



HAL
open science

Subcutaneous anti- globulin application is a safe treatment option of immune thrombocytopenia in children

Monika M. Trebo, Eva Frey, Helmut Gadner, Milen Minkov

► **To cite this version:**

Monika M. Trebo, Eva Frey, Helmut Gadner, Milen Minkov. Subcutaneous anti- globulin application is a safe treatment option of immune thrombocytopenia in children. *Annals of Hematology*, 2009, 89 (4), pp.415-418. 10.1007/s00277-009-0848-x . hal-00535099

HAL Id: hal-00535099

<https://hal.science/hal-00535099>

Submitted on 11 Nov 2010

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Subcutaneous anti-D globulin application is a safe treatment option of immune thrombocytopenia in children

Monika M. Trebo · Eva Frey · Helmut Gadner · Milen Minkov

Received: 9 February 2009 / Accepted: 1 October 2009 / Published online: 13 October 2009
© Springer-Verlag 2009

Abstract Subcutaneous (sc) administration of anti-D seems to offer the same efficacy as intravenous administration but with less side effects. Here we report our experience with sc anti-D for pediatric immune thrombocytopenia (ITP). A total of 12 children with a median age of 11.2 years had been treated by sc anti-D. They received a median of 2 sc anti-D applications (range 1–31) with a dosage of 250–375 IE/kg body weight. Only in one out of a total of 102 single applications, a minimal and self-limited side effect (chills) had been observed. The mean platelet count was almost doubled after sc anti-D ($p < 0.0001$). After a median follow-up of 11.4 months, all patients are alive without major bleeding and stay well. We conclude that sc anti-D is not only an efficient means of treating ITP in children but is also a safe and convenient one.

Keywords Immune thrombocytopenia · Childhood · Anti-D · Subcutaneous injection · Side-effects

Introduction

Childhood-onset immune thrombocytopenia (ITP) has a benign course with spontaneous resolution within 6 months in 75–80% of the cases. In another 20%, it lasts for more than 6 months and is usually described as persistent or chronic. Even in one third of those cases, spontaneous resolution can occur later. Therefore, a conservative approach is advocated, and treatment is usually reserved

for the minority of patients with very low platelet counts and clinical signs of bleeding. Established treatment options are steroids, intravenous globulins (IVIg), anti-D globulin (anti-D), and splenectomy [1]. Compared to steroids and IVIg, anti-D gains on interest due to its moderate cost and safety profile. Nevertheless, when applied intravenously, anti-D can cause systemic reactions like chills, fever, headache, and vomiting. Of special concern are the cases of severe hemolysis observed after intravenous application [2–6] and the rapid irreversible encephalopathy reported by Christopher et al. [7]. Meyer et al. suggested that subcutaneous (sc) bolus could be a convenient and safer route of administration of anti-D in adults [8].

We report on our experience with sc anti-D for persistent ITP in pediatric patients.

Methods

Retrospective evaluation of 12 consecutive patients treated for persistent ITP by sc application of anti-D in our institution since 2001. The clinical assessment of bleeding was performed according to the score of Buchanan et al. [9]. First-line therapies were steroids or IVIg in all patients. Anti-D was applied as a second choice in patients with lacking or insufficient response to steroids and IVIg and those with considerable side effects or compliance problems. Indications for anti-D treatment were low platelet counts ($< 20 \times 10^9/L$) and either presence of clinical signs of bleeding (bleeding score 2–3 according to Buchanan) or noncompliance (mostly teenage patients, active athletes) or inability (mostly preschool children, poor social background) to follow physical activity restrictions in daily life. We chose the subcutaneous route of administration according to Meyer et al. [8] and after a personal communication with Prof.

M. M. Trebo (✉) · E. Frey · H. Gadner · M. Minkov
Division of Hemato-Oncology, St. Anna Children's Hospital,
Kinderspitalgasse 6,
1090 Vienna, Austria
e-mail: m.trebo@utanet.at

Salama (Charité Campus Virchow-Klinikum, Berlin, Germany). Written informed consent for therapy was obtained from the parents or guardians of the children and, when appropriate, from the subjects themselves, about the off-label use of the drug. The retrospective study has been approved by our Institutional Review Board.

Anti-D was applied in dosages between 250 and 375 IE/kg body weight as a 20-minute subcutaneous drip of 1 ml/1,000 IE after a local application of EMLA cream for 30–60 min. In order to avoid unnecessary time waste, the parents had usually applied EMLA in due time before the office visit. In the first few patients, a bolus injection as suggested by Prof. Salama had been performed. However, as the patients felt more comfortable with a longer injection time, the application mode has been changed to a 20-minute subcutaneous drip. After the first two applications, platelet count and hemoglobin had been measured 2 and 7 days after anti-D treatment, but afterwards, the blood counts had been controlled only at the next scheduled visit (usually 4 weeks later) or as clinically indicated by bleeding scores. The parents had been instructed to come back in case of bleeding events and febrile episodes.

Dose repetitions were performed with intervals of at least 3–4 weeks. If a dose repetition was needed in less than 4 weeks due to insufficient hemostatic effect or no increase of the platelet counts, the treatment was considered ineffective. In patients with no bleeding signs and/or platelets $>20 \times 10^9/L$ after 4 weeks, the intervals were extended accordingly. The side effects were documented as observed by the medical personnel, evident from the laboratory tests and reported by the patients/parents.

The collected data have been analyzed by statistical means, using the software package SPSS 10 for Windows™. Continuous variables have been compared by one-way analysis of variance. A *p* value <0.05 has been considered statistically significant.

Results

A total of 12 children (three boys, nine girls) with a median age of 11.2 years (range 3–15.7 years) had been treated by sc anti-D (Table 1). Most patients had several series of oral steroids or IVIG for a median pretreatment duration of 21.2 months (range 1–61 months), before sc anti-D treatment had been commenced. The median number of sc anti-D applications was 2 (range 1–31 applications). In the first cases, when the platelet count has been measured within 1 week after application, a dramatic improvement of platelet count after sc anti-D has been noted after 7 days already: In one case, the platelet count rose from $7 \times 10^9/L$ before treatment up to $252 \times 10^9/L$ after treatment. In another case, the platelets rose from $13 \times 10^9/L$ up to $111 \times 10^9/L$. In the most impressive

case, the platelet count rose from $14 \times 10^9/L$ before therapy up to $356 \times 10^9/L$ 7 days after sc anti-D treatment. Improvement or disappearance of the clinical bleeding signs was observed in parallel to the increment of the platelet counts. Reappearance of bleeding signs heralded the need for subsequent anti-D application. The maximal overall bleeding score assessed within 4 weeks after a previous anti-D application was as follows: 0 in two (17%) patients, between 1 and 2 in nine (75%) patients, and 3 in one (8%) patient.

Only in one out of a total of 102 single applications, a minimal side effect had been experienced. In detail, the patient, a then 18-year-old girl, who had been treated for more than 2 years with corticosteroids before sc anti-D, had a short reaction with chills 6 h after its third anti-D application. There were no hives, respectively, symptoms of hemolysis. The chills were readily controlled by antihistamines, and no more similar episodes were observed after the 26 subsequent sc anti-D applications.

Summarizing the blood count tests before and after the first two applications in each patient, we found that the mean platelet count was almost doubled after sc anti-D ($p < 0.0001$), while the hemoglobin level remained unchanged (Table 2).

After a median follow-up of 11.4 months, all patients are alive without major bleeding signs and stay well. Because of a concomitant mucoviscidosis with severe bleeding diathesis, case 11 had 31 applications of sc anti-D until now and will further continue. Four patients failed to respond to anti-D treatment. Three of them have normal platelet counts since final treatment with rituximab (Mabthera®); only one out of 12 patients had to be splenectomized for an ultimate control of the disease. Interestingly, this was the same patient who experienced the chills and who did not even respond to rituximab but has normal platelet counts ever since splenectomy.

Discussion

The most widely accepted and used treatment options for chronic ITP in childhood are steroids, IVIG, and anti-D [1]. To date, there is no convincing evidence that medical therapy given early in the course of childhood chronic ITP can favorably change the natural history of chronic ITP in children. Good short-term platelet enhancement is seen with all three modalities, but this has to be weighed against the side effects associated with these drugs. The lack of sustained platelet-enhancing effects in most of the cases leads in turn to frequent drug application and, hence, to more side effects. This is particularly true for steroids.

The durable effects of a regimen using pulses of high-dose oral dexamethasone in adults could not be confirmed in subsequent pediatric series [10–13]. Moreover, given every 3–4 weeks, these pulses are associated with high

Table 1 Comprehensive overview of patient's data

Patient number	Gender	Age at diagnosis (years)	Prior therapy with	Duration prior therapy (months)	SC anti-D applications	Side effects	Follow-up (months)	Comments
1	Female	10.2	Prednisolon, IgG, dexamethason	28.1	2	None	30.0	After rituximab normal thrombocyte count
2	Female	15.5	Prednisolon, IgG, dexamethason	1.8	2	None	26.5	After rituximab normal thrombocyte count
3	Female	16.1	Prednisolon, IgG, dexamethason	29.5	29	Chills	7.1	After splenectomy normal thrombocyte count
4	Female	8.1	IgG	1.03	9	None	17.1	
5	Female	10.9	Prednisolon	6.9	2	None	11.0	
6	Female	2.5	Prednisolon	19.3	2	None	91.7	After rituximab normal thrombocyte count
7	Male	3.0	Methylprednisolon	32.7	10	None	11.7	
8	Male	13.9	Prednisolon	1.0	2	None	9.6	
9	Male	5.5	IgG, prednisolon, dexamethason	61.0	1	None	2.2	
10	Female	13.8	Prednisolon	20.9	11	None	1.6	
11	Female	11.5	IgG	46.7	31	None	40.3	Mucoviscidosis; severe bleeding diathesis
12	Female	15.7	IgG	21.4	1	None	2.4	

incidence of weight gain, acne, striae, fatigue, mood changes, irritability, abdominal discomfort, and sleep disturbances, therefore, considerably reducing compliance in adolescents [14]. For this reason, the recommendation [15] to complete at least six courses of steroids before considering another option needs a critical revision. The introduction of IVIG brought about a conceptual shift in the treatment of both acute and chronic ITP. However, the role of IVIG in the treatment of chronic ITP is limited by the high cost, the mostly temporary increase of the platelet counts, long infusion duration, and relatively high frequency of adverse effects.

In Rh-positive subjects, anti-D is a further option. Its mechanism of action is believed to be mediated through the destruction of Rh(D) positive red cells, which are preferentially removed by the reticuloendothelial system, particularly the spleen, thus sparing autoantibody-coated platelets through Fc receptor blockade [16]. Intravenous anti-D treatment was first reported in 1984 [17]. Reviewing 25 papers about IV anti-D, Kjaersgaard and colleagues [1] conclude that in about 70% of children, a single administration of 50 µg/kg IV anti-D within 3 days increases platelet count to $\geq 20 \times 10^9/L$. Therefore, it is preferred over

IVIG because of its ease of administration, comparable efficacy, and lower cost. However, in accordance with its mechanism of action, hemolysis is a concern. Other, less dramatic side effects, like headache, nausea, chills, fever, and dizziness have been observed in 3.2% of cases [18].

Other routes of anti-D administration have been explored. Those are intramuscular [19–21] and sc injection. The latter has been first described by Meyer and coworkers [8], who used subcutaneously injected anti-D in a first series of seven adults and two children and found a high degree of efficacy and a low risk of bleeding. In a second, larger, series of 18 adults and four children [22], they confirmed their initial findings, reporting good results over a 3-year period, 78% experiencing a rise in platelet count, in most cases within 2 days. In both series, there was no single side effect.

Analyzing our long-term series of 12 children and adolescents, we can confirm not only the extraordinary efficacy of sc anti-D, leading to a doubling of platelet counts after application, but also its safety. The only reaction in a total experience of 102 applications was a chill reaction 6 h after sc injection successfully controlled by antihistamines. While the real etiology of this single

Table 2 Platelets and hemoglobin before and after treatment

	Median	Mean	SEM	95% CI	<i>p</i> value
Platelets before treatment ($\times 10^9/L$)	16.5	18.8	1.3	16.2–21.3	<0.001
Platelets after treatment ($\times 10^9/L$)	23	43.6	5.7	32.2–55.0	
Hemoglobin before treatment (g/dl)	12.1	12	0.16	11.7–12.3	0.397
Hemoglobin after treatment (g/dl)	11.95	11.8	0.16	11.5–12.1	

episode remained unclear, it must be emphasized that an anaphylactic reaction is highly unlikely as the same patient tolerated 26 more sc anti-D injections without any reaction. As for the theoretically present risk of hemolysis after anti-D, there was no single episode of hemolysis in our series.

The duration of conventional treatment in our series ranged from 0.1 to 61 months. This illustrates well the practical dilemma which must be faced in the treatment of ITP. We applied sc anti-D only in patients with severe ITP (PLT $<20 \times 10^9/L$ and bleeding signs). In addition, the patient's compliance was very variable. While some patients accepted readily the sc anti-D because they suffered under the side effects of corticosteroids, others refused sc anti-D after a few applications and returned to corticosteroid therapy for reasons of personal preference. There was still another patient group which was presenting not so much because of a manifest bleeding, but because they wanted to participate in a sportive event. Thus, the indication of any therapy for ITP must be carefully balanced between clinical needs and personal preferences of the patients.

The fact that our patients had up to 31 applications of sc anti-D, which means a treatment duration of more than 30 months, shows that this therapy can be tolerated over a very long time, without loss of efficacy and obviously without immunological sensitization. Therefore, sc anti-D can be successfully applied in an outpatient setting, leaving the children in their home environment. The children had only mild bleeding signs, mostly developing just before the subsequent application (an average within 3–4 weeks).

In conclusion, our data show that sc anti-D is not only an efficient means of treating ITP in children but also a safe and convenient one for application. Summarizing the experience at our institution with this type of treatment, we can strongly recommend it as a long-term outpatient treatment for chronic ITP in childhood.

Acknowledgments We thank Prof. A. Salama from Charité Campus Virchow-Klinikum, Berlin, Germany for sharing his personal experience with us and for his critical review of the manuscript.

Conflict of interest The authors have no conflicts of interest to disclose.

References

- Kjaersgaard M, Hasle H (2006) A review of anti-D treatment of childhood idiopathic thrombocytopenic purpura. *Pediatr Blood Cancer* 47:717–720
- Moser AM, Shalev H, Kapelushnik J (2002) Anti-D exerts a very early response in childhood acute idiopathic thrombocytopenic purpura. *Pediatr Hematol Oncol* 19:407–411
- Alioglu B, Avci Z, Ozyurek E, Ozbek N (2007) Anti-D immunoglobulin-induced prolonged intravascular hemolysis and neutropenia. *J Pediatr Hematol Oncol* 29:636–639
- Gaines AR (2005) Disseminated intravascular coagulation associated with acute hemoglobinemia or hemoglobinuria following Rh(0)(D) immune globulin intravenous administration for immune thrombocytopenic purpura. *Blood* 106:1532–1537
- Imbach P, Kuhne T (2000) Sequelae of treatment of ITP with anti-D (Rho) immunoglobulin. *Lancet* 356:447–448
- Levendoglu-Tugal O, Jayabose S (2001) Intravenous anti-D immune globulin-induced intravascular hemolysis in Epstein-Barr virus-related thrombocytopenia. *J Pediatr Hematol Oncol* 23:460–463
- Christopher K, Horkan C, Barb IT, Arbelaez C, Hodgdon TA, Yodice PC (2004) Rapid irreversible encephalopathy associated with anti-D immune globulin treatment for idiopathic thrombocytopenic purpura. *Am J Hematol* 77:299–302
- Meyer O, Kiesewetter H, Hermsen M, Salama A (2004) Efficacy and safety of anti-D given by subcutaneous injection to patients with autoimmune thrombocytopenia. *Eur J Haematol* 73:71–72
- Buchanan GR, Adix L (2002) Grading of hemorrhage in children with idiopathic thrombocytopenic purpura. *J Pediatr* 141:683–688
- Adams DM, Kinney TR, O'Branski-Rupp E, Ware RE (1996) High-dose oral dexamethasone therapy for chronic childhood idiopathic thrombocytopenic purpura. *J Pediatr* 128:281–283
- Borgna-Pignatti C, Rugolotto S, Nobili B, Amendola G, De Stefano P, Maccario R, Locatelli F (1997) A trial of high-dose dexamethasone therapy for chronic idiopathic thrombocytopenic purpura in childhood. *J Pediatr* 130:13–16
- Chen JS, Wu JM, Chen YJ, Yeh TF (1997) Pulsed high-dose dexamethasone therapy in children with chronic idiopathic thrombocytopenic purpura. *J Pediatr Hematol Oncol* 19:526–529
- Tarantino MD (2000) Treatment options for chronic immune (idiopathic) thrombocytopenia purpura in children. *Semin Hematol* 37:35–41
- Hedlund-Treutiger I, Henter JJ, Elinder G (2003) Randomized study of IVIg and high-dose dexamethasone therapy for children with chronic idiopathic thrombocytopenic purpura. *J Pediatr Hematol Oncol* 25:139–144
- Eden OB, Lilleyman JS (1992) Guidelines for management of idiopathic thrombocytopenic purpura. The British Paediatric Haematology Group. *Arch Dis Child* 67:1056–1058
- Bussel JB, Graziano JN, Kimberly RP, Pahwa S, Aledort LM (1991) Intravenous anti-D treatment of immune thrombocytopenic purpura: analysis of efficacy, toxicity, and mechanism of effect. *Blood* 77:1884–1893
- Salama A, Kiefel V, Amberg R, Mueller-Eckhardt C (1984) Treatment of autoimmune thrombocytopenic purpura with rhesus antibodies (anti-Rh0(D)). *Blut* 49:29–35
- Zimmerman SA, Malinoski FJ, Ware RE (1998) Immunologic effects of anti-D (WinRho-SD) in children with immune thrombocytopenic purpura. *Am J Hematol* 57:131–138
- Borgna-Pignatti C, Battisti L, Zecca M, Locatelli F (1994) Treatment of chronic childhood immune thrombocytopenic purpura with intramuscular anti-D immunoglobulins. *Br J Haematol* 88:618–620
- Caglayan S, Aksit S, Yaprak I, Aydinlioglu H, Ozdogru E, Ozerkan E (1993) Steroid-free interval with anti-D in chronic idiopathic thrombocytopenic purpura. *Acta Paediatr Jpn* 35:36–38
- Krishnamurti L, Charan VD, Desai N, Pati H, Choudhry VP (1994) Anti-D immunoglobulin in the treatment of idiopathic thrombocytopenic purpura. *Indian J Pediatr* 61:179–182
- Meyer O, Kiesewetter H, Hermsen M, Petriedes P, Rose M, Seibt H, Salama A (2006) Replacement of intravenous administration of anti-D by subcutaneous administration in patients with autoimmune thrombocytopenia. *Pediatr Blood Cancer* 47:721–722