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One Year Follow-Up of Children and Adolescents With Chronic Immune Thrombocytopenic Purpura (ITP) Treated With Rituximab

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Abstract

Background—We previously showed in a prospective study that rituximab appears to be effective in some children and adolescents with severe chronic immune thrombocytopenia. Eleven of 36 patients achieved and maintained platelet counts over 50,000/mm^3 within the first 12 weeks. These patients were followed for the next year.

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A complete list of the members of the Rituximab/ITP Study Group and the Glaser Pediatric Research Network appears on-line as supplemental material.

Additional supporting information may be found in the online version of this article.

Methods—Platelet counts were monitored monthly and all subsequent bleeding manifestations and need for further treatment was noted.

Results—Eight of the 11 initial responders maintained a platelet count over 150,000/mm^3 without further treatment intervention. Three patients had a late relapse. One initial non-responder achieved a remission after 16 weeks, and two additional patients maintained platelet counts around 50,000/mm^3 without the need for further intervention.

Conclusions—Rituximab resulted in sustained efficacy with platelet counts of 50,000/mm^3 or higher in 11 of 36 patients (31%).

Keywords

clinical trial; immune thrombocytopenia; rituximab

INTRODUCTION

Immune thrombocytopenia (ITP) is usually self-limited in children, but a subgroup of patients will develop chronic ITP (of more than 6 months duration) associated with clinically significant bleeding manifestations [1–3]. Treatment options include corticosteroids, intravenous immunoglobulin (IVIG), anti-D immunoglobulin, or chemotherapeutic agents, such as vincristine or cyclophosphamide [4–6]. Recently, Bennett et al. [7] demonstrated the safety and efficacy of rituximab for the treatment of such children. Eleven of 36 patients with severe, chronic ITP responded within 1–7 weeks to three or four doses of rituximab, by maintaining their platelet count over 50,000/mm^3 for at least 12 weeks [7]. The follow-up of these children 1 year later is reported here by determining the sustainability of the response at the 150,000/mm^3 and the 50,000/mm^3 levels.

METHODS

The study protocol has been previously described in detail [7,8]. In short, ten clinical sites and a data-coordinating center (Supplemental Appendix) participated in this study, which was approved by the Institutional Review Boards at the participating institutions.

ITP was defined by the criteria developed by Buchanan and Adix [9], and Evans' Syndrome was defined as ITP with evidence of autoimmune hemolytic anemia with positive direct antiglobulin test. Patients were eligible if they suffered from severe, chronic ITP (either primary or secondary), were between 18 months to 18 years of age at enrollment and had a platelet count of less than 30,000/mm^3 at screening (for more details see Refs. [7,8]). Rituximab (anti-CD20, Genentech, South San Francisco, CA/Biogen, Cambridge, MA/IDEC, San Diego, CA) was given as an intravenous infusion at a dose of 375 mg/m^2 weekly for four doses. Treatment success defined as a sustained platelet count ≥ 50,000/mm^3 during four consecutive weeks starting during weeks 9–12, was achieved by 11 of 36 patients (31%) with a median time to response of 1 week (range 1–7 weeks).

All patients were followed for at least 1 year. Any bleeding episodes or further interventions were noted, and platelet counts were obtained monthly. A sustained response was defined as a platelet count over 150,000/mm^3 without further intervention during the observation phase.

A partial response was defined as a platelet count over 50,000/mm^3 without further intervention. Relapse was defined as an initial platelet count >150,000 cells/mm^3 that later declined and necessitated further treatment.

Statistics

Fisher's exact test and the Wilcoxon rank-sum test were used to assess the association of persistent response to rituximab with various demographic and clinical factors. SAS software (SAS Institute, Cary, NC) was used for all computations.

RESULTS

All 36 patients were evaluable. Of the 11 patients previously defined as responders (4 males and 7 females, age range 7.5–17.4 years; Table I), 8 maintained a platelet count >150,000/mm^3 for the whole study duration (Fig. 1a).

Three patients with an initial response relapsed later (Fig. 1b). One patient had a late decrease in platelet count to 113,000/mm^3 and was treated for severe bleeding prompting therapy with amicar and solumedrol. A second patient had brief decreases in platelet count fell to 23,000/mm^3 at week 39 and 4,000/mm^3 at week 49 but did not receive additional treatment. A third patient relapsed at week 32 with a platelet count of 7,000/mm^3, received intravenous immunoglobulin, and then maintained platelet counts around 50,000/mm^3 without further intervention.

Three patients initially classified as non-responders later improved (Fig. 1c). One whose platelet count at week 12 was 4,000/mm^3 recovered after an additional dose of IVIG and methylprednisolone and maintained a platelet count over 50,000/mm^3 thereafter without the need for further treatment. Another who was still receiving steroids at week 12 maintained a platelet count >50,000/mm^3 without steroid therapy until week 38, then experienced a decline to 33,000/mm^3 but recovered without further treatment after a short course of steroids. A third patient reached a platelet count of 56,000/mm^3 at the end of the evaluation period and stayed close to that level thru week 52.

Six patients had Evans syndrome. Two were non-responders, two relapsed (one of them, as described above, developed severe bleeding symptoms at a platelet count of 113,000/mm^3) and two maintained a normal platelet count.

The bleeding score [7] was generally low in patients with sustained response (see Table I). No grade 4 bleeding occurred, while grade 3 bleeding was observed in three patients. All of the eight Caucasian responders maintained their response, whereas all three African-American responders relapsed (P=0.006). No other factor (gender, age, Hispanic ethnicity, previous treatment history or rapidity of response to rituximab) predicted a sustained response (P>0.15).

Five of the 25 initial non-responders underwent a splenectomy after week 12. In two this was successful (platelets within normal range without further intervention) and three continue to need occasional treatment with steroids. No adverse events related to study medication were reported after week 12. Immunoglobulin levels were consistently abnormal

in two patients. One patient had persistently low IgG (708 mg/dl initially, 508 mg/dl at week 52), IgM and IgA and another developed low IgM levels at week 12, and later also developed low IgG (decrease from 995 mg/dl at baseline to 581 mg/dl at weeks 28 and 52) and IgA levels. None of the patients had infections related to a decreased immune response.

DISCUSSION

Rituximab, a monoclonal anti-CD20 antibody, was initially licensed for B cell non-Hodgkin's lymphoma, but has since been used for other indications, including immune thrombocytopenia [7,10–17]. The early results of this prospective study of rituximab in childhood and adolescent ITP showed an encouraging response rate of over 30% in patients with previously treatment-refractory disease [7]. The longer follow-up presented in this report demonstrates that most children (72%) who initially respond to rituximab will maintain their platelet count in an accepted and considered range (i.e., over 50,000/mm^3) without further intervention and with no or only minimal bleeding symptoms. This is very similar to the results obtained by Wang et al. [16], in which an overall sustained response in 9 of 24 children (37%), including 9 of 15 (60%) initial responders was reported.

After 1 year of follow-up none of the patients had severe infectious episodes despite the decrease in B cells and immunoglobulin levels in a few patients. By the end of the study, 12 of 36 children (33%) had undergone splenectomy, seven before entering the study and 5 after they did not respond to treatment with rituximab.

Rituximab appears to offer a safe treatment option for children with severe, treatment-refractory ITP resulting in sustained responses in some patients, but continued follow-up is necessary especially in children who have not yet normalized their platelet counts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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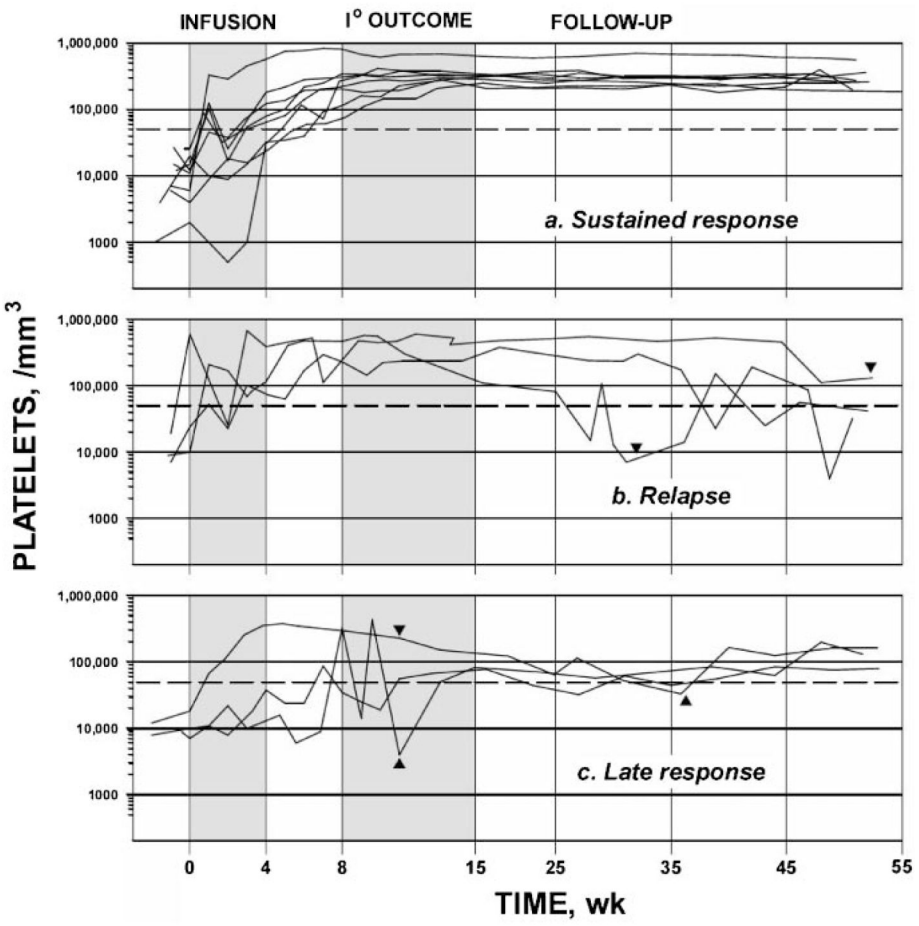

Fig. 1.

Platelet levels during observation time. Rituximab infusions were administered weekly × 4 during the first month. **a**: Responders with a sustained response thru week 52. **b**: Initial responders who later relapsed. **c**: Initial non-responders who attained and maintained response thru week 52. Dashed line indicates target platelet count, 50,000/mm^3. Arrows indicate treatment for low platelet count or bleeding; see text for details.

TABLE I

Comparison of Patients With Sustained Response to Rituximab, Those Who Relapsed After Improvement at 12 Weeks, and Non-Responders *

	Sustained response	Relapse	Non-responders
Demographics			
Subjects	8	3	25
Race			
White	8 (100)	0 (0)	20 (80)
Black	0 (0)	3 (100)	1 (4)
Other	0 (0)	0 (0)	4 (16)
Gender			
Male	3 (38)	1 (33)	17 (68)
Female	5 (62)	2 (67)	8 (32)
Age, years	12.5 (7.5–17.4)	12.4 (7.9–16.9)	10.6 (2.6–18.3)
Prior to trial			
Duration of ITP, years	4.3 (0.6–11.6)	5.8 (1.4–9.5)	3.9 (0.6–12.1)
Number of treatments	4.4 (3–8)	4.7 (3–6)	4.0 (2–7)
Response[a]			
Steroids	8 (100)	3 (100)	16 (64)
IVIG	6 (75)	3 (100)	19 (86)
Anti-D	3 (60)	1 (100)	17 (81)
Splenectomy	1 (13)	2 (67)	4 (16)
Refractory	5 (63)	3 (100)	19 (76)
During trial			
Early response	8 (100)	2 (67)	1 (4)
Bleeding episodes, grade 4	0	1	2
Bleeding episodes, grade 3	6	6	54
Splenectomy	0 (0)	0 (0)	5 (20)

* Shown are n (%) or mean (minimum–maximum);

[a] Among those receiving the indicated treatment.