The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune thrombocytopenic purpura

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Summary

Because of its B-cell depleting effect, rituximab has entered clinical trials in several autoimmune conditions. This study assesses the efficacy and safety of rituximab in 57 adults with chronic immune thrombocytopenic purpura (ITP). All patients had platelet counts $<30 \times 10^9$/l, all had received two or more previous ITP treatments and 31 had undergone splenectomy. Patients received rituximab 375 mg/m^2 weekly for 4 weeks. Thirty-one patients (54%) responded, achieving a platelet count $>50 \times 10^9$/l: 18 achieved a complete response (CR: platelet count $>150 \times 10^9$/l) and 13 a partial response (PR: platelet count $50–150 \times 10^9$/l). Twenty-nine responses occurred within 8 weeks of the first infusion. Sixteen of 18 CR patients (28% overall), including eight who had failed splenectomy, continued in CR after a median of 72·5 weeks; 15 of 16 are >1 year from the first infusion. Only two of 13 maintained a PR. Thirty-three patients experienced grade 1–2 adverse events and one a grade 3 event, but they all completed treatment. Circulating B cells fell to $<0{\cdot}03 \times 10^9$/l. No changes in immunoglobulin levels or infectious complications were seen. In summary, rituximab was well tolerated with no immediate complications and induced a lasting, substantial response in 32% of adults with chronic ITP.

Keywords: rituximab, immune thrombocytopenic purpura, neutropenia, gammaglobulins, autoimmunity.

Rituximab is an anti-CD20, chimaeric monoclonal antibody, extensively used in the treatment of B-cell lymphomas (Maloney *et al*, 1997; Czuczman *et al*, 1999; Coiffier *et al*, 2002; Pettengell & Linch, 2003). CD20 is a transmembrane protein present on the surface of essentially all B cells but not on mature plasma cells. Studies of lymphoma patients have shown that administration of rituximab at a dose of 375 mg/m^2 weekly for 4 weeks causes a marked reduction of not only malignant B cells but also non-malignant B cells in the peripheral blood (>99%), bone marrow (>90%) and lymph nodes (>80%) (Reff *et al*, 1994; Zaja *et al*, 2002). Because of its depleting effect on peripheral B cells, it is being explored in a number of autoantibody-mediated diseases such as systemic lupus erythematosus (Leandro *et al*, 2002a), rheumatoid arthritis (Leandro *et al*, 2002b), autoimmune haemolytic anaemia (Zecca *et al*, 2003), cryoglobulin disease (Zaja *et al*, 2003a), acquired factor VIII antibodies (Wiestner *et al*, 2002), IgM polyneuropathies (Pestronk *et al*, 2003), glomerulonephropathies (Remuzzi *et al*, 2002) as well as immune thrombocytopenic purpura (ITP) (Stasi *et al*, 2001, 2002; Giagounidis *et al*, 2002; Wang *et al*, 2003; Zaja *et al*, 2003b).

Immune thrombocytopenic purpura is a model autoantibody-mediated disease in which the platelet count is readily available to document the state of the disease. Previous studies of the use of rituximab in ITP have reported small numbers of patients with limited follow-up (maximum 480 d). The study reported here combines the data from 32 patients in two preliminary reports with two further patients treated in Italy and 23 treated in the USA (Stasi *et al*, 2001, 2002). A critical component in this report is the substantially longer follow-up involving the previously published patients. By combining these two identical studies and including the longer follow-up available in the Italian patients, this study provides a more comprehensive analysis of the response to rituximab, including

the timing and duration of the response to treatment. It also analyses factors affecting the response including the surprising lack of effect of splenectomy.

The large group of patients reported here also enabled a comprehensive assessment of the safety of this therapy in patients with non-malignant conditions. It includes the neutrophil counts and immunoglobulin levels following rituximab therapy and evaluates the infectious risk of B-cell depletion in this population of patients. Given the recent reports of prolonged neutropenia, hypogammaglobulinaemia and serious and unexpected viral infections when this therapy is used in combination with chemotherapy and bone marrow transplantation (Goldberg *et al*, 2002; Matteucci *et al*, 2002; Chaiwatanatorn *et al*, 2003; Quartier *et al*, 2003; Sirvent-Von Bueltzingsloewen *et al*, 2003; Voog *et al*, 2003), this data provide important information for clinicians considering the use of rituximab in patients with non-malignant conditions.

Patients and methods

Data reported in this series come from two separate institutional review board-approved trials. Data accrual was completed as of 30 September 2002. Twenty-three patients were enrolled at the New York Presbyterian Hospital, Cornell campus, New York, NY, USA, between October 2000 and October 2001 and 34 enrolled at Regina Apostolorum Hospital, Albano Laziale and the University of Rome, Italy from February 1999 to February 2002. Preliminary data from 32 of the 34 Italian patients were previously reported (Stasi *et al*, 2001, 2002). These previous reports included a median of 57 weeks follow-up on the nine patients who had had durable responses to rituximab. The data reported here provide a median 44 additional weeks in these patients as well as approximately doubling the number of patients. The combined data enabled us to establish novel, comprehensive assessments of the timing of response and relapse, as well as correlates of response and toxicity. The combination of the two groups also allowed more balanced assessment of both the pre- and postsplenectomy patient groups.

Eligibility criteria

Patients were required to have primary ITP of 3 months duration; all but one patient had had ITP for >6 months (chronic ITP). Four patients enrolled onto the USA study had a platelet count of 20–30 $\times 10^9$/l; all other patients on both studies had platelet counts <20 $\times 10^9$/l. In order to be entered into the trial, patients were required not to have received intravenous immunoglobulin (IVIG) or i.v. anti-D for at least 2 weeks and to be on a stable or decreasing dose of steroids or danazol. Eight patients had counts >30 $\times 10^9$/l during the 3 weeks prior to study following IVIG, i.v. anti-D or steroids for low counts and/or bleeding symptoms. The remaining patients had counts persistently below 30 $\times 10^9$/l.

Table I. Comparison of the two patient groups.

	USA	Italy	Combined
Patients	23	34	57
Men	8	10	18
Women	15	24	39
Splenectomy ($P < 0{\cdot}004$)			
Yes	19	12	31
No	4	22	26
Age (years)			
Median	46·0	46·0	46·0
Range	21–79	22–74	21–79
Duration of ITP (months) ($P < 0{\cdot}0001$)			
Median	127·0	20·5	34·0
Range	3–360	10–84	3–360
Number of previous treatments ($P < 0{\cdot}001$)			
Median	5·0	3·0	3·0
Range	2–8	2–5	2–8

The characteristics of each group are shown in Table I. The groups were comparable in age, sex distribution and initial platelet count. United States patients had a longer duration of ITP ($P < 0{\cdot}0001$) and had received more previous therapies ($P < 0{\cdot}0001$) including more frequent splenectomy ($P < 0{\cdot}001$). The increased number of splenectomies in patients treated in the USA probably reflects the fact that these patients had a longer duration of disease.

Treatment

Patients received rituximab (Rituxan; Genentech, Inc., San Francisco, CA, USA and IDEC Pharmaceutical Corporation, San Diego, CA, USA or Mabthera; Roche, Milan, Italy) 375 mg/m^2 intravenously weekly for four consecutive weeks. Patients in Italy received premedication with oral acetaminophen 500 mg and diphenhydramine 50 mg or i.v. chlorpheniramine 10 mg. Patients in the USA received premedication with 25–50 mg diphenhydramine and 650 mg acetaminophen orally. Seventeen USA patients also received prednisone (60 mg with the first infusion, 20 mg with the second infusion and none subsequently) after reactions were seen in the first six patients. During the initial treatment period, according to the protocol at both centres for bleeding and/or platelet counts <10 $\times 10^9$/l, 12 patients received short term 'rescue' therapy with IVIG or prednisone.

As part of the study protocol, patients who responded and subsequently relapsed could be re-treated with the same course of rituximab. The re-treatment data will be published separately.

Response criteria

A complete response (CR) was defined as an increase in platelet counts to >150 $\times 10^9$/l on two consecutive occasions,

1 week apart. A partial response (PR) was defined as an increase in the platelet count to between 50 and 150 $\times 10^9$/l on two consecutive occasions, 1 week apart.

Duration of response was considered from the day of the initial infusion to the first time of relapse (platelet count $<30 \times 10^9$/l) or to time of analysis (30 September 2002).

Laboratory studies

Blood counts were taken pretreatment, weekly for 5 weeks, every 2 weeks for the first 2–6 months depending on response, then monthly. Blood urea nitrogen, electrolytes and liver function tests were assessed pretreatment and at regular intervals throughout the study. IgM and IgG levels were assessed pretreatment and at 11 and 51 weeks after treatment. Thirty-four patients had evaluable IgG and IgM levels at 11 weeks; 10 patients were excluded from analysis because they had relapsed and received IVIG within 4 weeks of testing. Flow cytometry with CD19 quantification of B cells was assessed pretreatment, and at weeks 5, 26 and 52; data following rituximab re-treatment were excluded as was immunoglobulin data following re-treatment with IVIG. B-cell recovery was defined as a count above $0{\cdot}03 \times 10^9$/l.

Statistical analysis

Analysis of data was primarily descriptive using mean values and standard deviations, or medians and ranges. The Kruskal–Wallis, Mann–Whitney *U*, and chi-squared tests were used to assess differences between the Italian and the USA patients and between responders and non-responders. A Kaplan–Meier analysis was conducted to assess the differences in the time to relapse between the PR and CR groups. The paired *t*-test was used to assess the difference between pre- and postrituximab IgG and IgM levels and neutrophil counts. The STATISTICA v6.0 (StatSoft, Inc., Tulsa, OK, USA) statistics package was used. $P < 0{\cdot}05$ was considered significant.

Results

There was no difference in response to therapy between the Italian and the USA patients ($\chi^2 = 0{\cdot}336$). Therefore, the two groups were combined for all subsequent analyses (Table I).

Among the 32 Italian patients who had been preliminarily reported, there were two PR and seven CR patients who had maintained their responses. These nine patients have had an average of eight additional months of follow-up, to bring the total in the current report to 101 weeks in the CR patients, and 74 and 178 months in the two PR patients with persisting responses.

Non-splenectomized patients

Prior to receiving rituximab in this study, only one of 26 patients had ITP for <6 months and only seven of 26 had ITP for <1 year. The 26 non-splenectomized patients had all received multiple treatments without lasting effect: 10 had received two previous treatments (IVIG and steroids), 10 had received three treatments, and six had received four previous treatments. While there were transient responses to certain of the therapies (i.e. IVIG), these patients with persistent, chronic disease were appropriate for exploration of a treatment designed to create substantial, lasting responses.

Splenectomized patients

The 31 splenectomized patients had all received multiple treatments without lasting effect: seven had received two previous treatments (IVIG and steroids) in addition to splenectomy, six had received three treatments, and 18 had received four or more previous treatments.

Subsequent analyses combine the two groups.

Platelet response. Thirty-one of 57 patients (54%) responded to rituximab in achieving platelet counts $>50 \times 10^9$/l with 18 CRs (platelet counts $>150 \times 10^9$/l) and 13 PRs (platelet counts 50–150 $\times 10^9$/l).

Timing of platelet response. Twenty-nine of the 31 responders (94%) had a platelet increase to $>50 \times 10^9$/l within 8 weeks of the initial infusion. The median time to achieve this count was 3·5 weeks (range 1–19 weeks).

Patterns of response in CR patients

The 18 patients who achieved a CR had three distinct patterns of platelet response (Fig 1). Seven had early platelet increases; achieving normal platelet counts before the fourth infusion of rituximab. Five had little change for 3–4 weeks but then achieved normal counts between weeks 7 and 11. The remaining six patients had a slow, steady increase in their platelet count, achieving counts $>50 \times 10^9$/l by a median of 8 weeks from initial infusion, but reaching normal counts only between weeks 13 and 31. These late responders had minor platelet responses within the first few weeks of therapy, achieving platelet counts $\geq 30 \times 10^9$/l by week 8 of treatment and required no further ITP therapy, which indicated that the platelet increment was associated with rituximab therapy.

Seven of the responders received overlapping treatments because their platelet counts were so low that it was considered unethical to suspend existing conventional treatment. Five received IVIG therapy within the first few weeks of therapy. Four (including two who also received IVIG) continued to receive low dose prednisone until a durable response had been established.

Two of the patients receiving IVIG were considered late responders and had platelet counts $<50 \times 10^9$/l within the first few weeks despite IVIG therapy. One was a delayed responder, who again did not have a significant response to IVIG and a

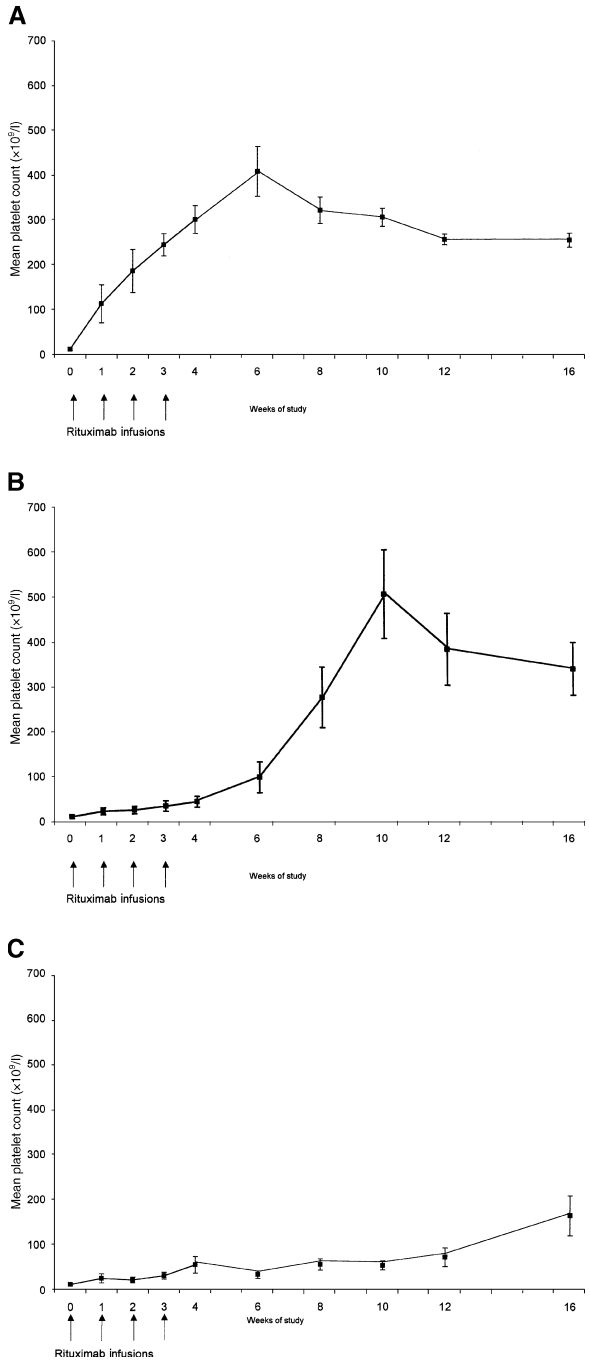

Fig 1. Three distinct patterns of complete responses. The *x*-axis represents the number of weeks from the first rituximab infusion and the *y*-axis shows the mean platelet count ($\times 10^9$/l) with the standard error of the mean. The four, weekly infusions of rituximab are indicated by arrows under the *x*-axis at weeks 0–3. There were three distinct patterns of platelet increase in the complete responders. (A) Seven patients had an immediate response, achieving normal counts by week 4; (B) five patients responded between weeks 7 and 11; and (C) six patients achieved a normal platelet count from weeks 13 to 31. These distinctive time courses of platelet response suggest that there may be more than one mechanism whereby rituximab increases the platelet count in patients with immune thrombocytopenic purpura (ITP).

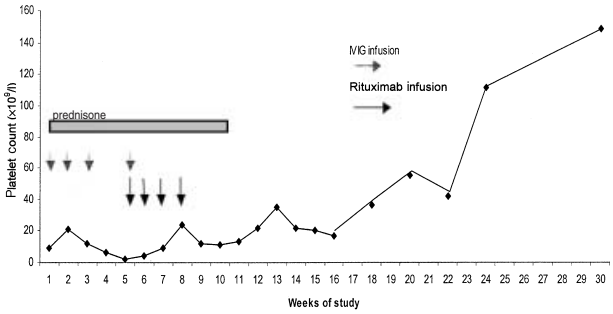

Fig 2. Platelet counts over time of patient U10, including the 4 weeks before starting rituximab. Three intravenous immunoglobulin (IVIG) treatments were given during the prestudy period and one after rituximab was started (shown as grey dotted arrows). The four doses of rituximab are shown as black arrows. Prednisone was continued for 6 weeks of the study and is shown as a grey block. It was tapered and stopped when the platelet count was persistently above 20×10^9/l.

fourth patient was a partial responder who required two doses of IVIG within the first few weeks before achieving a sustained platelet response.

Only one patient who received IVIG had an immediate response to rituximab, which could have confused the timing of response.

The patients receiving low dose prednisone were two delayed responders and two late responders. In all cases, the prednisone dose was tapered as soon as the response was thought to be durable. There was no increase in the dose of prednisone over the course of study in patients who responded to treatment. Figure 2 shows the platelet counts over time for one of the patients receiving IVIG rescue therapy.

Duration of response

The duration of response to treatment was strongly correlated with the magnitude of the response. As of 30 September 2002, 16 of 18 patients who had achieved a CR still had normal platelet counts at a median of 72·5 weeks (range 24–165 weeks) from the initial infusion (Fig 3). Fifteen of the 16 patients who still maintained a CR were more than 1 year from the initial infusion of rituximab with no additional ITP treatment. The two CR patients who relapsed did so at 32 and 52 weeks. In contrast, only two of 13 patients who achieved a PR still had counts $>50 \times 10^9$/l, at 74 and 178 weeks from treatment. The remaining 11 PR patients relapsed at a median of 10 weeks.

Factors associated with response to rituximab

Splenectomy did not influence either the likelihood of a response to rituximab or characteristics of the response, defined as time to achieve response, duration of response, or type of response (all $P > 0{\cdot}2$). Of the 18 CR patients, nine had undergone splenectomy prior to rituximab therapy. Similarly, of the 13 PR patients, six had undergone splenectomy.

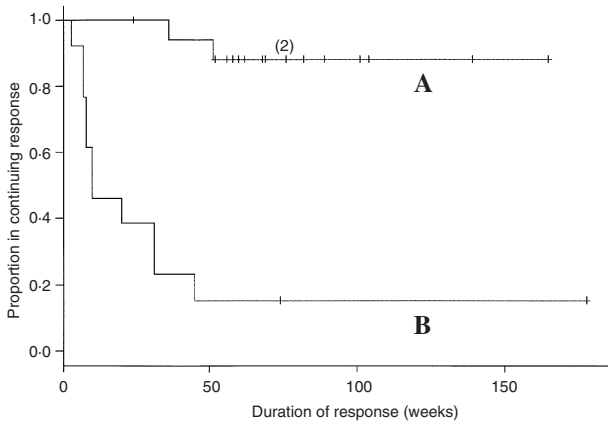

Fig 3. Kaplan–Meier analysis of response duration. The *x*-axis represents the number of weeks from the initial infusion of rituximab. The *y*-axis is the proportion of patients in each category that maintained their response without additional treatment. The representation is a Kaplan–Meier analysis. Each tick mark represents the last follow-up of an ongoing response (one of the marks represents two patients). Each vertical line represents the proportion of patients with that amount of follow-up who relapsed at that particular time point. Sixteen of 18 patients who had a complete response (CR) to treatment (A) had a long lasting, ongoing effect of treatment, whereas almost all of those with partial responses (PRs) relapsed (11 of 13) (B). Fifteen of 16 patients in durable CR reported in this figure have been followed more than 1 year from their initial treatment, as have both of the patients with durable PRs. Nine of the 18 CR patients, including eight with durable responses, had already failed to respond to splenectomy.

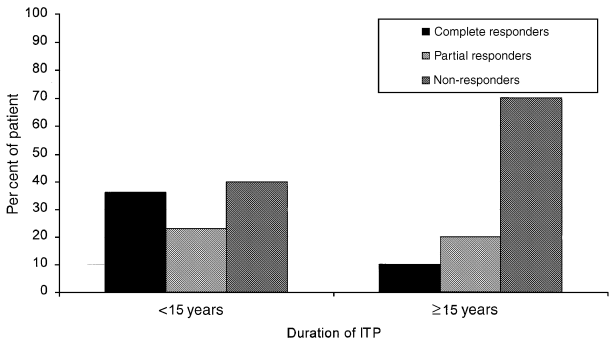

Fig 4. The duration of immune thrombocytopenic purpura (ITP) *versus* response. Figure 4 is divided into two parts: duration of ITP <15 and ≥15 years. The *x*-axis also represents the different categories of response: complete, partial and minimal, and no responses combined. The *y*-axis represents the percentage of patients with each type of response. The duration of ITP prior to rituximab was correlated with the response to treatment ($P < 0{\cdot}05$).

Patients who had a longer duration of ITP (>15 years) were less likely to respond (Fig 4, $P < 0{\cdot}05$). Patients who had not undergone splenectomy had a tendency towards a lesser response if their duration of ITP was more than 2·5 years. The prerituximab platelet count, number of previous treatments, and sex or age of the patient, did not affect response.

Infusion reactions

No patient had a severe adverse event related to rituximab and all 57 patients completed the four infusions. There was one grade 3 event, bronchospasm. Thirty-three of 57 (58%) patients experienced grade 1 or 2 reactions to the first infusion. There were no reactions attributed to rituximab with subsequent infusions. All patients were premedicated with acetaminophen and diphenhydramine or chlorpheniramine. Twenty-seven patients also received prednisone premedication. These patients had fewer side-effects; 11 of 27 patients (41%) who received prednisone had reactions compared with 22 of 30 patients (73%) who did not ($P < 0{\cdot}05$). This primarily reflected fewer fever and chill reactions. Fourteen episodes occurred in those who did not receive prednisone premedication whereas only three were seen in those who did receive prednisone.

Peripheral blood B-cell depletion and recovery

Circulating CD19 positive B cells fell to $<0{\cdot}03 \times 10^9$/l within 4 weeks in all 45 patients measured at this time point. Recovery of circulating B cells began between weeks 12 and 26; by week 52 only one of 33 patients had B cells $<0{\cdot}03 \times 10^9$/l. Non-responders had significantly higher numbers of B cells than responders (CR and PR) at week 26 [$0{\cdot}055 \pm 0{\cdot}0114$ vs. $0{\cdot}0170 \pm 0{\cdot}0221 \times 10^9$/l (mean ± standard error of the mean, SEM), $P < 0{\cdot}01$] (Fig 5). There was no significant difference between PRs and CRs in B-cell recovery.

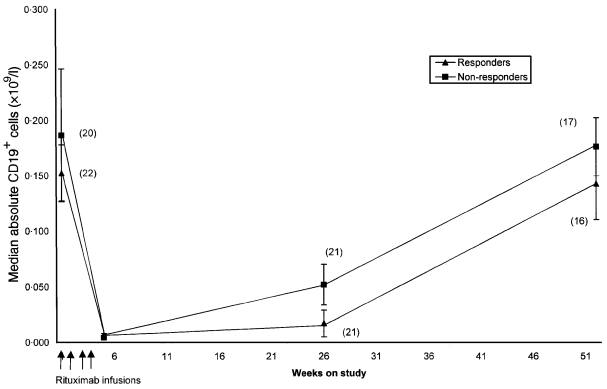

Fig 5. B-cell depletion and return with rituximab. The *x*-axis is the number of weeks from the first rituximab infusion with data indicated at weeks 1 (pre), 5, 26 and 52. The *y*-axis shows the median number of $CD19^+$ B cells ($\times 10^9$/l). This figure shows the median absolute number of $CD19^+$ B cells ($\times 10^9$/l) in partial and complete responders (triangles) *versus* non-responders (squares). The number of patients at each of the time points is indicated within parentheses. B cells were substantially reduced to undetectable levels by week 5 of treatment in essentially all patients. There was a significantly higher absolute number of B cells in non-responders than in complete and partial responders at 26 weeks from the initial infusion. This suggests that the degree of B-cell depletion may be important to the degree of response.

Recovery of B cells did not result in relapse in those patients who achieved a CR. Nine patients in ongoing CR have recovered their B cells to baseline levels for a median of 31 weeks (range 17–114 weeks). Patients who achieved a PR relapsed at a median of 10 weeks. However, B-cell assessment was only performed at weeks 5, 25 and 51. More detailed analysis of the relationship between B-cell recovery and relapse was unfortunately not possible in these patients.

Immunoglobulin levels

There was no significant change in the IgG or IgM levels after rituximab. Patients with normal IgM levels pretreatment maintained normal levels throughout the study; two patients with low initial IgM levels and one with a low initial IgG level did not have any further fall in their IgM and IgG levels. Only one patient had a decrease in their IgG levels from normal (8·2 g/l) to just below normal [week 12 level, 7·64 g/l (normal 8·0–18·0 g/l); week 52, 7·44 g/l].

Neutrophil counts

The absolute neutrophil count (ANC) fell from a median baseline count of $4{\cdot}8 \times 10^9$/l to a week 5 median of $4{\cdot}4 \times 10^9$/l ($P = 0{\cdot}02$). Four patients had ANC below $2{\cdot}0 \times 10^9$/l during the study period, including two below $1{\cdot}0 \times 10^9$/l. Two of the four had neutrophil counts that were consistently $<2{\cdot}0 \times 10^9$/l before the study; one patients' ANC normalized following rituximab therapy. Two patients had isolated decreases in their ANC, to 1·3 and $1{\cdot}7 \times 10^9$/l at weeks 3 and 5, but these recovered to normal levels the following week.

Infections

There were no serious infections or increase in minor infections throughout the study period.

Discussion

This study describes 57 patients treated with rituximab for a non-malignant, autoantibody-mediated disease: chronic ITP. The patients described here had persistent, severe ITP, with patients receiving a median of four previous therapies and 31 patients refractory to splenectomy. As of September 2002, a total of 18 patients (32%) were still maintaining durable and significant platelet responses (platelet counts $>50 \times 10^9$/l), without other ITP medication, a median of 74 weeks from the first infusion; 17 for more than 1 year. Sixteen of the 57 patients (28%) were maintaining a CR. A further 13 patients had less durable CRs or PRs, but avoided other ITP therapy for as long as 52 weeks.

While pilot studies of small numbers of patients have reported lasting effects following treatment such as azathioprine (Quiquandon *et al*, 1990), cyclophosphamide (Reiner *et al*, 1995) and autologous bone marrow transplantation (Huhn *et al*, 2003), these studies were based on limited follow-up and often reported significant side-effects. The long-lasting CR and PR with little associated toxicity, seen following rituximab treatment, especially in those who had failed to respond to splenectomy, are rarely seen in adults with chronic ITP.

The responses seen were considered to be related to rituximab because of the temporal nature of response (94% of responses occurred within 8 weeks of treatment). Although the delay in response in some patients meant that a number required rescue therapy within these 8 weeks, there was no objective difference in timing of response or duration of response in those patients who required rescue therapy.

Patients who had been diagnosed with ITP for more than 15 years were less likely to respond. This group of patients were the most refractory group of patients. There were no other predictors of outcome. Perhaps surprisingly, splenectomy did not influence the response to treatment.

In addition to the durability of response, and its usefulness in both pre- and postsplenectomy patients and in adolescents (Wang *et al*, 2003), rituximab compares favourably to other therapies because of its lack of toxicity. All patients completed treatment and the addition of prednisone as premedication reduced infusion-related reactions. Although there was a significant decrease in the neutrophil count 5 weeks after infusion, this was not clinically significant and no patient developed sustained neutropenia. A more profound post-chemotherapy neutropenia has been noted in patients receiving rituximab with CHOP (cyclophosphamide, hydroxydaunomycin, Oncovin, prednisone) chemotherapy when compared with CHOP alone (Czuczman *et al*, 1999; Coiffier *et al*, 2002) and a delayed and prolonged neutropenia has been described in a number of patients receiving rituximab for B-cell lymphomas when combined with other chemotherapy agents (Chaiwatanatorn *et al*, 2003; Voog *et al*, 2003). There have also been a number of reports of unexpected viral infections including echovirus, papovavirus and cytomegalovirus in patients with malignancy receiving rituximab. All were either in the context of bone marrow transplantation or other immunosuppressive treatment (Goldberg *et al*, 2002; Matteucci *et al*, 2002; Quartier *et al*, 2003; Sirvent-Von Bueltzingsloewen *et al*, 2003). There were no unusual infections, no increase in minor infections and no change in immunoglobulin levels in the population of patients described in this study. The complications related to rituximab therapy appear therefore to occur only with the more marked lymphopenia and hypogammaglobulinaemia seen when used in combination with other immunosuppressive agents.

While the therapeutic benefit is clear and the toxicity appears low, the mechanism of rituximab remains uncertain. For example, it is not clear why there are different magnitudes and different durations of response despite universal B-cell

depletion. Patients who did not respond had higher B-cell levels at 25 weeks than responders, suggesting that non-responding patients may have had less complete 'B-cell depletion'. This may be either in the peripheral blood, beyond the sensitivity of flow cytometry, or in the unmeasurable extravascular B-cell compartment. Alternatively, the timing, extent and/or duration of responses seen may have been influenced by the mechanism of B-cell depletion, i.e. apoptosis or extravascular clearance (Flieger *et al*, 2000; Shan *et al*, 2000).

More complete B-cell clearance may also enable platelet tolerance to be re-established, as platelets are no longer being destroyed and presented by antigen presenting cells. This could explain why patients achieving a CR have a more durable response to treatment, continuing to respond long after the return of B cells. In contrast, patients achieving a PR, in whom presumably the antibody producing cells were not as completely depleted and platelets were still being destroyed, tended to relapse within 6 months (Fig 3).

Finally, do the different patterns of response in patients who achieved a CR (Fig 1) mean that different mechanisms were primary in each subgroup? There is no compelling data supporting any specific mechanism. Possibilities for the different patterns (timing) of response include FcR blockade in the immediate responders, although the long lasting nature of the response makes this unlikely, depletion of autoantibody-secreting B cells in the intermediate group and failure to replace short-lived, autoantibody-secreting plasma cells in the delayed group.

Rituximab provides a clinical effect not seen with other therapies, inducing a durable response in one-third of adults with ITP. It is especially useful in the third of patients who respond despite being refractory to splenectomy, for whom other curative therapy is rarely available, rituximab appears also to be useful in a proportion of patients who have not yet undergone splenectomy. If longer follow-up continues to demonstrate no long-term complications of transient B-cell depletion in autoimmune diseases, the use of rituximab in the treatment of ITP and other autoimmune diseases may be expanded. Furthermore, exploration of the role of B cells and plasma cells, taking advantage of this model of a transient human B-cell 'knockout', may help to clarify their role in the aetiology and persistence of autoimmunity.

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