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Systematic Review: Efficacy and Safety of Rituximab for Adults with Idiopathic Thrombocytopenic Purpura

Donald M. Arnold, MD, MSc; Francesco Dentali, MD; Mark A. Crowther, MD, MSc; Ralph M. Meyer, MD; Richard J. Cook, PhD; Christopher Sigouin, MSc; Graeme A. Fraser, MD; Wendy Lim, MD, MSc; and John G. Kelton, MD

Background: Rituximab, a monoclonal anti-CD20 antibody, is increasingly used to treat idiopathic thrombocytopenic purpura (ITP).

Purpose: To systematically review the literature on the efficacy and safety of rituximab for the treatment of adults with ITP.

Data Sources: MEDLINE, EMBASE, the Cochrane Library, abstracts from the American Societies of Hematology and Clinical Oncology annual meetings, and bibliographies of relevant articles and reviews were searched in duplicate until April 2006.

Study Selection: Descriptive and comparative studies in any language that met predefined inclusion criteria were eligible. Efficacy analysis was restricted to studies enrolling 5 or more patients.

Data Extraction: Platelet count response, toxicities, dose, previous treatments, baseline platelet count, duration of ITP, study design, and sources of funding were extracted in duplicate.

Data Synthesis: We identified 19 eligible reports on efficacy (313 patients) and 29 on safety (306 patients). Weighted means for complete response (platelet count $> 150 \times 10^9$ cells/L) and overall response (platelet count $> 50 \times 10^9$ cells/L) with rituximab were 43.6% (95% CI, 29.5% to 57.7%) and 62.5% (CI, 52.6% to 72.5%), respectively. Responses lasted from 2 to 48 months. Nearly all patients had received corticosteroids, and 53.8% had undergone splenectomy. Nine patients (2.9%) died.

Limitations: There were no controlled studies, and no studies met all criteria for study quality. Reported deaths could not necessarily be attributed to rituximab. Overall, the number of rituximab-treated patients with ITP reported in the literature is small.

Conclusions: Rituximab resulted in an overall platelet count response in 62.5% of adults with ITP. However, this finding derives from uncontrolled studies that also reported significant toxicities, including death in 2.9% of cases. These data suggest that providers should avoid indiscriminate use of rituximab and that randomized, controlled trials of rituximab for ITP are urgently needed.

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For author affiliations, see end of text.

Idiopathic thrombocytopenic purpura (ITP) is a common hematologic disorder characterized by platelet autoantibodies, low platelet counts, and bleeding. Rituximab is a chimeric, monoclonal anti-CD20 antibody that targets B lymphocytes and causes Fc-mediated cell lysis (1–4). It is currently indicated for the treatment of lymphoma (5–8), but because of its ability to deplete autoantibody-producing B lymphocytes and its favorable toxicity profile (9), it has been used in patients with various autoimmune diseases (10–12), including ITP. In some patients with ITP, rituximab has been associated with a reduction in specific platelet-associated autoantibodies and an increase in platelet count (13).

Early success with rituximab in ITP has lead to its widespread use and incorporation into recent treatment algorithms (14, 15). However, the evidence to support the use of rituximab in ITP is uncertain. We performed a systematic review of the literature to evaluate the efficacy and safety of this treatment.

Methods

Search Strategy

One hematologist and one internist independently searched the literature in June 2005 and updated the search in April 2006. The electronic databases of MEDLINE (from 1966) and EMBASE (from 1980) were searched by using the explode function for the Medical Subject Heading (MeSH) terms *antibodies, monoclonal* and *purpura, thrombocytopenic, idiopathic* and the textwords *rituximab*, *rituxan*, *mabthera*, *anti CD20*, *anti CD20 antibody*, *immune thrombocytopenic purpura*, and *idiopathic thrombocytopenic purpura*. The MEDLINE database was also searched with the PubMed search engine by using the MeSH term *purpura, thrombocytopenic, idiopathic* and the textwords *rituximab* and *rituxan*. The Cochrane Registry for Controlled Trials was searched by using the terms *rituximab*, *immune thrombocytopenic purpura*, and *ITP*. Scientific abstracts were identified by searching the electronic databases of the American Society of Hematology and the American Society of Clinical Oncology from 1997 (the year of licensure of rituximab) to 2005 by using the search terms *ritux**, *thrombocytopenic,* and *ITP*. Bibliographies of relevant articles and reviews were manually searched, and authors were canvassed for additional citations.

Eligibility Criteria and Study Selection

Exclusion criteria were secondary causes of thrombocytopenia, including splenomegaly, hepatitis B or C virus infection, HIV infection, lupus, antiphospholipid antibody syndrome, bone marrow failure syndromes, and drug-

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induced thrombocytopenia; malignancy, including chronic lymphocytic leukemia and lymphoma; the Evan syndrome; and rituximab re-treatments. Children (<16 years of age) were excluded because the biology and natural history of ITP in children were believed to differ considerably from those in adults. There was no restriction on study design or language of publication. Reports published only in abstract form were eligible. Where duplicate or redundant publications were uncovered, the latest and most informative version was retained. Initially, titles and abstracts of all articles were evaluated independently by 2 reviewers. Full-text articles were retrieved when they were judged by at least 1 reviewer to possibly contain relevant original data. Final article selection was done independently by both reviewers, and disagreements were resolved by consensus in all cases.

Data Extraction

The following data were collected in duplicate: proportion of patients with complete, partial, or minimal platelet count responses (and their definitions); time to platelet count responses; duration of platelet count responses; dose and schedule of rituximab administration; toxicities; previous ITP treatments; baseline platelet count; duration of ITP before rituximab treatment; study design and use of controls; and sources of funding. Individual-patient data were used where possible.

Assessment of Methodologic Quality

Study quality was assessed independently by 2 hematologists with expertise in research methods. Reviewers evaluated 4 key design features for each study: prospective data collection, consecutive patient enrollment, a clearly stated duration of follow-up, and a description of losses to follow-up. Assessors were blinded to study author, journal, publication date, and main results. Disagreements were resolved by independent adjudication.

Statistical Analysis

Patient demographic characteristics and platelet count responses were analyzed only from those studies enrolling 5 or more patients because we felt that smaller studies may be subject to extreme reporting bias. To determine estimates of response, we defined complete response as the achievement of a platelet count greater than 150×10^9 cells/L; partial response as a platelet count between 50 and 150×10^9 cells/L; and overall response as a platelet count greater than 50×10^9 cells/L. These definitions were chosen to reflect the most common criteria used in primary reports. Toxicities were considered from all studies, including those enrolling fewer than 5 patients each, to provide the most thorough description of safety. We determined estimates of effect of rituximab by calculating the weighted mean proportion by using a random-effects model. This model estimated the between-study variance by using the method of moments and assumed that the proportion from each study was sampled from the normal distribution, with variance calculated from the data. Continuous variables, including time to response, response duration, and follow-up, were summarized with medians, minimum and maximum values, and interquartile ranges assuming a normal distribution of the data. Unweighted chance-corrected κ values were used to assess agreement between reviewers for study selection (16).

Role of the Funding Source

This systematic review had no external source of funding. The organizations that fund the individual authors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, and approval of the manuscript.

RESULTS

Study Selection

We identified 599 citations through our comprehensive literature search, of which 60 were retrieved for detailed review (**Figure 1**). Agreement between reviewers for initial study inclusion was excellent ($\kappa = 0.87$). After exclusion of ineligible studies, redundant or duplicate publications, and reports that did not contain original data, 31 reports were included. Nineteen studies (313 patients) enrolled at least 5 patients each and were included in the efficacy analysis (13, 17–34), and 29 studies (306 patients) reported toxicity data (13, 17–19, 21–28, 30–46). Of the 19 reports describing efficacy outcomes, 9 were published in abstract form only. Abstracts were carefully scrutinized, and authors were contacted when necessary to ensure that redundant publications were excluded.

Study Designs and Sources of Funding

There was 1 dose-finding phase II study (28) and 18 single-arm cohort studies (13, 17–27, 29–34). Source of funding was not reported in 26 of 31 reports; of the remaining 5, 1 was industry-sponsored (19), 3 were funded by nonprofit organizations (21, 31, 41), and 1 reported that it had no funding information to disclose (32).

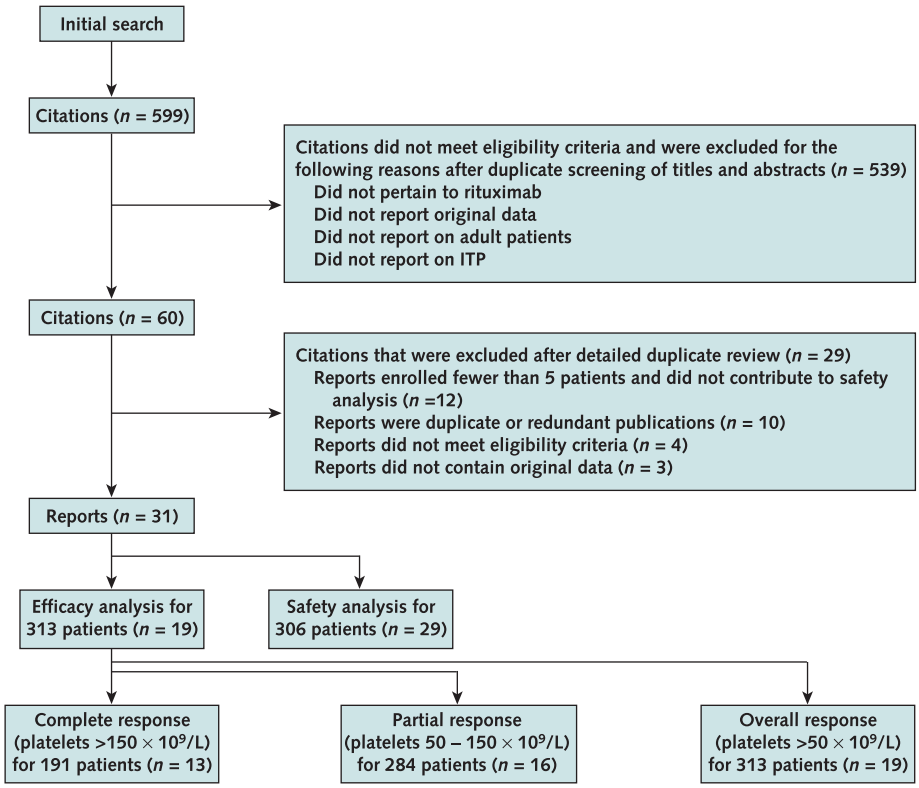
Description of Patients

Patients were 16 to 89 years of age, had had ITP for 1 to 360 months, and had a platelet count that ranged from 1 to 89×10^9 cells/L before rituximab treatment (**Table 1**). Nearly all (99.0%) patients had received corticosteroids, and 158 (50.5%) had had splenectomy. Other previous treatments were immunosuppressants, including cyclosporine, azathioprine, or mycophenylate ($n = 26$); cyclophosphamide ($n = 12$); vinca alkaloids ($n = 18$); and danazol ($n = 17$). The number of previous treatments varied between and within reports.

Rituximab Dose and Schedule

Rituximab was administered as a weekly infusion of 375 mg/m^2 for 4 consecutive weeks in 16 of 19 studies. Of the remaining 3 studies, 1 did not report the dosing schedule (30); 1 used a schedule of 1 to 8 infusions of 325 mg/m^2 per dose (29); and 1 used a low dose of rituximab (50 mg/m^2 on day 1, then 150 mg/m^2 on days 8 and 15), an

Figure 1. **Article selection.**



Results of article search and selection conducted in accordance with guidelines on reporting systematic reviews of observational studies (56). ITP = idiopathic thrombocytopenic purpura.

Table 1. **Characteristics of Patients with Idiopathic Thrombocytopenic Purpura in Rituximab Studies Enrolling 5 or More Patients Each (*n* = 313)***

Study, Year (Reference)	Patients, *n*	Country	Age, *y*†	Duration of ITP, *mo*†	Platelet Count before Rituximab Therapy, *x 10⁹cells/L*†
Cooper et al., 2004 (19)	57	USA/Italy	46 (21–79)	34 (3–360)	<30
Zaja et al., 2005 (33)‡	37	Italy	54	134 (1–264)	11
Brændstrup et al., 2005 (17)	35	Denmark	52 (17–82)	49 (1–288)§	14 (1–49)§
Saleh et al., 2000 (28)	23	USA	59 (21–77)	NR	<75
Case et al., 2005 (18)‡	22	USA	58 (24–83)	NR	<30
Zaja et al., 2003 (32)	16	Italy	59 (16–76)	49 (4–264)	4–55
Sanal et al., 2004 (29)	15	USA	46 (19–83)	21 (6–122)	10–78
Garcia-Chavez et al., 2005 (20)‡	14	Mexico	17–70	NR	3–37
Ahn et al., 2005 (13)‡	12	USA	43 (22–87)§	NR	NR
Giagounidis et al., 2002 (21)	12	Germany	45 (28–71)	48 (36–84)	1–29
Shanafelt et al., 2003 (30)	12	USA	51 (22–79)	NR	1–38
Zalzaleh et al., 2004 (34)‡	10	USA	NR	NR	NR
Perrotta et al., 1999 (27)‡	9	USA	NR	NR	2–77
Wang et al., 2005 (31)	9	USA	17 (16–19)	33 (7–108)	3–85
Jacoub et al., 2004 (23)‡	8	USA	44 (20–79)	34 (1–204)	NR
Narat et al., 2005 (26)	6	England	59 (28–89) §	NR	8–89
Narang et al., 2003 (25)	6	USA	53 (30–70)	53 (5–36)	<10
Lieb et al., 2003 (24)‡	5	USA	55 (30–79)	NR	8 (1–30)
Grossi et al., 2000 (22)‡	5	Italy	NR	NR	<30

* ITP = idiopathic thrombocytopenic pupura; NR = not reported; USA = United States of America.
† Unless otherwise noted, values are the median (range [i.e., minimum, maximum]).
‡ Abstract.
§ Values are the mean (range).

Table 2. **Overall, Complete, and Partial Platelet Count Response after Treatment with Rituximab in Adults with Idiopathic Thrombocytopenic Purpura according to Studies Enrolling at Least 5 Patients Each***

Platelet Count Response, × 10^9 cells/L	Pooled Estimate (95% CI), %	Contributing Reports (Patients), *n* (*n*)
Overall response (>50)	62.5 (52.6–72.5)	19 (313)
Complete response (>150)	46.3 (29.5–57.7)	13 (191)
Partial response (50–150)	24.0 (15.2–32.7)	16 (284)

* Platelet count response criteria were based on the most common criteria used in primary reports.

intermediate dose (150 mg/m^2 on day 1, then 375 mg/m^2 weekly for 3 weeks), and a standard dose (28).

Platelet Count Response

In most reports, complete response and partial response were defined according to the achievement of predefined platelet count thresholds; however, these thresholds varied. Certain reports used additional criteria to define a response, including the discontinuation of steroid therapy (32) and the resolution of bleeding symptoms (26). One report defined complete response as the achievement of a platelet count that was "adequate for hemostasis" (25); in 2 reports, neither complete response nor partial response was defined (22, 27). The timing of platelet count measurements in the definitions of a response was specified in 2 reports: 12 weeks after the first rituximab infusion (29) and 2 weeks after the last infusion (30). In 1 report, a response was considered only if it lasted at least 30 days (21), and in another, at least 4 months (13).

Where reporting of studies included homogenous criteria to define platelet count responses to therapy, treatment with rituximab resulted in a complete response (platelet count $> 150 \times 10^9$ cells/L) in 46.3% of patients (95% CI, 29.5% to 57.7%), partial response (50 to 150×10^9 cells/L) in 24.0% (CI, 15.2% to 32.7%), and overall response ($>50 \times 10^9$ cells/L) in 62.5% (CI, 52.6% to 72.5%). Rates of complete, partial, and overall response were based on 191, 284, and 313 eligible patients, respectively (**Table 2**). In a sensitivity analysis that excluded abstract-only publications, results were similar.

Time to Response and Response Duration

The median time to response was 5.5 weeks from the first dose of rituximab (interquartile range [IQR], 3.0 to 6.6 weeks) among the 6 studies (123 patients) that reported this outcome. Median response duration was 10.5 months (IQR, 6.3 to 17.8 months) as reported in 16 studies (252 patients), and median follow-up was 9.5 months (IQR, 6.0 to 21.3 months) as reported in 10 studies (187 patients) (**Table 3**). Thrombocytopenia recurred in 33 of 313 patients (10.5%); however, the duration of follow-up varied. In the largest prospective study (57 patients), 16 of the 18 patients (88.9%) who achieved a complete response (platelet count $> 150 \times 10^9$ cells/L) maintained normal platelet counts after a median of 72.5 weeks. In contrast, only 2 of the 13 patients (15.4%) who achieved a partial response (platelet counts between 50 and 150×10^9 cells/L) maintained a response; the others relapsed after a median of 10 weeks (19).

Predictors of a Response to Rituximab

Zaja and colleagues (33) found that a shorter period between diagnosis and rituximab administration was associated with improved relapse-free survival. Similarly, Cooper and colleagues (19) reported that duration of ITP for more than 15 years was associated with a poor response. Splenectomy, pretreatment platelet count, number of previous treatments, sex, and age were not significant predictors in 2 studies (17, 19). Younger age was associated with a favorable response in Sanal and colleagues' report (29); however, the authors did not report the age criteria used in their regression analysis.

Toxicities

Among the 29 reports (306 patients) that described toxicities, including the studies enrolling fewer than 5 patients, 66 patients (21.6%) experienced mild or moderate adverse events (grade 1 to 2 as per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 [47]), of which 55 were infusional re-

Table 3. **Time to Response, Response Duration, and Follow-up of Patients with Idiopathic Thrombocytopenic Purpura Treated with Rituximab***

Variable	Median	Interquartile Range	Range	Contributing Reports (Patients), *n* (*n*)
Time to response, *wk*	5.5	3.0–6.6	2.0–18.0	6 (123)
Response duration, *mo*	10.5	6.3–17.8	3.0–20.0	16 (252)
Follow-up, *mo*	9.5	6.0–21.3	2.0–25.0	10 (187)

* Summary variables and interquartile ranges were calculated on the basis of the assumption that the data were normally distributed. Only studies that enrolled 5 or more patients each were analyzed.

Table 4. **Toxicities Observed after Rituximab Infusions in Adults with Idiopathic Thrombocytopenic Purpura as Reported in 29 Studies (306 Patients)***

Study, Year (Reference)	Patients, *n*	Grade 1–2	Grade 3–4	Grade 5
Cooper et al., 2004 (19)	57	Infusional (33)	Bronchospasm (1)	NR
Zaja et al., 2005 (33)†	37	Infusional (1) Serum sickness (1)	NR	NR
Brændstrup et al., 2005 (17)	35	Infusional (3) Swelling, rash (5) Leg cramps/diarrhea (1)	Anaphylactoid reaction (1) Muscle pain/leg swelling (1)	Respiratory failure (1) Pneumonia (1)
Saleh et al., 2000 (28)	23	Infusional (?)	NR	NR
Case et al., 2005 (18)†	22	Infusional (6)	NR	NR
Zaja et al., 2003 (32)	16	Infusional (1)	NR	NR
Ahn et al., 2005 (13)†	12	None observed	NR	NR
Giagounidis et al., 2002 (21)	12	Infusional (4) Thrombocytosis (1)	Meningococcal meningitis (1)	
Shanafelt et al., 2003 (30)	12	NR	NR	Central nervous system hemorrhage (1) Hemorrhage (1) Unknown causes (1)
Zalzaleh et al., 2004 (34)†	10	Allergic reaction (1)	NR	NR
Perrotta et al., 1999 (27)†	9	None observed	NR	NR
Wang et al., 2005 (31)	9	Infusional (4)	NR	NR
Jacoub et al., 2004 (23)†	8	Infusional (1)	Pneumonia (1)	Hepatic failure (1)
Narat et al., 2005 (26)	6	None observed	NR	NR
Narang et al., 2003 (25)	6		Pneumonia (1)	NR
Lieb et al., 2003 (24)†	5	NR	NR	Infection (1)
Grossi et al., 2000 (22)†	5	NR	NR	Bleeding/infection (1)
Lalayanni et al., 2004 (39)	4	NR	NR	Pulmonary embolism (1)
Delgado et al., 2002 (38)	4	Infusional (1)	NR	NR
Zaja et al., 2001 (45)†	3	Panniculitis (1)	Retinal artery thrombosis (1)	NR
Ahrens et al., 2002 (35)	2	Infusional (1)	NR	NR
Rosenthal et al., 2001 (42)†	2	NR	Bacterial pneumonia (1)	NR
Zhou et al., 2005 (46)	1	Skin rash (1)	NR	NR
Swords et al., 2004 (43)	1	NR	Interstitial pneumonitis (1)	NR
Thude et al., 2004 (44)	1	None observed	NR	NR
D'Arena et al., 2003 (36)	1	None observed	NR	NR
Riksen et al., 2003 (41)	1	None observed	NR	NR
de Roux Serratrice et al., 2002 (37)	1	None observed	NR	NR
Mow and Hook, 1999 (40)†	1	NR	Pulmonary embolism (1)	NR
Total	306	66	10	9

* Toxicity grades are National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (47): grade 1–2 = mild to moderate; grade 3–4 = serious to life-threatening; grade 5 = fatal. The number of patients in each category is reported. NR = not reported.
† Abstract.

actions. Ten patients (3.7%) experienced severe or life-threatening events (grade 3 to 4), and 9 patients died (2.9%) (grade 5) (**Table 4**). Causes of death were respiratory insufficiency 6 days after the administration of rituximab in a 71-year-old woman with severe chronic respiratory disease (17); pneumonia 13 weeks after rituximab treatment in a 73-year-old man with severe chronic obstructive lung disease (17); central nervous system hemorrhage less than 1 week after rituximab treatment (30); hemorrhagic complications within 3 weeks of receipt of rituximab (30); infection (no time frame provided) (24); bleeding and polymicrobial infection (no time frame provided) (22); pulmonary embolism 2 days after surgical drainage of a hepatic abscess and 4 months after rituximab treatments (39); hepatic failure characterized by marked cholestasis and loss of bile ducts 4 months after re-treatment with rituximab (23), and death from unknown causes within 3 weeks of receipt of rituximab (30).

Study Quality

None of the identified studies included a control group. Of the 19 efficacy studies, 7 were prospective, 7 were retrospective, and 5 were of uncertain type (**Table 5**). The enrollment of consecutive patients was described in 1 report, duration of follow-up was clearly stated in 11, and losses to follow-up were reported in 3. Nine of the 19 reports were published in abstract form only. To examine the association between study precision and response, we plotted sample size against overall platelet count response (**Figure 2**). From this figure we observe that small studies reporting high rates of response were overrepresented in this cohort.

DISCUSSION

This systematic review summarizes the efficacy and safety of rituximab for the treatment of adults with ITP.

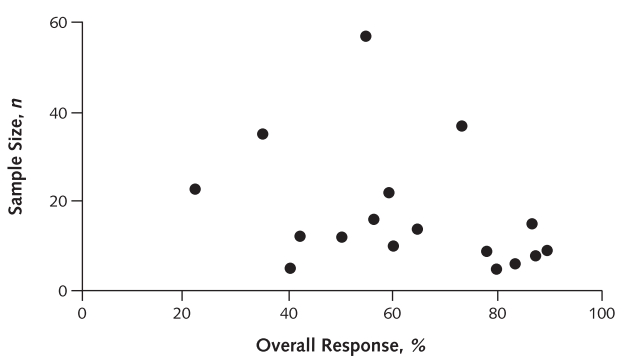
Table 5. **Results of Duplicate Methodologic Quality Assessments of the 19 Reports That Contributed to the Efficacy Analysis***

Study, Year (Reference)	Data Collection Was Prospective	Consecutive Patients Were Enrolled	Duration of Follow-up Was Clearly Stated	Losses to Follow-up Were Described
Cooper et al., 2004 (19)	Y	NR	Y	NR
Zaja et al., 2005 (33)†	NR	NR	Y	NR
Brændstrup et al., 2005 (17)	N	NA	N	NA
Saleh et al., 2000 (28)	Y	NR	Y	Y
Case et al., 2005 (18)†	NR	NR	N	NR
Zaja et al., 2003 (32)	NR	NR	Y	NR
Sanal et al., 2004 (29)	N	NA	N	NA
Garcia-Chavez et al., 2005 (20)†	Y	Y	N	NR
Ahn et al., 2005 (13)†	NR	NR	N	NR
Giagounidis et al., 2002 (21)	Y	NR	Y	NR
Shanafelt et al., 2003 (30)	N	NA	Y	NA
Zalzaleh et al., 2004 (34)†	Y	NR	Y	NR
Perrotta et al., 1999 (27)†	N	NA	N	NA
Wang et al., 2005 (31)	Y	NR	Y	Y
Jacoub et al., 2004 (23)†	N	NA	N	NA
Narat et al., 2005 (26)	N	NA	N	NA
Narang et al., 2003 (25)	NR	NR	Y	Y
Lieb et al., 2003 (24)†	N	NA	N	NA
Grossi et al., 2000 (22)†	Y	NR	Y	NR

* Consecutive patient enrollment and losses to follow-up were not applicable to retrospective studies. Y = yes; N = no; NA = not applicable; NR = not reported.
† Abstract.

Rituximab resulted in complete response (platelet count $> 150 \times 10^9$ cells/L) in 43.6% of patients (CI, 29.5% to 57.7%) and an overall response (platelet count $> 50 \times 10^9$ cells/L) in 62.5% (CI, 52.6% to 72.5%). Median response duration was 10.5 months (IQR, 6.3 to 17.8 months) and median follow-up was 9.5 months (IQR, 6.0 to 21.3 months). Most patients received 4 weekly infusions of 375 mg/m^2. Nearly all patients had received corticosteroids, half had had splenectomy that failed, and most were refractory to multiple treatments before receiving rituximab. Mortality (9 deaths among 306 patients), which included all deaths in rituximab-treated patients, was surprisingly high.

Figure 2. **Relationship between sample size and reported rates of overall response (platelet count > 50 × 10^9 cells/L).**



Each circle represents a unique study of rituximab in adults with idiopathic thrombocytopenic purpura that enrolled 5 or more patients each (19 studies).

This review is important at this time because of the extraordinarily widespread use of rituximab for the treatment of various autoimmune conditions, including ITP, hemolytic anemia, thrombotic thrombocytopenic purpura, systemic lupus erythematosus, and other "autoimmune" conditions, in the absence of rigorous data supporting its use for most of these indications (12). Despite extensive use, only 1 randomized trial has examined the efficacy of rituximab outside the hematologic malignant conditions (10).

Formal meta-analytic methods could not be used to combine the results of our literature review because of a lack of controlled trials, extreme heterogeneity, and bias inherent to these observational data. Instead, we used rigorous methods to scrutinize and synthesize evidence describing the efficacy and safety of rituximab in patients with ITP (48). As expected, small studies tended to report greater response rates than larger studies, as shown when sample size was plotted against overall response (akin to a funnel plot used to detect reporting bias in randomized trials). Patients were heterogeneous with respect to the duration of ITP, splenectomy status, and previous treatments; however, analysis of these subgroups was not possible because these data were often not reported separately. Although studies of patients with chronic lymphocytic leukemia or lymphoma were exclusions, 6 of 313 patients had these diagnoses, which may have inflated our estimates of response somewhat. Our literature search uncovered a report of a survey describing 89 patients with ITP treated with rituximab (49). We excluded this study because it did not report original data; nevertheless, the response rates were similar.

Important differences among studies were also noted in the definitions of complete, partial, and minimal platelet

count response. This observation emphasizes the need for standardization of treatment response criteria in ITP, which should include a minimum duration of response and the absence of clinically relevant end points, such as bleeding and the need for ongoing treatments. We chose to define overall response as a platelet count greater than 50×10^9 cells/L on the basis of convention and on the availability of data from the primary studies, even though the achievement of a platelet count lower than this may still be high enough to prevent serious bleeding (50).

Close to 60% of patients in the largest prospective study (57 patients) experienced mild infusional side effects with rituximab (19); however, across all studies, infusional reactions were far less common, occurring in 55 of 306 patients (18%) overall. Reporting bias and nonstandardized data collection undoubtedly account for some of the discrepancy. The mortality rate that we observed probably overestimates the number of deaths attributable to rituximab, also as a result of bias inherent to these observational studies. More likely, these deaths were the result of long courses of complex treatment regimens or the selection of patients with advanced disease. Authors assessed attribution for 2 of the 9 reported deaths; rituximab administration was not felt to be related to the case of fatal pneumonia (17) but was thought to be possibly related to the case of fatal hepatic failure (23). Our observed mortality rate was similar to that in 2 of the largest retrospective cohort studies in ITP: Portieljie and colleagues (51) reported 6 ITP-related deaths among 152 patients (3.9%), and Stasi and colleagues (52) reported 5 deaths among 208 patients (2.4%). Similarly, an overview of ITP studies uncovered 49 cases of fatal hemorrhage among 1817 patients (2.7%) (53). In patients with lymphoma, the number of deaths directly attributable to rituximab is far lower than the number of death reported here, estimated at 4 to 7 per 10 000 patients treated (54). Even though none of the reported deaths in this review were fatal infusional reactions, the possibility that this cohort of ITP patients was prone to toxicities and death from monoclonal antibody therapy cannot be excluded.

The optimal timing and dose of rituximab in ITP remain uncertain. Data from a recent meta-analysis suggested that intravenous immunoglobulin given as initial therapy to children may reduce the proportion of patients who develop chronic ITP (55). Rituximab may have a similar disease-modifying effect through immune modulation if given early in the course of the disease. Also in favor of early administration is the improvement in relapse-free survival observed in patients with a short duration of ITP before rituximab treatment (33) and an improvement in response duration in patients who achieved a complete response (19, 49). On the other hand, a favorable response following the early administration of rituximab may simply reflect spontaneous platelet count recovery, underscoring the need for randomized, controlled trials to resolve this issue. Additional studies are also needed to determine the optimal dose and schedule of rituximab in ITP because these have been adopted from lymphoma treatment regimens in which the goal of treatment, to eradicate malignant B-cell tumors, is different.

None of the studies in this review included a control group, and none met all predetermined methodologic quality criteria for observational studies (56, 57). In addition, many reports were published in abstract form only, providing insufficient detail with which to scrutinize the design, analysis, and results. Overall, relatively few rituximab-treated patients with ITP have been described in the literature to date. Thus, we conclude that the quality of the evidence in support of rituximab for the treatment of adult ITP is poor. Given the lack of control groups, the efficacy of rituximab compared with standard treatments for ITP cannot be determined.

In conclusion, rituximab was associated with a platelet count response in approximately 60% of patients with chronic ITP; however, this finding must be balanced against the poor quality of the underlying data. In addition, many deaths were reported after the use of rituximab in patients with ITP, even though the data preclude inferences of causation. There is an urgent need for randomized, controlled trials of rituximab in ITP. Until then, we would caution against the indiscriminate use of this treatment.

From McMaster University and Juravinski Cancer Centre, Hamilton, Ontario, Canada; Insubria University, Varese, Italy; National Cancer Institute of Canada Clinical Trials Group, Kingston, Ontario, Canada; Queen's University, Kingston, Ontario, Canada; University of Waterloo, Waterloo, Ontario, Canada.

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Corresponding Author: Donald M. Arnold, MD, McMaster University Health Sciences Center, Room 3N-43, 1200 Main Street West, Hamilton, Ontario L8N 3Z5, Canada; e-mail, arnold@mcmaster.ca.

Current author addresses are available at www.annals.org.

References

1. **Di Gaetano N, Cittera E, Nota R, Vecchi A, Grieco V, Scanziani E, et al.** Complement activation determines the therapeutic activity of rituximab in vivo. J Immunol. 2003;171:1581-7. [PMID: 12874252]

2. **Golay J, Zaffaroni L, Vaccari T, Lazzari M, Borleri GM, Bernasconi S, et al.** Biologic response of B lymphoma cells to anti-CD20 monoclonal antibody rituximab in vitro: CD55 and CD59 regulate complement-mediated cell lysis. Blood. 2000;95:3900-8. [PMID: 10845926]

3. **Golay J, Lazzari M, Facchinetti V, Bernasconi S, Borleri G, Barbui T, et al.** CD20 levels determine the in vitro susceptibility to rituximab and complement of B-cell chronic lymphocytic leukemia: further regulation by CD55 and CD59. Blood. 2001;98:3383-9. [PMID: 11719378]

4. **Golay J, Gramigna R, Facchinetti V, Capello D, Gaidano G, Introna M.** Acquired immunodeficiency syndrome-associated lymphomas are efficiently lysed through complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity by rituximab. Br J Haematol. 2002;119:923-9. [PMID: 12472569]

5. **Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al.** CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346:235-42. [PMID: 11807147]

6. **Feugier P, Van Hoof A, Sebban C, Solal-Celigny P, Bouabdallah R, Fermé C, et al.** Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol. 2005;23:4117-26. [PMID: 15867204]

7. **Maloney DG, Grillo-López AJ, White CA, Bodkin D, Schilder RJ, Neidhart JA, et al.** IDEC-C2B8 (Rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. Blood. 1997;90: 2188-95. [PMID: 9310469]

8. **Maloney DG, Grillo-López AJ, Bodkin DJ, White CA, Liles TM, Royston I, et al.** IDEC-C2B8: results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. J Clin Oncol. 1997;15:3266-74. [PMID: 9336364]

9. **Kimby E.** Tolerability and safety of rituximab (MabThera). Cancer Treat Rev. 2005;31:456-73. [PMID: 16054760]

10. **Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al.** Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004;350:2572-81. [PMID: 15201414]

11. **Leandro MJ, Cambridge G, Edwards JC, Ehrenstein MR, Isenberg DA.** B-cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients. Rheumatology (Oxford). 2005;44:1542-5. [PMID: 16188950]

12. **George JN, Woodson RD, Kiss JE, Kojouri K, Vesely SK.** Rituximab therapy for thrombotic thrombocytopenic purpura: a proposed study of the Transfusion Medicine/Hemostasis Clinical Trials Network with a systematic review of rituximab therapy for immune-mediated disorders. J Clin Apher. 2006; 21:49-56. [PMID: 16619232]

13. **Ahn ER, Bidot CJ, Fontana V, Dudkiewicz P, Jy W, Horstman L, et al.** Rituximab therapy induces long lasting clinical remissions and reduction of antiplatelet glycoprotein autoantibodies in patients with chronic immune thrombocytopenic purpura (ITP) [Abstract]. Blood. 2005;106:

14. **Cines DB, McMillan R.** Management of adult idiopathic thrombocytopenic purpura. Annu Rev Med. 2005;56:425-42. [PMID: 15660520]

15. **Cines DB, Bussel JB.** How I treat idiopathic thrombocytopenic purpura (ITP). Blood. 2005;106:2244-51. [PMID: 15941913]

16. **Landis JR, Koch GG.** The measurement of observer agreement for categorical data. Biometrics. 1977;33:159-74. [PMID: 843571]

17. **Braendstrup P, Bjerrum OW, Nielsen OJ, Jensen BA, Clausen NT, Hansen PB, et al.** Rituximab chimeric anti-CD20 monoclonal antibody treatment for adult refractory idiopathic thrombocytopenic purpura. Am J Hematol. 2005;78: 275-80. [PMID: 15795920]

18. **Case DC Jr., Hedlund JA, Ebrahim KS, Boyd MA.** Rituximab produces long-term responses in immune thrombocytopenic purpura (ITP) [Abstract]. Blood. 2005;106

19. **Cooper N, Stasi R, Cunningham-Rundles S, Feuerstein MA, Leonard JP, Amadori S, et al.** The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune thrombocytopenic purpura. Br J Haematol. 2004;125:232-9. [PMID: 15059147]

20. **Garcia-Chavez J, Vela-Ojeda J, Gonzalez-Acosta JC, Ovilla-Martinez R.** Treatment of refractory chronic immune thrombocytopaenic purpura (ITP) with rituximab: report of a cases series [Abstract]. Blood. 2005;106: 4007.

21. **Giagounidis AA, Anhuf J, Schneider P, Germing U, Söhngen D, Quabeck K, et al.** Treatment of relapsed idiopathic thrombocytopenic purpura with the anti-CD20 monoclonal antibody rituximab: a pilot study. Eur J Haematol. 2002; 69:95-100. [PMID: 12366712]

22. **Grossi A, Santini V, Longo G, Balestri F, Ferrini P.** Treatment with anti-CD 20 antibodies of patients with autoimmune thrombocytopenia with or without haemolytic anemia; worsening in hemoglobin level [Abstract]. Blood.2000;96 (suppl):253a.

23. **Jacoub J, Mchlayeh W, Tabbara I, Dave H, Siegel R, Schecter G.** The use of anti-cd20 chimeric monoclonal antibody, rituximab in adult patients with treatment refractory immune thrombocytopenia [Abstract]. Blood. 2004;104: 3950.

24. **Lieb J, Rossetti J, Shadduck R, Gryn J, Kaplan R, Zeigler Z, et al.** Rituximab therapy for relapsed or refractory autoimmune thrombocytopenia [Abstract]. Blood. 2003;102:4038.

25. **Narang M, Penner JA, Williams D.** Refractory autoimmune thrombocytopenic purpura: responses to treatment with a recombinant antibody to lymphocyte membrane antigen CD20 (rituximab). Am J Hematol. 2003;74:263-7. [PMID: 14635207]

26. **Narat S, Gandla J, Hoffbrand AV, Hughes RG, Mehta AB.** Rituximab in the treatment of refractory autoimmune cytopenias in adults [Letter]. Haematologica. 2005;90:1273-4. [PMID: 16154853]

27. **Perrotta A, Sunnenberg T, Scott J, Ratanatharaphorn V, Hook C, Attas L, et al.** Rituxan in the treatment of chronic idiopathic thrombocytopenia purpura (ITP) [Abstract]. Blood. 1999;94(Suppl):14a.

28. **Saleh MN, Gutheil J, Moore M, Bunch PW, Butler J, Kunkel L, et al.** A pilot study of the anti-CD20 monoclonal antibody rituximab in patients with refractory immune thrombocytopenia. Semin Oncol. 2000;27:99-103. [PMID: 11226008]

29. **Sanal S, Hanson M, Dees M.** Rituximab induces high response rates and prolonged remission in chronic idiopathic thrombocytopenic purpura (ITP): a retrospective analysis [Abstract]. Blood. 2004;104:3956.

30. **Shanafelt TD, Madueme HL, Wolf RC, Tefferi A.** Rituximab for immune cytopenia in adults: idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, and Evans syndrome. Mayo Clin Proc. 2003;78:1340-6. [PMID: 14601692]

31. **Wang J, Wiley JM, Luddy R, Greenberg J, Feuerstein MA, Bussel JB.** Chronic immune thrombocytopenic purpura in children: assessment of rituximab treatment. J Pediatr. 2005;146:217-21. [PMID: 15689912]

32. **Zaja F, Vianelli N, Sperotto A, De Vita S, Iacona I, Zaccaria A, et al.** B-cell compartment as the selective target for the treatment of immune thrombocytopenias. Haematologica. 2003;88:538-46. [PMID: 12745273]

33. **Zaja FF, Vianelli NN, Battista MM, Sperotto AA, Patriarca FF, Tomadini VV, et al.** Earlier administration of rituximab allows higher rate of long-lasting response in adult patients with autoimmune thrombocytopenia [Abstract]. Blood. 2005;106: 3991.

34. **Zalzaleh G, Jajeh A, Tamoseviciene D.** Rituximab in the treatment of adults with chronic idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA) [Abstract]. Blood. 2004;104: 3930.

35. **Ahrens N, Heymann G, Meyer O, Kiesewetter H, Salama A.** Results of treatment with rituximab (anti-CD20) in three patients with autoimmune hemolytic anemia and/or immune thrombocytopenia and a concise review of reported cases. Infusionstherapie und Transfusionsmedizin. 2002;29:277-81.

36. **D'Arena G, Luigiavigliotti M, Coccaro M, Iodice G, Tartarone A, Matera R, et al.** Late and long-lasting response in an adult chronic idiopathic thrombocytopenic purpura after extended course of rituximab [Letter]. Leuk Lymphoma. 2003;44:561-2. [PMID: 12688335]

37. **de Roux Serratrice C, Brandi Y, Caillères S, Brunel V, Allègre T, Blanc AP.** [Safety of monoclonal antibody anti-CD 20 in refractory thrombocytopenic idiopathic purpura] [Letter]. Rev Med Interne. 2002;23:869-70. [PMID: 12428493]

38. **Delgado J, Bustos JG, Jimenez-Yuste V, Hernandez-Navarro F.** Anti-CD20 monoclonal antibody therapy in refractory immune thrombocytopenic purpura [Letter]. Haematologica. 2002;87:215-6. [PMID: 11836172]

39. **Lalayanni C, Stavroyianni N, Saloum R, Tsompanakou A, Anagnostopoulos A.** Rituximab is effective for selected patients with chronic steroid-refractory immune thrombocytopenic purpura. Hematology. 2004;9:287-9. [PMID: 15621736]

40. **Mow B, Hook C.** Rituximab for the treatment of refractory immune throm-

bocytopenic purpura—case report [Abstract]. Blood. 1999;94(suppl):82b.
41. **Riksen NP, Keuning JJ, Vreugdenhil G.** Rituximab in the treatment of relapsing idiopathic thrombocytopenic purpura. Neth J Med. 2003;61:262-5. [PMID: 14567524]
42. **Rosenthal E, Karsenti J, Pesce A, Cassuto J.** Anti-CD20 monoclonal antibody (rituximab) Administration in patients with refractory immunologic thrombocytopenic purpura [Abstract]. Blood. 2001;98:525a.
43. **Swords R, Power D, Fay M, O'Donnell R, Murphy PT.** Interstitial pneumonitis following rituximab therapy for immune thrombocytopenic purpura (ITP) [Letter]. Am J Hematol. 2004;77:103-4. [PMID: 15307117]
44. **Thude H, Gruhn B, Werner U, Schorner U, Häfer R, Zintl F, et al.** Treatment of a patient with chronic immune thrombocytopenic purpura with rituximab and monitoring by flow cytometric analysis. Acta Haematol. 2004; 111:221-4. [PMID: 15153715]
45. **Zaja F, Russo D, De Via S, Sperotto A, Patriarca F, Michelutti A, et al.** Rituximab for the treatment of autoimmune disease [Abstract]. Blood. 2001;98: 41b .
46. **Zhou N, Hua BL, Wang SJ, Zhu TN, Zhao YQ.** [Rituximab monoclonal antibody in the treatment of retractable idiopathic thrombocytopenic purpura—a case report]. Zhonghua Yi Xue Za Zhi. 2005;85:432. [PMID: 15854541]
47. National Institute of Health. National Cancer Institute. Common Terminology Criteria for Adverse Events, Version 3.0. Accessed at http://ctep.info.nih.gov /reporting/ctc.html on 11 August 2006.
48. **Cook DJ, Mulrow CD, Haynes RB.** Systematic reviews: synthesis of best evidence for clinical decisions. Ann Intern Med. 1997;126:376-80. [PMID: 9054282]
49. **Multi-institutional Retrospective Spanish Study on the use of rituximab in refractory ITP.** Rituximab in the management of chronic immune thrombocytopenic purpura: an effective and safe therapeutic alternative in refractory patients. Ann Hematol. 2006;85:400-6. [PMID: 16550390]
50. **George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ, et al.** Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood. 1996;88:3-40. [PMID: 8704187]
51. **Portielje JE, Westendorp RG, Kluin-Nelemans HC, Brand A.** Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. Blood. 2001; 97:2549-54. [PMID: 11313240]
52. **Stasi R, Stipa E, Masi M, Cecconi M, Scimò MT, Oliva F, et al.** Long-term observation of 208 adults with chronic idiopathic thrombocytopenic purpura. Am J Med. 1995;98:436-42. [PMID: 7733121]
53. **Cohen YC, Djulbegovic B, Shamai-Lubovitz O, Mozes B.** The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. Arch Intern Med. 2000;160:1630-8. [PMID: 10847256]
54. **Grillo-López AJ, Hedrick E, Rashford M, Benyunes M.** Rituximab: ongoing and future clinical development. Semin Oncol. 2002;29:105-12. [PMID: 11842397]
55. **Beck CE, Nathan PC, Parkin PC, Blanchette VS, Macarthur C.** Corticosteroids versus intravenous immune globulin for the treatment of acute immune thrombocytopenic purpura in children: a systematic review and meta-analysis of randomized controlled trials. J Pediatr. 2005;147:521-7. [PMID: 16227040]
56. **Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al.** Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283:2008-12. [PMID: 10789670] (
57. **Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J.** Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg. 2003;73:712-6. [PMID: 12956787]

Current Author Addresses: Dr. Arnold and Mr. Sigouin: McMaster University Health Sciences Center, Room 3N-43, 1200 Main Street West, Hamilton, Ontario L8N 3Z5, Canada.
Dr. Dentali: Department of Clinical Medicine, Insubria University, Viale Borri 57, Varese, Italy 21100.
Dr. Crowther and Dr. Lim: St. Joseph's Hospital, 50 Charlton Avenue East, Room L-208, Hamilton, Ontario L8N 4A6, Canada.
Dr. Meyer: Clinical Trials Division, Cancer Research Institute, Queen's University, 10 Stuart Street, Kingston, Ontario K7L 3N6, Canada.
Dr. Cook: University of Waterloo, 200 University Avenue West, Waterloo, Ontario N2L 3G1, Canada.
Dr. Fraser: Juravinski Cancer Centre, 699 Concession Street, Hamilton, Ontario L8V 5C2, Canada.