1. Demographic and clinical characteristics of study subjects are shown in Table I. The mean age was 5.5 years with an excess of girls (51.2% vs. 49.8%). At baseline, mean platelet count was 14 200 ± 5316/μL.

**Efficacy**

Before initiation of treatment, mean platelet number was 14 200 ± 5316/μL. As shown in Figure 2, both IVIG and anti-D increased platelet count on the 3rd day of the treatment; however, anti-D caused a significant platelet rise (76 000 ± 44 381 /μL) vs. 43 400 ± 25 008 /μL, P < 0.001). On the 7th and 14th days, both drugs caused nearly a similar increase in platelet number. No significant difference was observed at these days.
Rate of response
From total of 60 patients who underwent medical treatment, in anti-D group, 14 (46.6%) patients had platelet count >50 000/µL on the 3rd day. At this time, 10 (33.3%) patients in IVIG group had platelet count >50 000/µL. On the 7th day, 12 (40%) patients in each group had platelet count >50 000/µL. On the 14th day, 1 (3.3%) patient had platelet count >50 000/µL in anti-D group and 5 (16.6%) patients in IVIG group had platelet count >50 000/µL. Three (10%) patients in each group did not response to the treatments until the 14th day.

Safety
After treatment, none of patients showed hemolytic anemia. Long-term follow-up of the patients showed no case of hemolytic anemia. As shown in Figure 3, fever was seen in both groups; however, rate of fever was higher with IVIG than with anti-D (P < 0.05). Allergy and headache were seen only in patients received IVIG (P < 0.01 and P < 0.001, respectively). At baseline, in patients who were given anti-D, mean hemoglobin concentration was 12.69 ± 0.91 g/dL. After 6 hours, it declined to 12.28 ± 0.98 g/dL (P < 0.001) without evidence of hemolysis. In patients who were administered IVIG, no significant drop was seen in hemoglobin concentration.

DISCUSSION
The results of this clinical trial suggest that anti-D therapy is associated with quick response and lower rate of adverse effects compared to IVIG. Our findings suggest that a single dose of anti-D, 50 µg/kg, was superior to the single dose of IVIG, 1 g/kg, on the third day of treatment. On the 7th and 14th day, both drugs had nearly equal response. It is noteworthy that anti-D caused a small but significant drop in Hb concentration. Of note, patients with acute and chronic ITP were included in our study. A study showed that anti-D administration was associated with shorter hospital stay and was more economic compared to IVIG in acute ITP patients [10]. Shahgholi’s [11] investigation reported that divided doses of IVIG were more effective than single dose of anti-D to treat acute ITP; however, anti-D was associated with lower side effects. Moreover, another study by Papagianni et al. [12] considered anti-D as a more effective therapy in newly diagnosed

<table>
<thead>
<tr>
<th>Table 1 Characteristics of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Male (%)</td>
</tr>
<tr>
<td>Platelet count (µL)</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>Illness duration (months)</td>
</tr>
<tr>
<td>Proportion of acute and chronic ITP (n/n)</td>
</tr>
</tbody>
</table>

Data are shown in mean ± SD or percent. ITP, immune thrombocytopenia; IVIG, IV immune globulin.
ITP. In the study by Son et al., it was indicated that single dose of anti-D, 50 μg/kg, was as effective as divided dose of IVIG, 2 g/kg, in Korean children presented with acute ITP. As expected, anti-D caused a drop in Hb concentration without the presence of serious adverse effects [13]. In addition, a work from Tarantino has shown that 75 μg/kg anti-D causes a quicker rise of platelets compared to 50 μg/kg anti-D and 0.8 g/kg IVIG in acute ITP [14]. In his work, 75 μg/kg anti-D have had same safety profile as 50 μg/kg anti-D and 0.8 g/kg IVIG suggesting proper safety and efficacy of 75 μg/kg anti-D which is not currently recommended as standard dose. Intravenous immunoglobulin and anti-D were hypothesized to have a common mechanism of action in ITP. It has long been postulated that IVIG can competitively inhibit Fc receptors (FcRs) of monocyte phagocytic system (MPS) via sensitized red cells, and for anti-D, it is assumed that antibody-coated red cells can inhibit Fc receptors of (MPS) [15–17] . Fc inhibition/blockade results in an increase in the platelet count. Evidence from diverse sources has provided data suggesting distinct differences in the mechanisms of action of these drugs. It is generally accepted that platelet clearance is performed via monocyte phagocyte system; however, some reports have introduced other mechanisms for platelet clearance [18]. In addition to Fc blockade, IVIG is able to regulate FcR expression. Support for this role comes from Teeling’s work [19]. It is noteworthy that anti-D is associated with modulation in cytokine production and regulation of FcR expression [20]. Taken together, inhibition of MPS is the most accepted mechanism of action for IVIG and anti-D. It should be noted that anti-D is not recommended in patients who underwent splenectomy, because they usually fail to response to anti-D treatment. In addition, it should not be used in children with significant anemia and reticulocytosis. A very important difference exists in cost of IVIG and anti-D. Due to large pool of donors, IVIG has much higher cost than anti-D. As we could show, anti-D had good response and low rate of adverse effects. As reported, several works have considered IVIG as a better therapy. Thus, when clinical outcomes are comparable, cost differences can be important in deciding on the therapy of choice. Pharmacoeconomic analysis at the time of study showed that there is approximately a fivefold increase in overall cost of treatment with IVIG compared to anti-D in Iran. Of note, rational drug therapy is very important in developing countries due to high rate of drug prescriptions [21].

Study limitation
The present study has a number of limitations that should be acknowledged. Due to limited number of patients, our findings should be confirmed in larger studies. Long-term follow-up of patients can clarify safety and efficacy effects of two treatments over time.

CONCLUSION
This study emphasized once again that anti-D was associated with quicker rise in platelet number compared to IVIG. In addition, anti-D had acceptable safety profile compared to IVIG.
ACKNOWLEDGMENTS

The author wish to thank the staff of Amir-Kabir Hospital for their prior and continuing collaborations.

FUNDING

The study was performed by a grant from the vice chancellor of research of Arak University of Medical Sciences.

CONFLICT OF INTEREST

None.

REFERENCES