# Rituximab and three dexamethasone cycles provide responses similar to splenectomy in women and those with immune thrombocytopenia of less than two years duration

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## ABSTRACT

Adults with newly diagnosed or persistent immunothrombocytopenia frequently relapse upon tapering steroids; adults and children with chronic disease have an even lower likelihood of lasting response. In adults with newly-diagnosed immunothrombocytopenia, two studies showed that dexamethasone 40 mg/day x four days and 4 rituximab infusions were superior to dexamethasone alone. Studies have also shown three cycles of dexamethasone are better than one and patients with persistent/chronic immunothrombocytopenia respond less well to either dexamethasone or rituximab. Therefore, 375 mg/m$^2$ x 4 rituximab was combined with three 4-day cycles of 28 mg/m$^2$ (max. 40 mg) dexamethasone at 2-week intervals and explored in 67 ITP patients. Best long-term response was assessed as complete (platelet count ≥100x10$^9$/L) or partial (50-99x10$^9$/L). Only 5 patients had not been previously treated. Fifty achieved complete (n=43, 64%) or partial (n=7, 10%) responses. Thirty-five of 50 responders maintained treatment-free platelet counts over 50x10$^9$/L at a median 17 months (range 4-67) projecting 44% event-free survival. Duration of immunothrombocytopenia less than 24 months, achieving complete responses, and being female were associated with better long-term response ($P$<0.01). Adverse events were generally mild-moderate, but 3 patients developed serum sickness and 2 colitis; there were no sequelae. Dexamethasone could be difficult to tolerate. Fourteen patients became hypogammaglobulinemic and half had increased frequency of minor infections; 9 of 12 evaluable patients recovered their IgG levels. Rituximab combined with three cycles of dexamethasone provides apparently better results to reported findings with rituximab alone, dexamethasone alone, or the combination with one cycle of dexamethasone. The results suggest medical cure may be achievable in immunothrombocytopenia, especially in women and in patients within two years of diagnosis. (*clinicaltrials.gov identifier:02050581*)

## Introduction

Immune thrombocytopenia (ITP) is characterized by auto-antiplatelet antibody-mediated thrombocytopenia. These antibodies mediate thrombocytopenia by accelerating the destruction of platelets in the peripheral blood, and binding to megakaryocytes and impairing platelet production.[1,2] Cytotoxic T cells may also destroy platelets and/or damage megakaryocytes.[3] Thrombocytopenia can result in bleeding; the goal of treatment is to stop ongoing bleeding and also decrease the risk of developing clinically-significant bleeding in the future.

As many as 70-80% of newly-diagnosed, previously-untreated patients respond to prednisone-based treatment, but the great majority have recurrence of thrombocytopenia when prednisone treatment is tapered, leading to a need for further therapy.[4-6] The optimal second-line treatment remains uncertain.[7] Children have a much higher rate of spontaneous improvement than adults, but those with severe chronic disease tend not to achieve remission and are often very difficult to manage.

In adults, one approach is to try to avoid the need for second-line therapy altogether by using at diagnosis high-dose dexamethasone, a glucocorticoid with a longer half-life than prednisone and no mineralocorticoid effect. As first-line treatment compared to prednisone, dexamethasone is thought to increase the lasting response rate and reduce the need for further treatment.[8] One study showed that a single 4-day cycle of dexamethasone at 40 mg/day was often effective in treating ITP patients at diagnosis;[8] however, treatment with dexamethasone is less effective in patients with persistent and especially chronic ITP.[9-11] Another study demonstrated that three or more 4-day cycles of dexamethasone were more efficacious than one cycle.[12]

Rituximab is a monoclonal antibody that binds to the CD20 antigen present on B lymphocytes. Originally developed for the treatment of B-cell lymphomas, it has now also been widely used for treatment of autoimmune, antibody-mediated diseases such as ITP.[13,14] Rituximab treatment in newly-diagnosed ITP patients appears to be more effective than in patients with persistent or chronic disease.[15] In studies of patients with persistent (3-12 months) and chronic (> 12 months) ITP, approximately 50% of patients experience a

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complete or partial response to rituximab.[16] However, only approximately 20% of initially-treated patients continue to have a lasting, treatment-free response.[17] Therefore, strategies to improve the efficacy of rituximab are of value.

Two small, parallel pilot studies investigated intensifications of standard rituximab therapy in patients with ITP. One doubled the dose of rituximab and the second administered rituximab with cyclophosphamide, vincristine and high-dose prednisone. Both strategies proved surprisingly ineffective in improving the long-term response to rituximab compared to that of rituximab alone.[18] A different approach to optimizing responsiveness to rituximab in ITP was undertaken by administering standard-dose rituximab with one 4-day cycle of 40 mg dexamethasone.[19,20] In previously-untreated patients, the great majority of whom were within one week of diagnosis, the R+1Dex combination induced a substantially higher, more durable response rate at six months than dexamethasone alone: 63% and 57% compared to 36% and 37% (in the second study in which additional dexamethasone was allowed part way through, only 5 of 62 responders received >1 cycle of dexamethasone).[20] No direct comparison was made to rituximab alone.

Given the individual activities of rituximab and of dexamethasone, their apparent additive activity in combination, and the greater efficacy of three than one cycles of dexamethasone, 67 patients at Weill Cornell Medical College (WCMC) with newly diagnosed, persistent, or chronic ITP were treated with a combination of rituximab and three cycles of dexamethasone (R+3Dex).

## Methods

### Study design

All adults and children diagnosed with primary ITP and treated with rituximab and dexamethasone between September 2007 and July 2013 were included in this initially retrospective (n=30 patients), then prospective (n=37 patients) treatment protocol. All patients were treated at (n=62 patients) or in direct consultation with (n=5 patients) the Platelet Disorders Center at the Weill Medical College of Cornell University. The protocol was approved by the Weill Cornell Medical College Institutional Review Board. Patients, who would previously have received rituximab alone, except for one diabetic patient, instead received dexamethasone and rituximab. Rituximab was dosed at 375 mg/m$^2$/infusion and given 4 times at weekly intervals. Dexamethasone was dosed at 28 mg/m$^2$ (max. 40 mg); patients received three 4-day cycles at 2-week intervals, usually intravenously (IV) on Days 1 and 15 and by oral administration the other ten days. Subjects were included if they had received at least one infusion of rituximab and one dexamethasone cycle. Variations in rituximab and/or dexamethasone dosage are detailed in Figure 1.

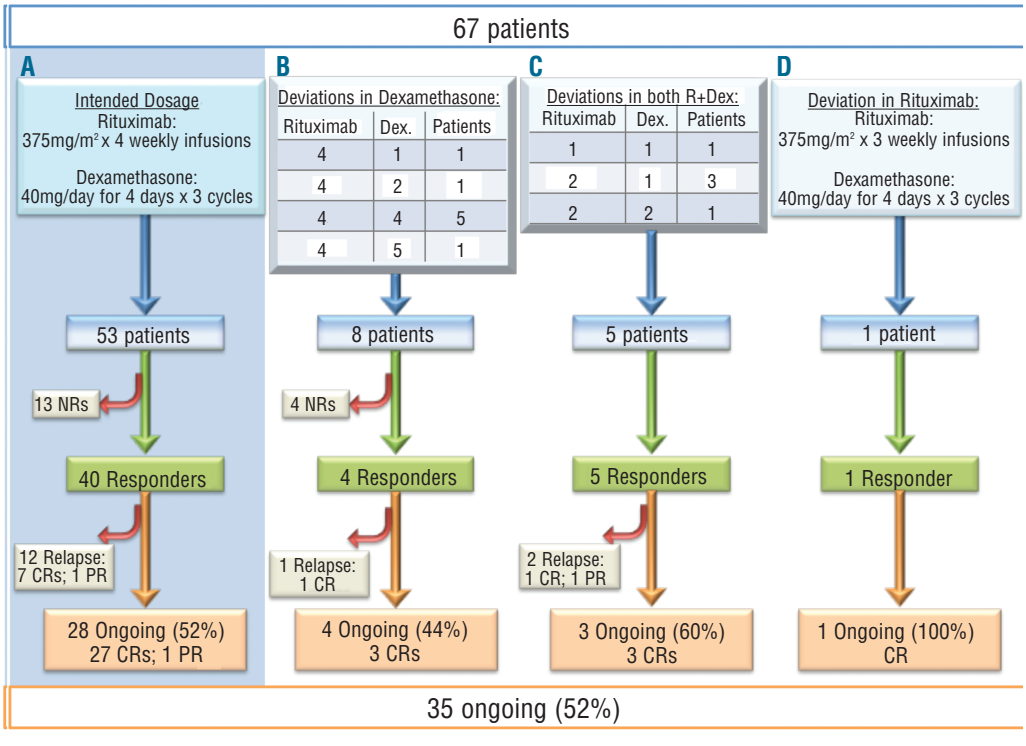


**Figure 1.** Dosing of R+Dex combination therapy. (A) 53 patients received the intended dosage of 4 weekly infusions of standard dose (375 mg/m$^2$) rituximab and three x 4-day cycles of 28 mg/m$^2$ dexamethasone (maximum 40 mg) at 2-week intervals. Four patients either received their dexamethasone before the rituximab (1), after the rituximab (1), had 1 cycle of dexamethasone and 2-3-infusion replacement treatments with high-dose methylprednisolone (1) or had 3 infusions of high-dose methylprednisolone with each rituximab (1). (B) 8 patients had deviations in their dexamethasone dosing including one patient who received 5 cycles of low-dose dexamethasone by choice of the referring physician. (C) 5 patients had side effects (2 colitis and 3 serum sickness) which resulted in their receiving a reduced number of infusions of rituximab and of dexamethasone. (D) one patient discontinued rituximab after the 3$^{rd}$ infusion due to allergic reactions but received 3 courses of dexamethasone.

Sixty-seven patients were treated with R+3Dex. Patients had primary ITP, had not received rituximab except in 4 patients, opted for curative therapy of their ITP, and did not have a contraindication to dexamethasone. Patients were treated for platelet counts less than $40x10^9$/L (all but 2 were < $30x10^9$/L); some were initially unable to discontinue previous ITP treatments.

Patients were monitored with blood counts (CBC) obtained weekly and then at less frequent intervals. Liver function, renal tests, and immunoglobulin levels were also monitored. Absolute immature platelet fraction (A-IPF) was measured using the Sysmex XE-2100.[21] B cells were determined by flow cytometry using a monoclonal antibody to CD19.[14]

Platelet response was assessed as initial response eight weeks following initiation of rituximab therapy to exclude transient responses to dexamethasone. Patients achieved a complete response (CR) if the platelet count became $100x10^9$/L or over. Partial response (PR) was a platelet count $50\text{-}99x10^9$/L. PR and CR required no recent rescue medication. Best response was highest response achieved (NR, PR or CR) after the 8-week time point without other therapies for ITP; this included patients who improved their response after eight weeks without further treat-

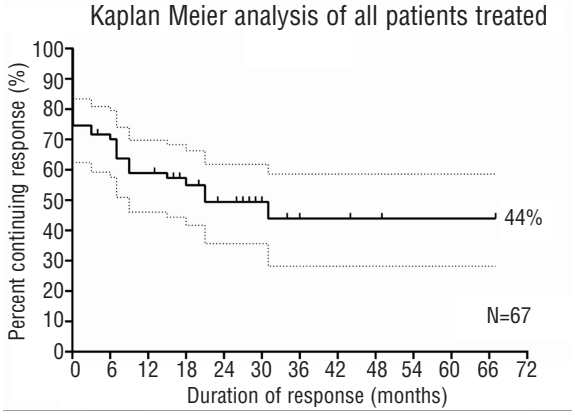


**Figure 2. Long-term analysis of all patients treated with R+3Dex. Kaplan-Meier analysis estimates the long-term response to R+3Dex. Vertical marks indicate the last follow up of an ongoing response. 44% of the 67 patients treated were estimated to have a long-term response at more than five years from treatment. Eight responders maintain their treatment-free response a median of nine months past the last relapse.**

**Table 1. Patients' demographics.**

| | | | | |
|---|---|---|---|---|
| Age | Overall<br>Median=21 years<br>Range=1-64 years | Pediatric | Median=12 years<br>Range=1-17 years | n=26 (39%) |
| | | Adult | Median=36 years<br>Range=18-64 years | n=41 (61%) |
| Gender | Overall<br>Male=30<br>Female=37 | Pediatric | Male<br>Female | n=12 (46%)<br>n=14 (53%) |
| | | Adult | Male<br>Female | n=19 (46%)<br>n=22 (53%) |
| Duration of ITP | Overall<br>Median=13 months<br>Range=0-286 months | Pediatric | Median=10 months<br>Range=1-159 months | |
| | | Adult | Median=16 months<br>Range=1- 286 months | |
| Prior therapies | Overall<br>Median=2 therapies<br>Range=0-7 therapies | Pediatric<br>Median =<br>2 therapies | None<br>Corticosteroids<br>IVIG<br>Anti-D<br>TPO-RA | n=2<br>n=19<br>n=20<br>n=12 |
| | | Range =<br>0-4 therapies | Romiplostim<br>Eltrombopag<br>Cytotoxic agents<br>Anti-proliferative agents<br>Splenectomy | n=3<br>n=0<br>n=1<br>n=0<br>n=1 |
| | | Adult | None<br>Corticosteroids | n=3<br>n=34 |
| | | Median =<br>2 therapies | IVIG<br>Anti-D<br>TPO-RA | n=21<br>n=9 |
| | | Range =<br>0-7 therapies | Romiplostim<br>Eltrombopag<br>Cytotoxic agents<br>Anti-proliferative agents<br>Splenectomy | n=1<br>n=4<br>n=4<br>n=4<br>n=3 |

*Corticosteroids: prednisone, methylprednisolone, dexamethasone; IVIG: intravenous immunoglobulin; Anti-D: anti-Rh(D) immunoglobulin (Winrho); TPO-RA: thrombopoietin receptor agonist - romiplostim, eltrombopag; cytotoxic: cyclophosphamide, rituximab; anti-proliferative: azathioprine, vincristine.*

ment. Relapse was defined as two consecutive counts less than $50x10^9$/L and/or need for treatment. The duration of response was calculated from date of first rituximab to relapse or latest follow up.

The *TUBB1* R307H polymorphism has been assessed since our previous study and showed an association between response to rituximab and the B-1 tubulin R307H single nucleotide polymorphism.[22,23]

Statistical analysis was descriptive. Fisher's exact test was used for patient age, duration of ITP, sex, number of prior therapies, response to therapies, and lymphocyte subsets. Absolute immature platelet fraction (A-IPF) was evaluated using one-way ANOVA. GraphPad-Prism-program-constructed Kaplan-Meier curves depicted duration of response, estimated from the date of achieving response to date of loss of response. Log rank test was used to determine the difference in response duration for the following subgroups: duration of ITP, depth of response, patient age and sex. Patients with an ongoing response were censored at last follow up. Two-tailed $P<0.05$ were considered significant.

## Results

Sixty-seven patients were most commonly treated with 4 infusions of rituximab concurrently with three cycles of pulse dexamethasone (R+3Dex) for ITP (Figure 1). The median patient age was 21 years; 26 were under 18 years of age and 8 were over 50 years. The median time since diagnosis of ITP was 13 months (Table 1). Patients had received a median of two prior therapies; 5 patients were previously untreated. Four patients had undergone splenectomy. Nine had newly diagnosed ITP (0-3 months from diagnosis) all of whom responded; 24 had persistent ITP (3-12 months from diagnosis) and 34 had chronic ITP (> 1 year) at initiation of R+3Dex.

The intended regimen was four weekly infusions of rituximab 375 mg/m$^2$ per infusion and three cycles of dexamethasone (three 4-day cycles of 28 mg/m$^2$ every 14 days with a max. daily dose of 40 mg). Sixty-one of 67 patients received four infusions of rituximab; 5 of 6 patients who

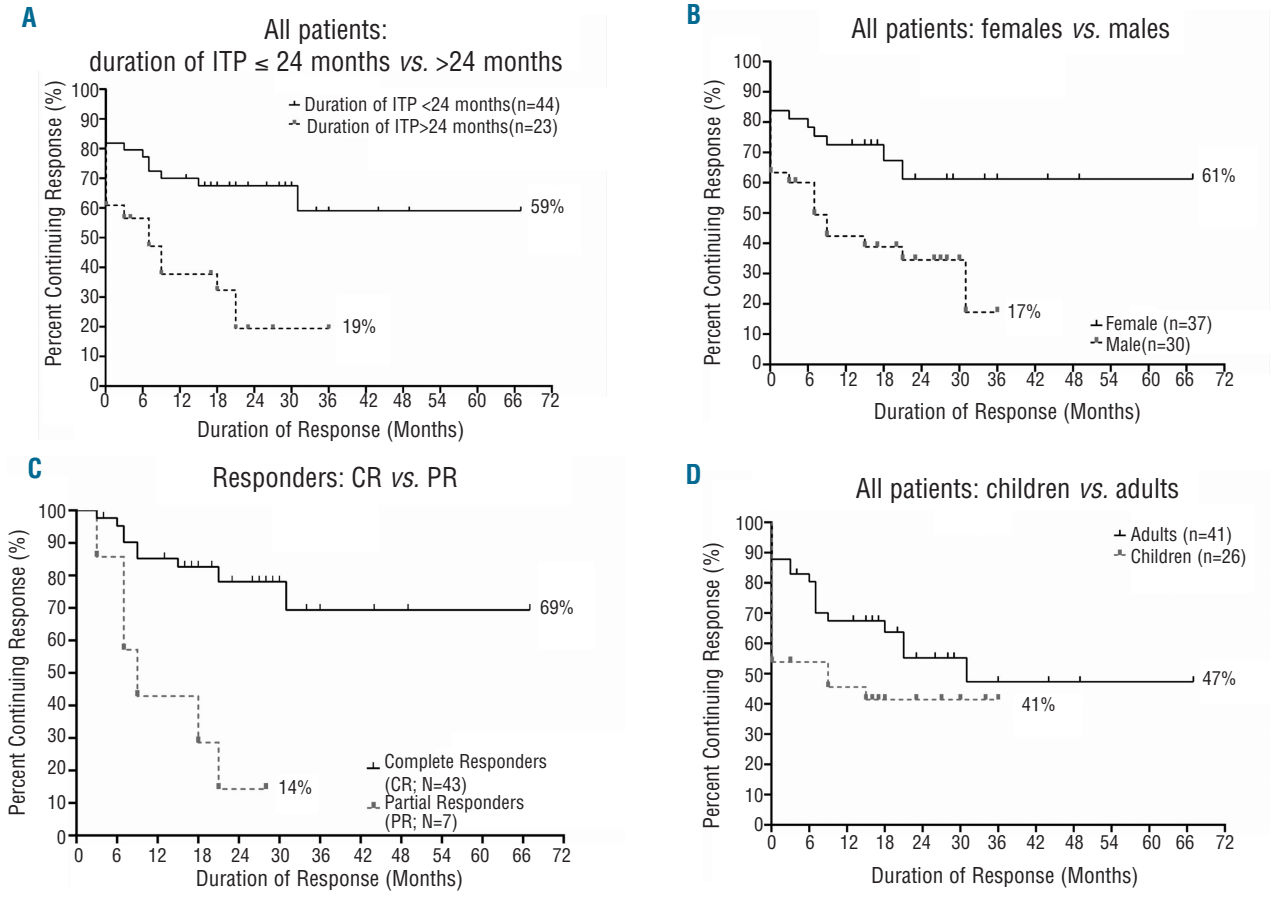


**Figure 3.** Kaplan-Meier analysis of variables related to response to R+3Dex: (A) Duration of ITP ≤ 24 months *vs.* > 24 months. Vertical tick marks (Duration of ITP ≤ 24 months) and square markers (Duration of ITP > 24 months ) indicate the last follow up of a response. In comparing shorter and longer durations of ITP (≤ and > 24 months), patients with shorter duration (solid lines) project better long-term responses (59%) than those with a longer history of disease (dotted lines; 19%) (log-rank $P = 0.002$). (B) Sex: females *vs.* males. Of 37 females, 31 responded and 25 had long-term treatment-free responses. Of 30 males, 19 responded and 10 had ongoing responses. Females had a better projected long-term outcome than males (females 61% *vs.* males 17%) (log-rank $P = 0.0078$). (C) Quality of Response: CR *vs.* PR CRs (solid line) projected a better long-term response than PRs (dotted line) (log-rank $P = 0.0002$). (D) Patient age: children *vs.* adults. Adults had a significantly higher initial response but responding children had a lower rate of relapse than responding adults so by 30 months from initial treatment there was no longer a significant difference in the projected long-term outcome of adults (47%) and children (41%).

received less than four rituximab infusions discontinued this treatment because of serum sickness or colitis (Figure 1C; see adverse event section below). Those receiving more than three cycles of dexamethasone could not tolerate the complete treatment (Figure 1). There was no difference in response for patients who received three or more cycles of dexamethasone *versus* patients who received fewer cycles, with 44 of 60 of those receiving at least three cycles of dexamethasone achieving a CR or PR *versus* 6 of 7 of those receiving less intensive steroid therapy. Since there were no differences in response among the different regimens, the 67 patients were combined for further analyses.

### Initial response

At or after eight weeks from initial treatment, 37 patients (55%) achieved CRs, 12 (18%) achieved PRs and 18 (27%) did not respond. Thrombocytopenia persisted in 17 of the 18 initially non-responding patients; they received additional ITP treatments. The 18$^{th}$ patient, however, achieved counts of 30-40 x10$^9$/L, was not treated, and later achieved a PR and then a CR.

### Overall response

Fifty of 67 (75%) patients treated with R+3Dex achieved a long-term best response of either a CR (n=43, 64%) or a PR (n=7, 10%). The median time to achieve a PR (all 50 responders) was 64 days (range 43-139 days) and to achieve a CR (43 patients) was 70 days (range 43-525 days). Five patients initially stabilized at a PR but subsequently improved to a CR: 3 at three months, one at five months, and one at 12 months.

Thirty-five (70%) of the 50 responding patients (52% of all patients treated) maintained platelet counts of 50x10$^9$/L or more at last visit without further treatment and with median follow up of 20 months (range 4-67 months). Fifteen responders (9 of 43 CRs and 6 of 7 PRs) relapsed at a median of nine months (range 3-31 months).

Two patients experienced temporary decreases in the platelet count soon after or during R+3Dex. One, following a single infusion of intravenous immunoglobulin (IVIG), maintained a CR for 21 months until relapse while the second, who also received a single infusion of IVIG, has maintained a PR for 28 months without relapse. These 2 patients had received multiple IVIG treatments previously with responses lasting less than three weeks; thus the long duration of response does not appear to have been caused by the IVIG infusions.

### Duration of response

The estimated probability of achieving a treatment-free sustained response was 44% at a follow-up period of 67 months (Figure 2). Considering only the 50 responders, the estimated probability of a treatment-free sustained response was 59%.

### Predictors of long-term response

*Duration*: the duration of ITP best associated with a long-term treatment-free response was of 24 months or less *versus* more than 24 months. For patients with ITP of 24 months or less, the estimated long-term response rate was 59% as compared to only 19% for those with ITP duration of more than 24 months (Figure 3A) ($P$=0.002). Of the 23 patients who had had ITP for more than 24 months, 14 responded initially (11 CR and 3 PR) but only 6 (26%) maintained a treatment-free response at a median of 20.5 months. There was a trend for the median duration of ITP in responders to be shorter: eight months (range 1-23 months) compared to 28 months (range 4-208 months) in non-responders ($P$=0.063).

*Sex*: 25 of 37 females had ongoing responses at last follow up compared to 10 of 30 males with estimated long-term response rates of 61% *versus* 17% ($P$=0.0076). Males had a higher rate of relapse following initial response (Figure 3B).

*Quality of response*: 34 of 43 (79%) patients whose best response was a CR never relapsed compared to only one of 7 (14%) patients with an ongoing PR (Figure 3C) ($P$=0.0002).

*Patient age*: there was a greater initial response rate to R+3Dex therapy in adults compared to children, with 36 of 41 (88%) adults and 14 of 26 (54%) children achieving an initial CR or PR ($P$=0.0002) (Figure 3D). However, there was no difference in the long-term estimated response rates between children (41%) and adults (47%) because of the higher relapse rate in adults (Figure 3D). Considering only adults aged 18 years and over, there was no relationship between age and response (median 36 years; range 18-64 years) (Figure 4).

Responses to previous treatments, e.g. steroids and IVIG, were not associated with response to R+3Dex.

*Age and duration of ITP*: combining patient age and the duration of ITP showed that adults with a short duration of ITP achieved a particularly high rate of lasting response. Of the 26 adults who had ITP of 24 months or less, 25 responded to R+3Dex (96%) and 20 (77%) of these patients continue to respond at last follow up.

*Other variables*: including lymphocyte subsets, AIPF, and the HB-tubulin polymorphism, were not significantly related to initial or persisting response. There were too few splenectomized patients or steroid non-responders to assess these variables.

- *lymphocyte subsets*: 54 of 57 patients assessed achieved a 0% B-cell count. Forty-one patients began recovering their B cells at a median of 177 days (6 months, IQR=127,254.5) and 18 of those recovered to base-line levels at a median 337 days (IQR=305-423);

- *HB-tubulin*: of the 53 of 67 patients genotyped for SNPs on Hβ-1 tubulin (*Online Supplementary Table S1*), 32 of 44 (73%) homozygous wild-type patients responded to R+3Dex as did 9 of 10 heterozygous SNP/WT patients.

### Adverse events

Three patients developed serum sickness resulting in discontinuation of rituximab. Two patients developed colitis (fever, diarrhea, and abdominal pain with negative stool cultures); both recovered within 2-3 weeks and have had no sequelae. One patient had outpatient pneumonia following the last injection of rituximab. One patient with hypogammaglobulinemia developed an autoimmune condition, acute disseminated encephalomyelitis (ADEM), and recovered while receiving 4-weekly IVIG treatment; whether his IgG level returned to normal could not be determined.

Adverse events related to R+3Dex were generally mild-moderate. No other treatment-related hospitalizations, severe or serious adverse events were noted. The most common toxicities included insomnia (n=10), gastrointestinal upset (nausea, diarrhea, indigestion, n=10), muscle and bone aches (n=10) and headache (n=5). One patient

with pre-existing diabetes mellitus experienced short-term, clinically significant worsening of hyperglycemia requiring increased insulin dose. Transient mood or behavioral changes occurred frequently.

*Hypogammaglobulinemia*: in 14 patients, IgG levels fell below the lower limit of normal for age (Figure 4) at a median 55 days from initiation of R+3Dex with the lowest IgG level occurring at a median 166 days; in one patient the starting value was not known because of antecedent IVIG. Eight of 14 fell just below normal but 6 of these fell to levels of 400 mg/dL or less. Four of 6 patients with nadir IgG levels less than 400 mg/dL had frequent minor infections as did one of the 8 with IgG levels just below normal. Nine of 12 evaluable hypogammaglobulinemic patients had their IgG levels return to normal. One patient experienced transient hypogammaglobulinemia without platelet relapse late in both of her pregnancies. A 15th patient had common variable immunodeficiency (CVID) diagnosed after study entry.

When testing became available, 15 patients were screened for BK/JC virus (the cause of progressive multifocal leukoencephalopathy) before and after R+3Dex; none became positive.

## Discussion

The primary goal of physicians and patients dealing with ITP is to achieve a persistently adequate, potentially normal treatment-free platelet count in the absence of clinically significant bleeding. The best-documented way to achieve a "cure" is for a patient to undergo splenectomy; however, there is increasing reluctance by patients and physicians to undergo this procedure for many reasons.[7,23-25]

Ideally, ITP would be cured with medical treatment to avoid operative risk and long-term concerns for post splenectomy complications, e.g. sepsis.[24] In the 1980s and 90s, combination chemotherapy and subsequently IV cyclophosphamide alone were tried and had some success in "curing" ITP.[26-28] Once other options became available, e.g. dexamethasone[8-12] and rituximab,[15-18] the toxicity of cyclophosphamide relegated it to being a tertiary option.

A single 4-day cycle of high-dose dexamethasone was first reported for use at diagnosis in 2003.[29] Subsequently, in 2007, a study suggested that 3-4 cycles were better than one. Rituximab may initially normalize platelet counts in 30-40% of patients but additional follow up demonstrated that the long-term cure rate may only be 20-25%.[17] Both rituximab and especially dexamethasone have been shown to be more successful when patients are treated at or very near diagnosis.[9-11,15]

Two studies then reported the results of the R+1Dex combination. In 2010, one cycle of four days of high-dose dexamethasone followed by four infusions of rituximab was reported to increase the "cure rate" of treatment-naïve patients compared to dexamethasone alone, almost all of whom were treated very close to diagnosis.[19] A second combination study, initially of R+1Dex, allowed more dexamethasone cycles (R+>1Dex) halfway through the study. However, this option was selected predominantly in non-responders; only 5 of 62 responders used R+>1Dex.[20] Both studies demonstrated that the 6-month outcome of the R+1Dex combination arm was superior to the dexamethasone alone arm with a 63% and 58% CR + PR rate *versus* 36% and 37% with dexamethasone alone at six months, respectively. The long-term combination outcomes were 34% in the first study and approximately 50% in the second study. In both of these studies, the great majority[20] or all[19] of the patients were newly diagnosed, a group that would be expected to have a higher response rate. The innovation in our treatment regimen was to use three 4-day cycles of 28 mg/m$^2$/day (max. 40 mg/day) dexamethasone instead of one cycle of dexamethasone combined with four infusions of 375 mg/m$^2$ of rituximab (R+3Dex). Why combine rituximab and dexamethasone? Mechanistically, rituximab (which knocks out B cells but not plasma cells) and dexamethasone (which in myeloma has been shown to be a potent anti-plasma cell agent) are a logical combination for treatment of antibody-mediated diseases like ITP. Clinically, rituximab and dexamethasone are the two medical treatments, other than cyclophosphamide, that have had the best-documented curative effects in patients with ITP.

We chose R+3Dex, because of their efficacy in combination[19,20] and because three cycles of dexamethasone are better than one cycle.[12] Since a number of patients had had

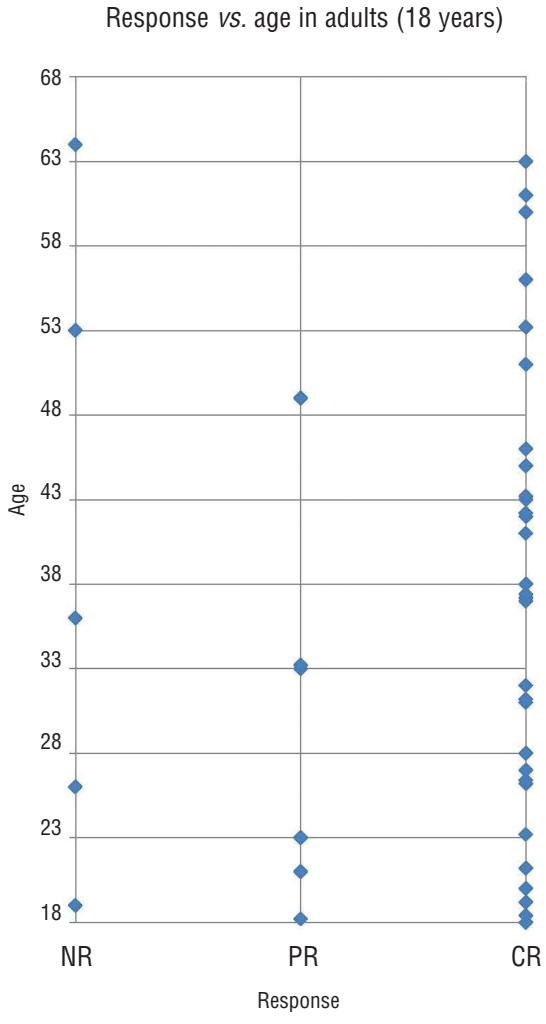


**Figure 4. Response *vs.* age (18 years). There was no relationship between age of adult patients and best response achieved. Median age in the adult population (18 years) was 36 years (range 18-64 years).**

difficulty tolerating multiple 4-day cycles of dexamethasone, it seemed that three cycles might be optimal. We did not choose to increase the dose of rituximab because a small pilot study of double-dose rituximab had failed to demonstrate a better response rate or longer duration of response.[18] Combinations of rituximab with other treatments of ITP have not been explored.

### Efficacy

The efficacy of R+3Dex was striking. Key findings included:

- a 75% initial response rate;
- most responses (43 of 50) CRs not PRs;
- overall, an almost 50% estimated long-term cure rate at five years;
- particularly good long-term responses in patients with ITP of less than two years duration, in women, and in those who achieved CRs.

These findings in patients with both short and long duration of ITP suggest a substantially better response to R+3Dex than that seen with rituximab alone or even R+1Dex. The overall results cannot be directly compared to the two previous studies using only or primarily one cycle of dexamethasone with rituximab (R+1Dex) since these studies included only untreated patients at diagnosis of their ITP, the most favorable group for treatment. In the current study, only 5 patients had never been previously treated for their ITP and the median duration of ITP was over one year. The results in patients with shorter duration of ITP and in females (60% projected long-term treatment-free responses) are comparable to what has been reported as overall response rates to splenectomy.[30,31]

Unlike the previous study[22] looking at rituximab alone, the beta1tubulin isoform SNP did not affect response to R+3Dex. Similarly, measurements of A-IPF did not predict nor correlate with response. Time to B-cell recovery was similar to that reported with rituximab alone suggesting that dexamethasone did not contribute its effect by longer-lasting depletion of B cells.[14]

### Toxicity

R+3Dex gave rise to several toxicities. One was the difficulty in tolerating 12 days (3 x 4-day cycles) of high-dose dexamethasone even at 2-week intervals; substitution of 1 gram infusions of IV methylprednisolone was required for several patients. Almost 10% of patients developed marked hypogammaglobulinemia unlike the approximately 1% seen with rituximab alone,[14] a finding generally attributed to the persistence of plasma cells.[30] Increased numbers of minor infections were seen in most of the patients with lower IgG levels. Dexamethasone alone has not been shown to cause hypogammaglobulinemia.[19] Two patients developed idiopathic colitis, both of whom recovered spontaneously; 3 developed serum sickness. Neither of these two latter AEs had long-term consequences.

The primary limitations of this initially retrospective, then prospective study are that it was a single arm clinical trial that was not pharmaceutically funded. Sixty-seven patients is larger than almost all other single-arm studies in ITP[14,32-34] and it was thus possible to reach hypothesis-generating conclusions about base-line characteristics associated with response. In this analysis, only 80% of patients received the intended dosing regimen (Figure 1); however, there was no difference in response between the 53 patients receiving R+3Dex and the 14 whose treatment regimen was slightly modified. Furthermore, all patients were treated either in or in consultation with the Platelet Disorders Center at Weill Cornell, so that clinical management was relatively uniform, complete details of treatment and toxicities were generally available, and deviations not caused by toxicity were relatively minor.

Additional studies of this combination treatment with R+3Dex are warranted to further the primary goal of development of a medical cure of ITP. If such studies confirm that adults with disease duration of two years or under and females have a more than 50% lasting response rate, then this approach would seem optimal in at least these groups of patients as second- or even first-line treatment in comparison to thrombopoietic agents, splenectomy, or immunosuppressive agents.[6] The findings reported here appear to be superior to the many studies published describing the results of rituximab alone and at least as good as the two studies of R + 1Dex.[14,16,19,20] Tolerability is a much greater problem with R+3Dex than with rituximab alone, but not to the extent that would preclude its widespread use. The tolerability, notable activity, and lasting responses observed in this preliminary study suggest that this combination therapeutic strategy might be an optimal approach in patients with both newly diagnosed persistent and early chronic ITP. It could also be the basis of a more comprehensive approach to patients with long-term duration of ITP.

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### Authorship and Disclosures

*Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.*

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