Original Article

Rituximab for Immune Cytopenia in Adults: Idiopathic Thrombocytopenic Purpura, Autoimmune Hemolytic Anemia, and Evans Syndrome

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• *Objective*: To evaluate the efficacy of rituximab for the treatment of adult patients with immune cytopenia, including idiopathic thrombocytopenic purpura (ITP), autoimmune hemolytic anemia, and Evans syndrome.

• *Patients and Methods*: We retrospectively reviewed the medical charts of all patients treated with rituximab for immune cytopenia at the Mayo Clinic in Rochester, Minn, through January 1, 2003. Fourteen patients (median age at first diagnosis, 51 years; range, 21-79 years) were identified who received 1 or more treatment courses of rituximab for treatment of refractory ITP (12 patients), autoimmune hemolytic anemia (AIHA) (5 patients), or both ITP and AIHA (classified as Evans syndrome) (4 patients). Data regarding age, diagnosis, date of diagnosis, previous treatments, comorbid conditions, blood cell counts before taking rituximab, number of rituximab treatments, and response to treatment were extracted and analyzed.

• *Results*: Of 12 patients treated for ITP, 6 were receiving corticosteroid-based treatment either alone or combined with other immunosuppressive therapy at the time they received rituximab. Complete remission occurred in 5 (42%) of 12 patients with ITP and in 2 (40%) of 5 patients with AIHA. Response to rituximab in patients with Evans syndrome was seen in either ITP or AIHA, but not both. Complete response was often durable in ITP. Responses were seen in both splenectomized and nonsplenectomized patients.

• *Conclusions*: Our findings, considered with the results of other studies, suggest that rituximab deserves early consideration as salvage therapy for immune cytopenias that are refractory to both corticosteroid treatment and splenectomy. This series represents the largest series of adult patients with AIHA and Evans syndrome.

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AIHA = autoimmune hemolytic anemia; CLL = chronic lymphocytic leukemia; CR = complete response; ITP = idiopathic thrombocytopenic purpura; IVIG = intravenous immunoglobulin; NR = no response; PR = partial response

The immune cytopenias, including idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA), affect 14 million individuals in the United States.[1] Idiopathic thrombocytopenic purpura and AIHA are diseases characterized by antibody-mediated destruction of hematologic cells with an incidence of 10 persons per 100,000 and 1 to 3 persons per 100,000, respectively.[2,3] Although ITP responds to treatment with corticosteroids in most adult patients, the majority will relapse during corticosteroid taper. Splenectomy salvages approximately 60% to 70% of these patients.[4] For individuals who do not respond or who relapse after splenectomy, various immunosuppressive treatments (danazol, vincristine, cyclophosphamide, pulse dexamethasone) have been found to be effective in increasing the platelet count; however, most of these increases are temporary. Similarly in AIHA, corticosteroid treatment will induce a remission in most patients; however, relapses are common during corticosteroid taper, and many patients will require a splenectomy and/or other immunosuppressive agents. Approximately 1 of 5 patients with idiopathic AIHA will develop a lymphoproliferative disorder.[5]

Rituximab is a chimeric murine/human anti-CD20 antibody primarily developed to treat clonal B-cell malignancies; it is an effective treatment for patients with indolent and aggressive non-Hodgkin lymphoma and chronic lymphocytic leukemia (CLL).[6-11] Because antibody-producing cells are $CD20^+$ B cells, rituximab has also been studied as treatment of various antibody-mediated autoimmune disorders,[12] including ITP and AIHA.[13-16]

In the largest study of ITP to date, Stasi et al[17] reported on the effectiveness of rituximab in 25 adult patients with chronic, refractory ITP, including 8 who had undergone splenectomy. Of 25 patients, 13 (52%) responded to treatment (5 had complete responses [CRs], 5 had partial responses [PRs], and 3 had minor responses), and 7 of these patients had durable responses beyond 6 months. In a follow-up report,[18] these investigators reported that 6 of 7 additional patients responded to rituximab (4 CRs, 2 PRs). Some patients experienced a delayed response 2 to 5 weeks after their final dose of rituximab, and platelet counts peaked 6 to 12 weeks after their final dose of rituximab.

Studies of rituximab for treatment of AIHA in children have demonstrated considerable efficacy. In the largest

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series, Zecca et al[19] treated 15 children with a combination of rituximab and intravenous immunoglobulin (IVIG) and reported an 87% response rate with a median increase in hemoglobin level of 4 g/dL. Although AIHA in children is often a self-limited process that occurs after viral infection, in adults AIHA tends to be a more chronic illness. In adults, AIHA occurring as a complication of a B-cell lymphoproliferative disorder appears to be responsive to rituximab,[20-27] but little is known about the effectiveness of rituximab for treating adults with *idiopathic* AIHA. In a case series of 7 patients with autoimmune cytopenias—4 with ITP, 2 with warm AIHA (due to warm-reactive antibodies), and 1 with cold AIHA (due to cold-reactive antibodies)—neither patient with warm AIHA responded to rituximab.[28] For patients with Evans syndrome, rituximab appears to be effective in small series of childhood cases,[19] but little is known about its effectiveness for adult patients.[29,30]

In this retrospective review from a single institution, which includes the largest series of adult patients with AIHA and Evans syndrome, we report on the efficacy of rituximab for refractory immune cytopenias in adult patients.

PATIENTS AND METHODS

Approval was obtained from the Mayo Foundation Institutional Review Board to review the medical charts of all patients who received rituximab for ITP or AIHA at the Mayo Clinic in Rochester, Minn, through January 1, 2003. Patients were identified through pharmacy records, which list all patients who receive rituximab and the indications for treatment. Patients who initiated treatment at the Mayo Clinic but received the rest of their treatment elsewhere were included if adequate follow-up was available to determine response. Patients with an underlying diagnosis of active non-Hodgkin lymphoma or CLL were excluded from analysis. Data extracted included age, diagnosis, date of diagnosis, previous treatments for immune cytopenias, comorbid conditions, blood cell counts before taking rituximab, number of rituximab treatments, and response to treatment.

A diagnosis of ITP required thrombocytopenia not clearly caused by medications, inadequate platelet production, platelet consumption due to nonimmune cause (microangiopathic hemolytic anemia), active lymphoproliferative disorder, or splenic sequestration of platelets (hypersplenism). All patients included in this analysis underwent a bone marrow biopsy before rituximab and had findings consistent with ITP (normal or increased megakaryocytes and no overt myelodysplastic syndrome on morphologic or cytogenetic studies).

For ITP, response was determined by assessing the highest platelet count documented at least 2 weeks after a patient completed rituximab treatment. For consistency with the literature, the response criteria used by Stasi et al[17] were used to classify response: CR (platelet counts, $>100 \times 10^9$/L), PR (platelets, $50\text{-}100 \times 10^9$/L), and minimal response (platelets, $30\text{-}50 \times 10^9$/L). Patients with platelet counts of less than 30×10^9/L were considered nonresponders.

The diagnosis of AIHA was based on laboratory evidence of hemolysis (increased reticulocyte count with increased indirect bilirubin, lactate dehydrogenase, or absent haptoglobin levels) and a positive Coombs test. One patient had no available reticulocyte count, and the diagnosis of AIHA was based on a hemoglobin level of 6 g/dL, a low haptoglobin level, smear findings suggestive of immune hemolysis, a strongly positive Coombs test, and a history of autoimmune hemolysis diagnosed elsewhere. All patients included in this analysis who underwent a bone marrow biopsy had findings consistent with AIHA (evidence of increased erythroid production).

For AIHA, response was determined by assessing the highest nontransfused hemoglobin level at least 1 month after completing rituximab treatment. Criteria were similar to those of other investigators[19]: patients whose hemoglobin levels increased at least 1.5 g/dL above their pretreatment hemoglobin level and had a nontransfused hemoglobin level greater than 10 g/dL at least 1 month after treatment were considered complete responders. Patients whose hemoglobin level increased less than 1.5 g/dL above their pretreatment hemoglobin level or had a nontransfused hemoglobin level lower than 10 g/dL were considered nonresponders.

Patients were considered to have Evans syndrome if they had either a simultaneous diagnosis of ITP and AIHA or sequential diagnosis of both diseases. Patients treated for Evans syndrome were evaluated for the response of their ITP and AIHA separately and in combination to determine whether response to treatment for one cytopenia predicted response to treatment for a second cytopenia.

Fourteen patients (6 women and 8 men) were identified who received at least 1 dose of intravenous rituximab (375 mg/m^2 body surface area) for an autoimmune cytopenia; 12 of these patients required treatment for refractory ITP and 5 for AIHA. Four patients had both ITP and AIHA at some point during their follow-up and were classified as having Evans syndrome. Two of these patients received rituximab for ITP at one time point and for AIHA at different time points at least 6 months apart. The third patient was treated for ITP and AIHA simultaneously, whereas the fourth patient was treated with rituximab for AIHA but not for ITP. The median age at first diagnosis of immune cytopenia was 51 years (range, 21-79 years).

RESULTS

Idiopathic Thrombocytopenic Purpura

For the 12 evaluable patients treated for ITP, age at diagnosis ranged from 22 to 79 years; 4 were women. All

12 patients underwent bone marrow biopsy before treatment with rituximab. Comorbid diseases, baseline characteristics, and previous treatments are presented in Table 1. Before initiating rituximab treatment, 10 (83%) of 12 patients had undergone splenectomy. The lowest documented platelet counts before treatment were 1×10^9/L to 38×10^9/L, with 11 (92%) of 12 patients having platelet counts less than 10×10^9/L at some time before treatment; 3 (25%) of 12 patients had a comorbid autoimmune disease other than AIHA diagnosed before treatment (1 with hypothyroidism, 1 with vasculitis, and 1 with hypothyroidism and antiphospholipid-antibody syndrome). Interestingly, 4 (33%) of 12 patients with ITP had a diagnosis of deep venous thrombosis/pulmonary embolism, one of whom had antiphospholipid-antibody syndrome. Six patients also received other immunosuppressive therapy when rituximab treatment was initiated (prednisone, 1; cyclophosphamide and prednisone, 1; vincristine and prednisone, 1; danazol, 1; cyclosporine, IVIG, and methylprednisolone, 1; and danazol and prednisone, 1 [Table 1]). The mean number of rituximab doses for the 12 patients with ITP was 3.2 (range, 1-4).

Complete response occurred in 5 (42%) of 12 patients with ITP, including 3 patients who were simultaneously receiving other drugs for ITP during rituximab therapy (cyclophosphamide and prednisone, 1; prednisone, 1; and danazol, 1). Of the 5 responders, 3 were still in CR with no additional treatment at the time of last follow-up at the Mayo Clinic (7 months, 10 months, and 11 months after rituximab); a fourth patient who received maintenance danazol therapy initiated simultaneously with rituximab was in CR 1 month after rituximab therapy ended. The fifth patient, who was taking prednisone when rituximab was initiated, relapsed when the prednisone dosage was tapered below 10 mg/d. Patient 11, who received simultaneous rituximab, methylprednisolone, cyclosporine, and IVIG, achieved a stable platelet count between 50×10^9/L and 90×10^9/L while taking maintenance methylprednisolone and cyclosporine for 3 weeks after rituximab and was technically classified as PR. Of the remaining 6 patients, 5 had no response (NR) and 1 died of central nervous system hemorrhage less than 1 week after rituximab. Two more patients died within 3 weeks of initiation of rituximab (1 due to hemorrhagic complications and 1 due to unknown causes). One patient with NR to rituximab had CR after splenectomy, and a second patient with NR had CR with prednisone maintenance after undergoing autologous bone marrow transplantation.

Autoimmune Hemolytic Anemia

For the 5 evaluable patients with AIHA, ages ranged from 21 to 79 years, and 2 were women. Of these 5 patients, 3 underwent bone marrow biopsy before treatment with rituximab. Comorbid diseases, baseline characteristics, and previous treatments are presented in Table 2. Splenectomies were performed in 3 (60%) of the 5 patients before they received rituximab treatment. The lowest documented hemoglobin level before treatment ranged from 5.1 to 8.3 g/dL. Before treatment, 2 of the 5 patients were diagnosed as having a comorbid autoimmune disease (1 had Sjögren syndrome, primary sclerosing cholangitis, and hypothyroidism, and the other had sclerosing cholangitis and relapsing polychondritis). The mean number of rituximab doses for the 5 patients with AIHA was 4.8 (range, 3-8).

Complete response occurred in 2 (40%) of 5 patients. All patients who had at least a 1.5 g/dL increase in hemoglobin level with rituximab maintained a hemoglobin level greater than 10 g/dL at least 1 month after rituximab therapy ended. Both patients were still in CR at last follow-up (at 4 and 13 months after rituximab). Neither required additional treatment for AIHA. However, 1 of the 2 patients underwent bone marrow transplantation for refractory ITP. Of the remaining 3 patients who did not respond to rituximab, 1 achieved CR to cyclophosphamide and antithymocyte globulin (equine).

Evans Syndrome

Three patients received a diagnosis of both ITP and AIHA at some point during their course and were clinically diagnosed as having Evans syndrome. A fourth patient diagnosed with AIHA was believed to have Evans syndrome on chart review. This patient had moderate thrombocytopenia with a platelet count between 50×10^9/L and 100×10^9/L and a positive cell-bound antiplatelet antibody at the same time as AIHA but was never clinically diagnosed as having ITP. The diagnoses of ITP and AIHA were simultaneous in 1 patient, and in the other 2 patients, AIHA was diagnosed 3.66 and 6 years before ITP. No patient had CR of both ITP and AIHA with rituximab. One patient who had NR with rituximab for AIHA had CR with rituximab used for ITP 3 years later. A second patient who received rituximab for ITP and AIHA simultaneously had CR of AIHA but NR to ITP. Responses of treatment with rituximab for patients with Evans syndrome are presented in Table 3.

DISCUSSION

Refractory ITP and AIHA in adults are chronic diseases without effective treatment for many patients. Most, if not all, affected patients undergo splenectomy, and treatment with corticosteroids and other immunosuppressive drugs after splenectomy typically fails. Often, such patients go through a series of treatment trials with various drugs that include danazol, vincristine, vinblastine, cyclophosphamide, azathioprine, high-dose IVIG, and pulse dexamethasone.[4,31]

Table 1. **Characteristics of Patients With Idiopathic Thrombocytopenic Purpura*†**

Patient No./ age‡ (y)/ sex	Comorbid disease/condition	Other Tx before rituximab	Lowest pre-Tx platelet count ($\times 10^9$/L)	Tx cycles (No.)	Re-sponse	Tx concurrent with or after rituximab	Last platelet count ($\times 10^9$/L)	Status at last follow-up
1/70/F	Vasculitis, DVT/PE, chronic renal failure, hypertension, corticosteroid-induced myopathy, sensory neuropathy, chronic anemia	Prednisone, methyl-prednisolone, cyclo-phosphamide, IVIG, plasma exchange	38	4	CR	None	275	Alive in CR 11 mo after rituximab
2/46/M	DVT/PE, zoster, cholelithiasis	Prednisone, IVIG, splenectomy	9	4	CR	None	260	Alive in CR 7 mo after rituximab
3/71/M	CAD, history of cardiac arrest, coronary artery bypass, hypertension, history of polio, nephro-lithiasis, hyperlipidemia	Prednisone, methyl-prednisolone, IVIG	4	2	NR	Splenectomy	186	Alive in CR 31 mo after splenectomy
4/71/M	Hypothyroidism, DVT/PE, hypertension	Prednisone, methyl-prednisolone, IVIG, vincristine, cyclo-phosphamide, dana-zol, protein A col-umn, *Helicobacter pylori* eradication	3	1	NR	Danazol and prednisone simultaneously with rituximab§	4	Died of central nervous system hemorrhage 5 d after first Tx with rituximab
5/51/M	Diabetes, pulmonary hyper-tension, hypertension	Prednisone, IVIG, anti-D gammaglobulin, danazol, vincristine	4	4	NR	Colchicine cyclo-phosphamide, IVIG	33	Unknown
6/54/F	Hypertension, chronic renal failure, diabetes, history of thyroid cancer, hypothy-roidism, glomerulonephri-tis, alveolar hemorrhage, vitamin D deficiency	Prednisone, methyl-prednisolone, IVIG, vincristine, plasma exchange	5	2	CR	Oral cyclophos-phamide and prednisone simultaneously with rituximab, tapered over next several mo§	424	Alive in CR 10 mo after rituximab
7/79/M	Prostate cancer, chronic renal failure, aortic stenosis, AAA, COPD, CAD, GI bleeding, anemia	Prednisone, IVIG	2	2	N/A	Vincristine and prednisone simultaneously with rituximab§	3	Died 6 d after second Tx of rituximab
8/31/M	Hypogammaglobulinemia, chronic renal insufficiency, GI bleeding	Prednisone, IVIG	3	3	NR	None	4	Died 1 wk after third Tx of rituximab due to complications of pulmonary hemorrhage
9/39/M	Acute renal failure, sinusitis, endocarditis	Prednisone, IVIG, vincristine, plasma exchange, methyl-prednisolone	2	4	NR	Vincristine, IVIG, danazol, predni-sone, stem cell transplantation	236	In CR with prednisone after stem cell transplantation
10/43/F	Turner syndrome	Prednisone, IVIG, methylprednisolone	1	4	CR	Prednisone simul-taneously with rituximab. After relapse: IVIG, dexamethasone§	416	Platelets responded with rituximab and prednisone but re-lapsed when predni-sone reduced from 10 mg to 5 mg/d 2 wk after fourth Tx of rituximab
11/22/F	Antiphospholipid-antibody syndrome, hypothyroidism, mesenteric vein thrombosis	Prednisone, IVIG, plasma exchange	3	4	PR	IVIG, methylpred-nisolone, and cyclosporine simultaneously with rituximab§	80	PR on continued cyclosporine and methylprednisolone 1 mo after rituximab
12/49/M	History of non-Hodgkin lymphoma (not active), nephrolithiasis, arrhythmia	Prednisone, vincristine, danazol, dexametha-sone, IVIG	<10	4	CR	Danazol and rituximab started simultaneously§	582	In CR taking main-tenance danazol 1 mo after rituximab

*AAA = abdominal aortic aneurysm; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CR = complete response; DVT/PE = deep venous thrombosis/pulmonary embolism; GI = gastrointestinal; IVIG = intravenous immunoglobulin; N/A = not applicable; NR = no response; PR = partial response; Tx = treatment.

†All 12 patients underwent bone marrow biopsy before rituximab treatment. All patients had splenectomies before rituximab except for patients 1 and 3.

‡At diagnosis.

§Treatments given simultaneously with rituximab.

Table 2. **Characteristics of Patients With Autoimmune Hemolytic Anemia*†**

Patient No./ age‡ (y)/ sex	Comorbid disease/condition	Other Tx before rituximab	Lowest HGB pre-Tx (g/dL)	Tx cycles (No.)	Re-sponse	Tx after rituximab	Last HGB value (g/dL)	Status at last follow-up
2/42/M	DVT/PE, zoster, cholelithiasis	Prednisone, methyl-prednisolone, IVIG, splenectomy, cyclo-phosphamide/vin-cristine/prednisone, methyltrexate, dana-zol, cyclosporine	5.1	8	NR	IVIG, cyclophos-phamide, antithymocyte globulin	14.6	Responded to cyclo-phosphamide and antithymocyte globulin
8/25/M	Hypogammaglobulinemia, chronic renal insufficien-cy, gastrointestinal bleeding	Prednisone, IVIG	5.8	3	NR	None	8.8§	Died 1 wk after third Tx of rituximab due to pulmonary hemorrhagic complication
9/39/M	Acute renal failure, sinusitis, endocarditis	Prednisone, methyl-prednisolone, IVIG, vincristine, plasma exchange	6.6	4	CR	Treated for ITP with vincristine, prednisone, stem cell transplan-tation	11.6	Stable on prednisone after stem cell transplantation for ITP 13 mo after rituximab
13/79/F	Hepatocellular cancer, hypothyroidism, Sjögren syndrome, sclerosing cholangitis, pulmonary hypertension, iron deficiency anemia	Prednisone, IVIG	6.6	5	NR	None	8.9	Died in hospice care of hepatocellular carcinoma 2 mo after last rituximab dose
14/21/F	Inflammatory bowel dis-ease, diabetes, sclerosing cholangitis, relapsing polychondritis	Prednisone, azathioprine, cyclophosphamide	8.3	4	CR	None	11.5	Alive in CR 4 mo after rituximab

*CR = complete response; DVT/PE = deep venous thrombosis/pulmonary embolism; HGB = hemoglobin; ITP = idiopathic thrombocytopenic purpura; IVIG = intravenous immunoglobulin; NR = no response; Tx = treatment.
†All 5 patients had warm + autoantibody on Coombs testing. Patients 2, 8, and 9 had splenectomies and bone marrow biopsies before rituximab.
‡At diagnosis.
§After transfusion.

Rituximab is one of several recently described treatment modalities for refractory immune cytopenias that include cyclosporine,[32,33] mycophenolate mofetil,[34] alemtuzumab,[35] and both autologous and allogeneic hematopoietic stem cell transplantation.[36-38] By comparison, rituximab has the advantage of being directed specifically against antibody-producing B cells and displaying the better toxicity profile.

The current report represents one of the larger single-institution experiences using rituximab to treat ITP, AIHA, and Evans syndrome. The median age and extent of comorbid disease in our series are higher than in many previous reports, and we expressly excluded patients with known lymphoproliferative disorders. The study has several limitations, primarily due to its retrospective nature. No definitive conclusions can be made because of substantial patient heterogeneity regarding comorbid conditions, the number of treatment cycles with rituximab, duration of treatment, and the presence or absence of simultaneous treatment with other immunosuppressive drugs. Nevertheless, the findings confirm the efficacy of rituximab for refractory ITP and suggest benefit for some patients with AIHA and Evans syndrome.

With regard to ITP, our CR rate of 42% compares favorably with the experience of other investigators. In a prospective study of 12 adult patients with ITP in whom splenectomy and various immunosuppressive agents failed, the CR rate was 41%.[16] In an earlier study of 25 adult patients with chronic ITP, only 8 of whom had previously undergone splenectomy, the CR rate using the same response criteria was only 20% (PR = 20%).[17] In all 3 studies, CR was often durable, and there is evidence of extremely long unmaintained responses.[39] Rituximab also can induce PR and, although not observed in the current study, minimal responses, neither of which is as durable as rituximab-induced CR.[17] Interestingly, some patients who relapsed have responded to re-treatment with rituximab.[17] To date, pretreatment clinical or laboratory parameters that predict response have not been identified. The high incidence of venous thromboembolism in our patients with ITP is consistent with the findings of other investigators who report that antiphospholipid syndrome can develop in up to 45% of patients with ITP.[40]

To our knowledge, our series is the largest report on the use of rituximab for adult patients with AIHA and Evans

Table 3. **Characteristics of Patients With Evans Syndrome***

Patient No.	First diagnosis	Time to diagnosis of second cytopenia	Response of AIHA to rituximab	Response of ITP to rituximab	Comments
2	AIHA	3.66 y	NR	CR	AIHA responded to cyclophosphamide/ antithymocyte globulin
8	AIHA	6 y	NR	NR	Treated with rituximab for ITP/AIHA simultaneously
9	AIHA	Simultaneous	CR	NR	ITP responded to stem cell transplantation
13	AIHA	Simultaneous	NR	Not treated	Moderate thrombocytopenia with platelet count typically 50-100 $\times$ 10^9/L; never required separate treatment

*AIHA = autoimmune hemolytic anemia; CR = complete response; ITP = idiopathic thrombocytopenic purpura; NR = no response.

syndrome. In contrast to the greater than 80% response rate observed with rituximab in children with AIHA,[14,19] only 2 (40%) of 5 adult patients with AIHA in our series responded. The controlled trials using rituximab in children with AIHA combined rituximab with other immunosuppressive therapies (corticosteroids or IVIG), and the role of such combinations in adult patients needs to be explored. One nonresponder in our series responded to cyclophosphamide and antithymocyte globulin (equine).

The 2 published case reports of rituximab for the treatment of adult patients with Evans syndrome may not be widely generalizable because they describe 1 patient with an underlying lymphoproliferative disorder (CLL) who underwent treatment with fludarabine[29] and a second patient with drug-induced (interleukin 2) Evans syndrome.[30] Both patients experienced CR with rituximab for both their ITP and AIHA.

In our series of 4 adult patients with idiopathic Evans syndrome, no patient experienced CR for cytopenias of both cell lines. Response of AIHA to rituximab did not predict the response of ITP, and 1 patient who initially did not respond to rituximab for AIHA responded to rituximab for ITP more than 3 years later. The pathophysiological mechanisms behind the thrombocytopenia and hemolytic anemia in Evans syndrome are believed to be antibody-mediated processes; why one may respond to rituximab while the other does not is unclear. Stasi et al[18] have postulated 2 mechanisms by which rituximab may improve thrombocytopenia in patients with ITP: (1) early responses are mediated by opsonized B cells that block Fc receptors in the reticuloendothelial system and (2) late responses are mediated by decreased production of antiplatelet antibodies. The relative effect of these 2 mechanisms may be distinct with regard to ITP and AIHA, which may be one possible explanation for the differences we observed.

Of note, the retrospective nature of our review limited our ability to assess the frequency and severity of adverse reactions to rituximab. In other series, adverse reactions to rituximab have been limited primarily to infusion-related sequelae such as fevers, chills, tachycardia, and hypotension, which are believed to be due to an allergic response to the murine component of the antibody. In the largest prospective series of rituximab used for treating ITP, 17 of 25 patients experienced a National Cancer Institute grade 1 adverse effect during therapy with fever, chills, and nausea being the most common adverse effects.[17] Only a single patient experienced a National Cancer Institute grade 2 adverse effect in that series (chills). Bronchospasm, cardiac arrhythmia, increased risk for infection, and cytopenias are less common but have been reported in some series, and the late adverse effects of rituximab remain to be defined.

CONCLUSIONS

Our results confirm the efficacy of rituximab for a broad range of immune cytopenias. Prospective controlled trials are needed to answer key questions regarding response predictors, optimal dose and schedule, the role of combination therapy, and the role of rituximab as frontline therapy for autoimmune cytopenias. Our findings, along with those of other studies, suggest that rituximab deserves early consideration as salvage therapy for immune cytopenias that are refractory to both corticosteroid treatment and splenectomy. However, in many instances, salvage therapy may be unnecessary as long as the platelet count remains greater than 20 $\times$ 10^9/L and antiplatelet drugs, such as aspirin, are avoided.

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