# Treatment of Children with Persistent and Chronic Idiopathic Thrombocytopenic Purpura: 4 Infusions of Rituximab and Three 4-Day Cycles of Dexamethasone

Joseph H. Oved, MD, MA[1,2,3], Christina S. Y. Lee, BA[1], and James B. Bussel, MD[1]

**Objectives** To assess initial and long-term outcome of children with persistent/chronic idiopathic thrombocytopenic purpura (ITP) treated with 4 infusions of rituximab and three 4-day cycles of dexamethasone (4R+3Dex) including cohorts with most benefit and/or treatment associated toxicity.

**Study design** All pediatric patients with ITP at Weill-Cornell who received 4R+3Dex were included in this retrospective study. Duration was median time from first rituximab infusion to treatment failure. Patient cohort included 33 children ages 1-18 years with persistent/chronic ITP; 19 were female, 10 of whom were adolescents. Every patient had failed more than 1 and usually several ITP treatments.

**Results** Children were treated with rituximab, 375 mg/m$^2$ weekly for 4 weeks and three 4-day courses of dexamethasone 28 mg/m$^2$ (40 mg max). Average age of nonresponders was 7.75 years, and initial responders averaged 12.7 years ($P = .0073$); 30% maintained continuing response at 60 months or last check-up. Eight of the 10 patients who underwent remission were female with ITP <24 months prior to initiating 4R+3Dex. All responding male patients except 2 relapsed.

**Conclusions** Durable unmaintained ITP remission after 4R+3Dex was seen almost exclusively in female adolescents with <24 months duration of ITP. This provides a new therapeutic paradigm for a subpopulation with hard-to-treat chronic ITP. The pathophysiology of ITP underlying this distinction requires further elucidation. *(J Pediatr 2017;191:225-31).*

Idiopathic thrombocytopenic purpura (ITP) is the most common cause of acquired, nonchemotherapy-induced thrombocytopenia and is autoimmune in origin.[1] Autoimmunity in ITP is not only related to antiplatelet antibodies but also cytotoxic T cells.[2-4] Antiplatelet antibodies and likely cytotoxic T cells not only accelerate platelet destruction but also impair platelet production.[5,6]

Immunomodulation has been the traditional approach to treatment of ITP. Frontline approaches include steroids, intravenous immunoglobulin, intravenous anti-D, and observation.[7-9] However, even though ITP in most affected children will spontaneously improve, 13%-36% of patients will go on to develop chronic disease of greater than 1 year duration.[10] For these patients and for a number of those with persistent disease (3-12 months duration) who are difficult to manage, additional treatments may be required or at least advantageous. The most commonly used second line treatments include therapeutics such as thrombopoietic agents, rituximab, azathioprine, mycophenolate mofetil, and splenectomy.[11-15]

Splenectomy may be curative but typically is avoided if at all possible.[16] Rituximab alone has not been shown to provide any immediate benefit but may result in gradual long-term responses with increases in platelet counts over time.[17] However, rituximab is generally considered the other treatment, with the possible exception of cyclophosphamide, with curative potential.[18]

Rituximab is a monoclonal antibody directed against CD20.[19] As such it depletes circulating splenic and some nodal B cells but only a small fraction of plasma cells. Rituximab alone only achieves a 25% lasting response rate in children with ITP and long-term responses with dexamethasone alone are similarly disappointing.[20-22] However, 2 studies in adults in which rituximab was combined with 1 4-day cycle of dexamethasone, and 2 reports from our group combining 3 instead of 1 cycle of dexamethasone with rituximab, strongly suggest that this combination results in a better outcome not only in terms of short-term response but also in regard to long-term outcome ("cure").[17,23-25] In view of the experience using rituximab combined with dexamethasone in children with ITP, this

| | |
|---|---|
| 4R+3Dex | 4 infusions of rituximab and three 4-day cycles of dexamethasone |
| CR | Complete response |
| ITP | Idiopathic thrombocytopenic purpura |
| PR | Partial response |

From the [1]Division of Pediatric Hematology, Weill Cornell Medicine, New York, NY; [2]Division of Pediatric Hematology and Oncology, The Children's Hospital of Philadelphia, PA; and [3]Division of Pediatric Oncology, Weill Cornell Medicine, New York, NY

Funded by the Children's Cancer and Blood Foundation (J.B.B.). J.B.B. receives research support from Amgen, Boehringer Ingelheim, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Prophylix Pharma, Protalex, and Rigel Pharmaceuticals. J.B.B. has participated on Advisory Boards for Amgen, Momenta Pharmaceuticals, Novartis Pharmaceuticals, Prophylix Pharma, Protalex, and Rigel Pharmaceuticals. J.B.B. has participated in Speaker's Bureaus for Novartis Pharmaceuticals and Physicians Education Resource. J.B.B. receives honoraria from UpToDate, Inc. The other authors declare no conflicts of interest.



https://doi.org10.1016/j.jpeds.2017.08.036

study explored treatment of 4 infusions of rituximab interspersed with three 4-day cycles of dexamethasone in 33 children up to 18 years of age with persistent or chronic ITP. Because studies have shown that cohorts of younger adult women with ITP tend to respond better to rituximab than other adult ITP populations,[26] the goal of the study was to explore if the combination of rituximab with dexamethasone as a treatment protocol in pediatric patients is safe and tolerable, and what prognostic factors existed for long-term response.

## Methods

Inclusion criteria were pediatric patients, 1-18 years of age with persistent/chronic ITP (defined as ITP >6-month duration). Patients were referred for primary ITP, although 3 patients were subsequently determined to have evolving Evan's or common variable immune deficiency and one had acute disseminated encephalomyelitis, which declared during their prolonged course (prior to initiating 4 infusions of rituximab and three 4-day cycles of dexamethasone [4R+3Dex]). All patients had failed at least 1 previous therapy (usually 2 or 3) prior to initiation of 4R+3Dex. Patient demographics and clinical details are described in the **Table**. Antibody screening (ie, antinuclear antibody) was not routinely done if a patient had isolated thrombocytopenia. Although we did not determine Tanner stage for each patient upon enrollment, review of the medical charts indicated that on average, patient cohorts were of equal pubertal maturity. Patients were selected for this treatment protocol in discussion with families about the various therapies and trials available at that time and what would be most conducive to maintaining quality of life. The patients analyzed here received 4R+3Dex over a 5-year period (2010-2015). This retrospective chart review protocol was approved by the Weill Cornell Medicine Institutional Review Board but not listed on Clinicaltrials.gov because it was retrospective.

Thirty-three children were treated with 4R+3Dex at, or in close consultation with, the Platelet Disorders Center at Weill Cornell Medical College, and all such children in the specified time period of the study are included in this report. Children were treated with rituximab 375 mg/m$^2$ weekly for 4 weeks (days 1, 8, 15, 22) and three 4-day courses of dexamethasone

**Table. Patient demographics for children age 1-18 years old with ITP that participated in 4R+3Dex protocol**

| Sex | Age at therapy (y) | Prior treatment | Number of previous therapies | Starting platelet count (+ = therapy) | Number of rituximab cycles | Number of dexamethasone cycles | Duration of ITP (mo) |
|---|---|---|---|---|---|---|---|
| F | 7 | Prednisone, IVIG, WinRho, solumedrol | 4 | 69+ | 4 | 3 | 5 |
| M | 12 | IVIG, Nplate, prednisone | 3 | 129+ | 4 | 3 | 27 |
| M | 4 | Prednisone, anti-D, IVIG | 3 | 45+ | 4 | 3 | 24 |
| M | 4 | Prednisone, anti-D, IVIG | 3 | 49+ | 4 | 3 | 81 |
| F | 17 | Steroid, IVIG, WinRho, eltrombopag | 3 | 78+ | 4 | 3 | 6 |
| F | 7 | IVIG, rituximab, prednisone | 3 | 17 | 4 | 4 | 36 |
| F | 17 | Prednisone | 1 | 16 | 4 | 2 | 84 |
| F | 12 | IVIG | 1 | 20 | 4 | 3 | 21 |
| F | 17 | IVIG, anti-D | 2 | 16 | 4 | 3 | 159 |
| F | 15 | Prednisone, IVIG | 2 | 12+ | 4 | 3 | 1 |
| M | 17 | IVIG, dexamethasone | 2 | 8 | 4 | 3 | 12 |
| F | 3 | Prednisone, IVIG | 2 | 126+ | 4 | 3 | 7 |
| F | 15 | Prednisone, IVIG | 2 | 11 | 4 | 3 | 1 |
| M | 10 | Prednisone, IVIG | 2 | 7 | 4 | 3 | 7 |
| F | 15 | Anti-D | 1 | 39 | 4 | 3 | 7 |
| F | 8 | Prednisone, IVIG | 2 | 42 | 4 | 3 | 86 |
| M | 4 | IVIG, anti-D, methylpred, Nplate | 4 | 177+ | 4 | 4 | 10 |
| F | 4 | IVIG, prednisone | 2 | 25 | 4 | 3 | 11 |
| F | 15 | IVIG, anti-D, prednisone | 3 | 98+ | 4 | 3 | 9 |
| M | 13 | Prednisone for other health reasons | 1 | 5 | 2 | 1 | 12 |
| F | 4 | IVIG | 1 | 14 | 4 | 3 | 14 |
| F | 3 | IVIG, anti-D | 2 | 18 | 4 | 3 | 9 |
| F | 8 | Prednisone, IVIG | 2 | 9 | 2 | 1 | 3 |
| M | 4 | Prednisone, Nplate, anti-D, IVIG | 4 | 7+ | 4 | 3* | 4 |
| M | 2 | Prednisone, IVIG, Nplate, vincristine, anti-D | 5 | 5+ | 4 | 3 | 7 |
| F | 12 | IVIG | 1 | 9 | 4 | 3 | 9 |
| M | 10 | IVIG, solumedrol, dexamethasone, anti-D | 4 | 25 | 4 | 3 | 12 |
| M | 11 | Prednisone, anti-D | 2 | 36 | 4 | 3 | 28 |
| M | 15 | Prednisone, IVIG | 2 | 19 | 4 | 3 | 5 |
| M | 17 | Prednisone, IVIG | 2 | 19 | 4 | 3 | 84 |
| F | 1 | IVIG, anti-D | 2 | 35 | 4 | 1 | 8 |
| M | 11 | Prednisone, anti-D, Amicar | 2 | 18 | 4 | 3 | 49 |
| F | 14 | Prednisone, IVIG | 2 | 56+ | 4 | 3* | 11 |

*F*, female; *IVIG*, intravenous immunoglobulin; *M*, male.
Deidentified information on the 33 pediatric patients with ITP enrolled in the trial. The first column indicates sex, the next indicates age. The third column enumerates prior ITP treatments received, and the next column lists the number of previous therapies. The fifth column provides the platelet count at the outset of the 4R+3Dex trial, and the next 2 columns list how many cycles of rituximab and dexamethasone the patient ultimately received. The last column provides duration of ITP diagnosis until start of 4R+3Dex therapy. The * next to dexamethasone cycles indicates transition from dexamethasone to methylprednisolone. The + next to the platelet count indicates a recent (less than 4 weeks) ITP related treatment that may have transiently increased platelet counts prior to 4R+3Dex initiation.