Prospective phase I/II study of rituximab in childhood and adolescent chronic immune thrombocytopenic purpura.

Authors

A complete list of the members of the Rituximab/ITP Study Group and the Glaser Pediatric Research Network appears in the “Appendix.”

From the Division of Hematology/Oncology and the Clinical Research Program, Children’s Hospital Boston, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, and the Departments of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX, Weill Medical College at Cornell University, New York, NY, Baylor College of Medicine, Houston, TX, Emory University School of Medicine, Atlanta, GA, Van Eslander Cancer Center, St. John Hospital, Detroit, MI, University of California, Los Angeles (UCLA)/Mattel Children’s Hospital at UCLA, Los Angeles, CA, University of California, San Francisco, CA and Stanford University, Stanford, CA...
Submitted:

Reprints: Ellis J. Neufeld, Division of Hematology/Oncology, Children's Hospital Boston, 300 Longwood Avenue, Boston, MA 02115; email:

ellis.neufeld@childrens.harvard.edu

Supported by grants from an anonymous donor to the Boston Center for Genetic and Acquired Blood Disease, by the Glaser Pediatric Research Network, and by Genentech/Biogen-Idec. Additional support was provided by General Clinical Research Centers at the Baylor College of Medicine, (GCRC grant No. M01RR000188), Children’s Hospital, Boston (GCRC No. M01RR02172), the University of California, Los Angeles, (GCRG No. M01RR00865) and Weill Medical College at Cornell University (M01-RR00047) and the Pediatric Clinical Research Center at the University of California, San Francisco (Grant No M01-RR-01271). Support was also provided by the Lita Annenberg Hazen Foundation, University of California, Los Angeles.

Authorship Contributions:

The following authors designed the research protocol: C.M.B., J.B.B., T.C.A, B.E.G., T.A.O., A.N.L., S.A.F, G.R.B., H.A.F. and E.J.N.

The following authors controlled and analyzed the data: D.D.K., M.C.M., C.M.B., H.A.F., and E.J.N.

The following authors wrote the paper: C.M.B., Z.R.R., H.A.F., and E.J.N.

The online version of this article contains a data supplement.

Presented orally and in abstract form at the 18th annual meeting of the American Society of Pediatric Hematology/Oncology, Washington, D.C., May 15, 2005.
Abstract

We assessed safety and efficacy of rituximab in a prospective study of 36 patients, age 2.6-18.3 years, with severe chronic immune thrombocytopenic purpura (ITP). The primary outcome of sustained platelets > 50,000/mm$^3$ during four consecutive weeks, starting in weeks 9 to 12, was achieved by 11 of 36 patients (31%, CI 16-48%). Median response time was one week (range 1-7). Attainment of the primary outcome was not associated with age, prior pharmacologic responses, prior splenectomy, ITP duration, screening platelet count, refractoriness or IgM reduction. First dose, infusion-related toxicity was common (47%) despite premedication. Significant drug related toxicities included third-dose hypotension (n=1) and serum sickness (n=2). Peripheral B cells were depleted in all subjects. IgM decreased 3.4% per wk, but IgG did not significantly decrease. Rituximab was well tolerated, with manageable infusion-related side effects, but 6% of subjects developed serum sickness. Rituximab is beneficial for some pediatric patients with severe, chronic ITP.
Introduction

ITP in children is typically a self-limited disorder that resolves without significant morbidity or mortality. In approximately 20% of pediatric patients, the disease becomes chronic with thrombocytopenia persisting beyond 6 months. The standard treatments for children with chronic ITP include corticosteroid therapy, intravenous immunoglobulin (IVIG), anti-D immune globulin or splenectomy. Splenectomy is effective in many patients, but exposes young children to an increased risk of infection with encapsulated organisms. Some children with chronic ITP are refractory to all therapy and have chronically low platelets and intermittent bleeding.

Rituximab is a chimeric, monoclonal antibody directed against the CD20 antigen expressed on pre-B and mature B lymphocytes that is approved for use in the treatment of B cell lymphoma. Rituximab rapidly eliminates most circulating B cells with subsequent recovery of B cell counts 6 to 12 months after therapy. Reducing B cells in the circulation may be effective in the treatment of autoimmune diseases such as ITP. Several studies and case series in adults and children with severe chronic ITP have shown promising results.

We performed an investigator-initiated, multicenter, prospective open-label phase I/II trial of rituximab in 36 children with severe or refractory chronic ITP. This report summarizes the primary outcome data from this clinical trial, the only prospective study of rituximab therapy in pediatric patients with severe chronic ITP. In addition, this study is the first report of rituximab pharmacokinetic parameters in children (Supplemental document S2; see the Supplemental Materials link at the top of the online article, at the Blood website).
Methods

The study was carried out at ten clinical sites with a data-coordinating center (Appendix). The protocol was approved by the Institutional Review Boards at the participating institutions and carried out under IND number 10821. A Data and Safety Monitoring Board (Appendix) approved the protocol and supervised the conduct of the study. Signed informed consent was obtained from all patients’ parents and assent was obtained from patients age 12 years and older.

Eligibility criteria

Patients with severe, chronic ITP (either primary or secondary), including refractory ITP, age 18 months to 18 years (before 19th birthday) at enrollment and with a platelet count less than 30,000/mm³ at screening were eligible.

Primary Outcome

Treatment success was defined as a sustained platelet count ≥ 50,000/mm³ during four consecutive weeks starting during weeks 9-12, with the first and fourth measurements at least 22 days apart. Responses were required to be independent of rescue and supportive care regimens within 7 days of the first measurement or at anytime between measurements.

Assessment of Bleeding

Bleeding severity was assessed at screening and at each subsequent study visit using a modification of the scoring system of Buchanan and Adix (Table 1). Using this scoring system, bleeding is graded from 0-5. The modification from the published face-to-face assessment scale was to allow for recording of the “highest grade of bleed since the prior visit” which was ascertained by patient or parent/guardian interview.
Treatment

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/m² weekly for four doses (days 1, 8, 15 and 22). Subjects were treated within 4 weeks of enrollment.

Statistical Methods

Sample size was chosen in consideration of both the safety (Phase I) and efficacy (Phase II) aspects of the trial. Thirty-five subjects were sufficient to rule out an underlying adverse event rate of 10%, should no events be observed, and to provide 8% standard error for a success rate in the anticipated range (30-60%). The final sample size was 36 because two patients were enrolled simultaneously at separate sites. In this open-label, single-arm, trial there were no issues of blinding or randomization. The intention-to-treat principle was applied by analyzing data from all subjects who began treatment, regardless of whether they received all four planned infusions.

Analysis of the primary endpoint consisted of the point estimate of treatment success rate with an exact binomial 95% confidence interval. Standard descriptive statistics (mean, median, percentiles, percentages, confidence intervals) were employed for reporting clinical characteristics and secondary outcomes.

Fisher’s exact test and the exact Wilcoxon rank-sum test were used to compare characteristics of responders and non-responders. Trends in immune measures were assessed by repeated-measures analysis using generalized estimating equations with an exchangeable working correlation structure. We log-transformed IgG and IgM concentration so as to express the trends in percentage per week. For pair wise analysis
of changes in CD19 percentage between weeks 0–6 and weeks 6–12, we used the Wilcoxon signed-rank test.

Additional information on methods with regard to formal study definitions, eligibility, exclusion criteria, laboratory and adverse event monitoring, rescue and supportive care regimens and pharmacokinetics are given in Document S1 (see the Supplemental Materials link at the top of the online article, at the Blood website).
Results and Discussion

Patient Characteristics and Response to Therapy

Thirty-eight children and adolescents, median age 11.2 years (range 2.6 to 18.3 years) with severe ITP or Evans consented to participate. One patient had a spontaneous remission before treatment and another withdrew prior to treatment. Therefore, 36 patients were treated at eight sites from May 2003 to September 2004. Thirty-three of 36 patients received the scheduled 4 weekly doses of rituximab at 375 mg/m²/dose. Three patients did not complete all four doses due to adverse side effects: serum sickness in two patients and infusion-related hypotension in one patient.

Patient characteristics and responses to therapy are shown in Table 2. The patient population included 30 (83%) patients with primary ITP and 6 (17%) with Evans Syndrome. None of the Evans Syndrome patients had severe hemolytic anemia at the time of study entry. This was a heavily treated group of patients who received a median of 4 (range 2 to 8) different therapies in the course of their ITP. Seventy five percent of the subjects were refractory (or had intolerable side effects) to at least 2 therapies. Seven patients (19%) underwent splenectomy prior to the start of the study.

Eleven of 36 patients or 31% (95% CI 16 – 48) achieved the primary outcome of sustained platelet count over 50,000/mm³ in four consecutive weeks starting during weeks 9-12. The time to a first platelet measurement over 50,000/mm³ was short, with a median of 1 week and a range of 1 to 7 weeks (Figure 1). Of the 36 subjects, one was scored a treatment failure per protocol criteria despite elevated platelet counts at weeks 9-12, because of treatment with steroids other than the defined rescue/supportive care allowed through week 11 (See web Supplemental Document S1; see the Supplemental
Materials link at the top of the online article, at the Blood website). One patient in the treatment failure for the primary outcome group had a robust early response from 9,000/mm$^3$ to 300,000/mm$^3$ at week 2, but relapsed at week 10 with a platelet count under 20,000/mm$^3$.

The 31% response rate in this study is lower than previously reported in both adult and pediatric patients with severe chronic ITP treated with rituximab. In the largest adult study, 31 of 57 patients (54%) responded, achieving a platelet count of 50,000/mm$^3$. Earlier series in adults with chronic ITP reported response rates ranging from 25% to 65%. In a retrospective study of rituximab therapy in children with severe chronic ITP, 15 of 24 patients (63%) achieved a stable platelet count (>150,000/mm$^3$) for 4 to 30 months without additional therapy. The patient population in our study is not directly comparable to the one in this study by Wang, et al. For example, the patients in the present study were on the average more severely affected than those reported by Wang and colleagues. However, all of the published rituximab studies in ITP are small, and the 95% confidence intervals on success rates are broad and overlap.

Attainment of the primary outcome was associated weakly with Evans Syndrome, female gender and black race. Rituximab response was not associated with prior response to standard therapy or splenectomy, age, ITP duration, number of previous treatments, screening platelet count, refractoriness or reduction in IgM.

**Immunologic Studies**

Peripheral B cells (CD19+) were depleted in all patients, falling from a baseline mean of 19.5% to 2% at week 6 (p<0.001) and remaining unchanged at 2% between
week 6 and week 12 (p=0.31). Despite circulating B cell depletion in all patients, there was no significant hypogammaglobulinemia with mean IgG falling only 0.7 % per week (95% CI 0.0 – 1.4). In contrast, mean IgM levels did decrease significantly (Table 2). Based on these results, it would appear that IVIG replacement therapy for otherwise healthy, pediatric ITP patients without underlying immunodeficiency treated with rituximab is unnecessary.

Adverse Events and Safety

During the first 12 weeks of the study, 6 patients (17%) experienced 9 serious adverse events (SAEs). Since SAE’s were calculated by intent to treat and three patients did not complete all 4 doses, the rate may be higher that observed. Two patients, both non-responders, had serum sickness; one, a 12 year-old male patient presented with fever, fatigue and rash after the second dose of rituximab and the other, an 11 year-old female patient developed fever, joint pain and swelling, conjunctival hyperemia and cutaneous rash after the second rituximab dose. Another patient (non-responder) developed CTC grade 2 infusion-related hypotension with his third dose. Rituximab was discontinued in these three patients.

The rate of serum sickness appears to be higher than that reported in adults with lymphoma. In the study of Wang et al, three of 24 pediatric patients (12.5%) with chronic ITP developed serum sickness. This brings the total reported incidence of serum sickness in pediatric subjects with chronic ITP treated with rituximab to 12 % (5 of 60). The explanation for higher serum sickness rates in this population compared to lymphoma is not known.
One 13-year-old patient with Evans Syndrome who had been weaned off steroids at the start of the study developed primary varicella after the first rituximab infusion. This subject, a responder, was admitted to the hospital for treatment with VZIG, stress-dose steroids, and acyclovir and recovered completely. No other serious infections occurred during the study period. In addition, one patient was hospitalized for rescue IVIG therapy for grade 4 bleeding (epistaxis) and one patient had 4 hospitalizations related to recurrent bleeding. Both of these patients were non-responders. Side effects related to first-dose rituximab infusion, such as chills, fever, and respiratory symptoms, were common (47% of patients) and mild (CTC grade 1 and 2 only). There were no grade 5 bleeding episodes. Grade 3 or 4 bleeding was reported in 5 responders (45%) versus 15 non-responders (60%) during weeks 2 – 12.

Additional information regarding ancillary clinical results of the study and pharmacokinetics are given in Supplemental Document S2 (see the Supplemental Materials link at the top of the online article, at the Blood website).

We conclude that rituximab therapy is beneficial for some children with severe chronic ITP who are refractory to standard agents. The toxicity profile of rituximab is acceptable in the majority of patients, but there was a higher than expected incidence of serum sickness, which should be discussed with patients and families prior to initiating treatment. Given the favorable safety profile and results from other studies, rituximab may be preferable to splenectomy particularly in patients with Evans Syndrome\textsuperscript{18,19}, in whom splenectomy is generally not effective, and in younger patients who are at relatively higher risk of infection with encapsulated organisms.
Acknowledgments

We thank the patients and their families, and the research coordinators, nurses and physicians at the centers that participated in the study.
Appendix

Sites and investigators of the Pediatric ITP Rituximab Study Group with patient enrollment, listed alphabetically by site.

- *Baylor College of Medicine, Houston, TX: Donald H. Mahoney, MD, Brigitta U. Mueller, MD, Bogdan Dinu, MD, 5 patients.
- *Children’s Hospital, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA: Ellis J. Neufeld, MD, PhD, Carolyn M. Bennett, MD, Carol Sweeney, RN, BSN, Pamela Boardman, MPH, 11 patients.
- Duke University School of Medicine, Durham, NC: Russell E. Ware, MD, Ph.D., Sherri A. Zimmerman, MD, Nicole Mortier, MHS, PA-C, 0 patients.
- Emory University School of Medicine, Atlanta, GA: Thomas C. Abshire, M.D., Thomas A. Olson, M.D., Cara Brown, Kimberly Balark RN, 4 patients.
- *Stanford University School of Medicine, CA: Bertil E. Glader, MD, Keniki McNeil, RNC, 0 patients.
- University of Texas Southwestern Medical Center, Dallas, TX: George R. Buchanan, MD, Zora R. Rogers, MD, Leah Adix, CRA, 1 patient.
- *University of California, Los Angeles/Mattel Children’s Hospital at UCLA: Theodore B. Moore, MD, Stephen A. Feig, MD, Janet Mooney, RN, Helene Cohen, RN, Elena Khanukhova, 3 patients.
- *University of California, San Francisco: Mignon L. Loh, MD, William C. Mentzer, MD, Rosa Sanchez, MD, Laura Quill, PNP, Marcia Wertz, RN, MS, 2 patients.
- Van Eslander Cancer Center, St. John’s Hospital, Detroit, MI: Hadi Sawaf, MD, Adonis N. Lorenzana, MD, JoAnn Kapa, RN, Pamela Rennpage, CRA, 3 patients.
- Weill Medical College at Cornell University, New York, NY: James B. Bussel, MD, Megan Wissert, RNC, Joseph Cruse, 7 patients.

*Glaser Pediatric Research Network Site

**Design, Analysis and Coordinating Center (DACC)**

- Children’s Hospital, Boston, MA: Henry A. Feldman, PhD, Daniel D. Kinnamon, MS, Maggie McCarthy, MS, MPH

**Data and Safety Monitoring Board**

Victor S. Blanchette, MD (Chair)
Alan R. Cohen, MD
James N. George, MD
Sarah K. Vesely, Ph.D.
References


Table 1: Grading of Hemorrhage in Children with ITP

<table>
<thead>
<tr>
<th>Grade</th>
<th>Overall Bleeding Severity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>No new hemorrhage of any kind</td>
</tr>
<tr>
<td>1</td>
<td>Minor</td>
<td>Few petechiae (≤ 100 total) and/or ≤ 5 small bruises (≤ 3 cm diameter); no mucosal bleeding</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>Many petechiae (&gt; 100 total) and/or &gt; 5 large bruises (&gt; 3 cm diameter); no mucosal bleeding</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Overt mucosal bleeding (epistaxis, gum bleeding, oropharyngeal blood blisters, menorrhagia, gastrointestinal bleeding, etc.) that does not require immediate medical attention or intervention</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>Mucosal bleeding or suspected internal hemorrhage (in the brain, lung, muscle, joint, etc.) that requires immediate medical attention or intervention</td>
</tr>
<tr>
<td>5</td>
<td>Life-threatening/Fatal</td>
<td>Documented intracranial hemorrhage or life-threatening or fatal hemorrhage in any site</td>
</tr>
</tbody>
</table>
Table 2: Response to rituximab treatment, overall and in subgroups

<table>
<thead>
<tr>
<th>Group</th>
<th>N (%)</th>
<th>Responders</th>
<th>% Response (95% CI)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>36 (100)</td>
<td>11</td>
<td>31 (16–48)</td>
<td>—</td>
</tr>
<tr>
<td>Primary</td>
<td>30 (83)</td>
<td>7</td>
<td>23 (10–42)</td>
<td>0.06</td>
</tr>
<tr>
<td>Evans</td>
<td>6 (17)</td>
<td>4</td>
<td>67 (22–97)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (58)</td>
<td>4</td>
<td>19 (5–42)</td>
<td>0.14</td>
</tr>
<tr>
<td>Female</td>
<td>15 (42)</td>
<td>7</td>
<td>47 (21–73)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>28 (78)</td>
<td>8</td>
<td>29 (13–49)</td>
<td>0.09</td>
</tr>
<tr>
<td>Black</td>
<td>4 (11)</td>
<td>3</td>
<td>75 (19–99)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (11)</td>
<td>0</td>
<td>0 (0–60)</td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>6 (17)</td>
<td>1</td>
<td>17 (1–64)</td>
<td>0.64</td>
</tr>
<tr>
<td>Not</td>
<td>30 (83)</td>
<td>10</td>
<td>33 (17–53)</td>
<td></td>
</tr>
<tr>
<td>Refractory</td>
<td>27 (75)</td>
<td>8</td>
<td>30 (14–50)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Not</td>
<td>9 (25)</td>
<td>3</td>
<td>33 (7–70)</td>
<td></td>
</tr>
<tr>
<td>Splenectomy</td>
<td>7 (19)</td>
<td>3</td>
<td>43 (10–82)</td>
<td>0.65</td>
</tr>
<tr>
<td>No</td>
<td>29 (81)</td>
<td>8</td>
<td>28 (13–47)</td>
<td></td>
</tr>
<tr>
<td>Steroid responsive†</td>
<td>27 (75)</td>
<td>11</td>
<td>41 (22–61)</td>
<td>0.27</td>
</tr>
<tr>
<td>Non-responsive</td>
<td>4 (11)</td>
<td>0</td>
<td>0 (0–60)</td>
<td></td>
</tr>
<tr>
<td>Unknown‡</td>
<td>5 (14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVIG responsive†</td>
<td>28 (78)</td>
<td>9</td>
<td>32 (16–52)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Non-responsive</td>
<td>5 (14)</td>
<td>2</td>
<td>40 (5–85)</td>
<td></td>
</tr>
<tr>
<td>Unknown‡</td>
<td>3 (8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-D responsive†</td>
<td>21 (58)</td>
<td>4</td>
<td>19 (5–42)</td>
<td>0.59</td>
</tr>
<tr>
<td>Non-responsive</td>
<td>6 (17)</td>
<td>2</td>
<td>33 (4–78)</td>
<td></td>
</tr>
<tr>
<td>Unknown‡</td>
<td>9 (25)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measure</th>
<th>Median (Min, Max)</th>
<th>p§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment (yr)</td>
<td>Responders (11)</td>
<td>12.8 (7.5, 17.4)</td>
</tr>
<tr>
<td>ITP duration (yr)</td>
<td></td>
<td>4.6 (0.6, 11.6)</td>
</tr>
<tr>
<td>Prior treatments</td>
<td></td>
<td>4.0 (3.0, 8.0)</td>
</tr>
<tr>
<td>Initial platelets (k/mm³)</td>
<td></td>
<td>9.0 (1.0, 27.0)</td>
</tr>
<tr>
<td>Change in IgM (mg/dL)</td>
<td></td>
<td>−26.0 (−150.1, +23.6)</td>
</tr>
</tbody>
</table>

*Testing equal response in subgroups by Fisher’s exact test.
†From medical history prior to study.
‡Not administered or response unknown.
§ Testing equal distribution in responders and non-responders by exact Wilcoxon rank sum test.
Figure Legend

Figure 1. Platelet response to rituximab.

Boxplot of platelet counts (on log scale) over time in weeks for responders (gray) and non-responders (white) from weeks 0 though 16. The first rituximab dose was administered in week 1. The dashed horizontal line represents the primary outcome platelet count of 50,000/mm$^3$. The horizontal lines in each plot, from highest to lowest, are the 90th, 75th, 50th (median), 25th, and 10th percentiles.
Figure 1

[Graph showing platelet counts over time for responders and non-responders]
Prospective phase I/II study of rituximab in childhood and adolescent chronic immune thrombocytopenic purpura

Carolyn M Bennett, Zora R Rogers, Daniel D Kinnamon, James B Bussel, Donald H Mahoney, Thomas C Abshire, Hadi Sawaf, Theodore B Moore, Mignon L Loh, Bertil E Glader, Maggie C McCarthy, Brigitta U Mueller, Thomas A Olson, Adonis N Lorenzana, William C Mentzer, George R Buchanan, Henry A Feldman, Ellis J Neufeld and