

Rituximab for primary chronic cold agglutinin disease: a prospective study of 37 courses of therapy in 27 patients

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Conventional therapies for primary chronic cold agglutinin disease (CAD) are ineffective, but remissions after treatment with the anti-CD20 antibody rituximab have been described in a small, prospective trial and in some case reports. In this study we report on 37 courses of rituximab administered prospectively to 27 patients. Fourteen of 27 patients responded to their first course of rituximab, and 6 of 10 responded to re-treatment. In both groups combined, responses were achieved after 20 of 37

courses, giving an overall response rate of 54%. We observed 1 complete and 19 partial responses. Two nonresponders and 3 patients who experienced relapse received second-line therapy with interferon- α combined with a new course of rituximab, and 1 nonresponder and 2 patients who experienced relapse achieved partial responses. Responders achieved a median increase in hemoglobin levels of 40 g/L (4 g/dL). Median time to response was 1.5 months, and median observed response duration was 11

months. We conclude that rituximab is an effective and well-tolerated therapy for CAD. Histologic and flow cytometric findings suggest that some of the effect may be mediated by mechanisms other than the elimination of clonal lymphocytes. We were unable to predict responses from the hematologic, immunologic, or histologic parameters before therapy. (Blood. 2004;103:2925-2928)

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Introduction

Chronic cold agglutinin disease (CAD) is an uncommon autoimmune hemolytic anemia (AIHA) mediated by cold-reactive autoantibodies that bind to erythrocyte carbohydrate antigens, causing hemagglutination and complement-mediated hemolysis. CAD not associated with lymphoma or other diseases has traditionally been classified as primary or idiopathic. However, it has been shown that this condition represents a lymphoproliferative disorder of the bone marrow characterized by clonal proliferation of CD20⁺ κ ⁺ B cells that produce monoclonal immunoglobulin M (IgM) κ cold agglutinin.¹⁻³ Often, the histologic features are those of lymphoplasmacytic lymphoma.^{1,4} Trisomy of the q arm of chromosome 3 has been shown in some cases.⁵

The traditional classification of this disease as primary can, therefore, be questioned. In typical secondary CAD, however, the lymphoproliferative disorder is usually easily recognized as an aggressive lymphoma, and the monoclonal immunoglobulin tends to be of the IgM λ rather than the IgM κ type.^{6,7} In this work, we continued to apply the term primary CAD in patients not showing the typical criteria of the secondary type.

Many conventional treatment modalities used in other AIHA or indolent lymphomas, such as corticosteroids, alkylating agents, splenectomy, interferon- α (IFN- α) monotherapy, and purine analogs, have failed to demonstrate a convincing effect in primary CAD.^{1,8-11} Favorable responses to the chimeric human-murine, monoclonal anti-CD20 antibody rituximab have been described in a small, prospective study⁴ and some case reports.¹²⁻¹⁷

Complement-dependent cytotoxicity (CDC) is probably one of the mechanisms of action of rituximab and has been proposed by some authors as the most important mechanism.^{18,19} Low C3 and very low C4 complement levels observed in most CAD patients may theoretically restrict the efficacy of rituximab therapy.^{3,20,21} However, C4 levels may be increased by the administration of IFN,²² and this cytokine may also up-regulate CD20 expression.^{23,24} Furthermore, a synergistic antineoplastic effect of rituximab and IFN has been demonstrated in some lymphomas.²⁵

The purpose of this study was to further investigate the therapeutic efficacy of rituximab in CAD and to evaluate the effect of adding IFN- α in patients not responding to rituximab as a single agent. Most reports on therapy for CAD do not state any well-defined response criteria,²⁶ and results may be confounded by seasonal variations²⁷ or acute-phase reactions.^{20,21} We used previously published response definitions based on improvements in hemolytic anemia, serum paraprotein levels, and bone marrow disorder.^{4,11}

Patients and methods

Study design

Between October 1, 2001, and May 1, 2003, CAD patients from 10 Norwegian university and local hospitals were prospectively included in a phase 2 trial. The Regional Medical Research Ethics Committee of Southern Norway and the Norwegian Medicines Agency approved the

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Table 1. Baseline laboratory data

	Hemoglobin level, g/L	IgM level, g/L	Cold agglutinin titer, 4°C	κ/λ ratio of bone marrow aspirate
Mean	85	11.1	—	15.9
Median	82	5.0	6000	8.4
Range	62-123	0.6-51.7	64-256 000	4.7-77.0

— indicates not applicable.

protocol. We included in this report 6 patients who had been treated with rituximab in our previous prospective trial, findings of which have been published,⁴ using the same inclusion and exclusion criteria, infusion schedules, and response definitions.

Before inclusion, all patients underwent clinical examination, chest radiography, and abdominal ultrasonography. Hematologic, immunologic, and biochemical blood and serum parameters were recorded. Flow cytometric immunophenotyping of blood and bone marrow was performed as described previously.^{1,3} Bone marrow biopsy specimens were examined by an experienced lymphoma pathologist (R.L.) and were classified according to the World Health Organization (WHO) classification.²⁸

Inclusion and exclusion criteria

To be eligible for the study, each patient was required to have CAD, as defined by the combination of chronic hemolysis and a cold agglutinin titer of 64 or higher, and a typical pattern for the direct antiglobulin test (DAT). The typical pattern for DAT in CAD is a positive finding when performed with polyspecific antiserum, a negative or only weakly positive finding with anti-IgG, and a strongly positive finding with anti-C3d.^{1,27} Serum and bone marrow examinations had to confirm the presence of a clonal lymphoproliferation of the CD20⁺ κ ⁺ phenotype, as defined by the combination of monoclonal IgM κ band in serum with a clonal expansion of CD20⁺ κ ⁺ cells in the bone marrow, demonstrated by immune histochemistry, flow cytometric immunophenotyping, or both.^{1,29} Additional requirements were clinical symptoms requiring treatment (eg, anemia or Raynaud-like symptoms) and informed consent.

Patients with secondary CAD were ineligible. Patients were also excluded if they had blood lymphocyte counts higher than $50 \times 10^9/L$, nonlymphatic malignant disease, contraindications to rituximab therapy, severe disease other than CAD, or inability to cooperate.

Therapy

Eligible patients received rituximab as described previously^{30,31} at a dose of 375 mg/m² as an intravenous infusion on days 1, 8, 15, and 22. Patients who did not respond within 3 months or who had relapses during the study period were offered second-line therapy with the combination of rituximab and IFN if there were no contraindications to IFN. The combination consisted of a new, identical, 4-week cycle of rituximab with the addition of IFN administered subcutaneously at a dose of 5 million units 3 times a week for 20 weeks. IFN injections started 2 weeks before the first rituximab infusion.

Patients were assessed monthly for 6 months, and blood samples were collected at each visit. Cold-induced circulatory symptoms were assessed using a 0-2 scale (0 indicates no improvement; 2, complete resolution of clinical symptoms). Adverse effects related to rituximab or IFN were recorded. Bone marrow histology and flow cytometry were assessed after 3 and 6 months.

Response criteria

The criteria for complete response (CR) were absence of anemia, no signs of hemolysis, disappearance of clinical symptoms of CAD, undetectable monoclonal serum protein, and no signs of clonal lymphoproliferation as assessed by bone marrow histology, immunohistochemistry, and flow cytometry. Partial response (PR) was defined as a stable increase in hemoglobin (Hgb) level of at least 20 g/L (2 g/dL) or to the normal range, combined with a reduction of serum IgM concentrations by at least 50% of

the initial level or to the normal range, improvement of clinical symptoms, and transfusion independence. Patients were classified as nonresponders (NRs) if they did not achieve CR or PR.

Time to response was defined as the time from the first rituximab infusion to the achievement of any degree of response. Relapse was defined by Hgb level below 100g/L (10 g/dL) or a decrease in Hgb by at least 20 g/L (2 g/dL) from the highest level achieved after therapy, the need for re-treatment, or both.

Statistics

Mean values were calculated for numeric variables showing normal distribution. For the remaining numeric variables median values were used, with mean values stated in brackets, where appropriate, for comparison with other publications. For significance testing of differences between frequencies in cross tables, χ^2 analysis with Yates correction was used, and for continuous variables, differences between groups were determined using the Mann-Whitney *U* test.

Results

Baseline characteristics

Thirty-seven courses of rituximab were administered to 27 patients, 9 men and 18 women, with a mean age of 71 years (range, 51-91 years). Before their first courses of anti-CD20 therapy, 12 patients had been previously untreated, 10 had received 1 other treatment modality, and 5 had received 2 or more other treatment modalities (corticosteroids, alkylating agents, purine analogues, splenectomy). Additional baseline data are provided in Tables 1 and 2.

Response to rituximab first-line therapy and re-treatment

Fourteen of 27 patients responded to the first course of single-agent rituximab (1 CR and 13 PR), and 13 were nonresponders. Two nonresponders received re-treatment with the combination of rituximab and IFN, resulting in 1 PR and 1 NR. Eleven nonresponders did not receive second-line therapy during the study period.

Eight patients experienced relapses and were treated with rituximab plus IFN (*n* = 3) or rituximab monotherapy (*n* = 5), resulting in 5 PR and 3 NR. In those receiving IFN who experienced relapses, 2 achieved PR and 1 was a NR. IFN was omitted because of patient refusal in 1 case and investigator decision in 4 cases. Two patients were re-treated with rituximab monotherapy for a second relapse, and each achieved a new PR. Among all re-treated patients, responses were observed after 6 of 10 courses.

Overall response data

Overall response data are shown in Table 3. Altogether, responses were achieved after 20 of 37 courses of rituximab therapy. We observed 1 CR and 19 PR. Median time to response was 1.5 months (mean, 1.7 months; range, 0.5-4.0 months).

Table 2. Bone marrow histology at baseline

WHO classification	Frequency
Lymphoplasmacytic lymphoma	15
Marginal zone lymphoma	2
Small B-cell lymphoma	2
Unclassified clonal lymphoproliferation	6
Reactive lymphocytic infiltration/no clonal lymphoproliferative disorder	2
Total	27

Table 3. Overall response data

Response	Frequencies		Increase in Hgb level, g/L		IgM level reduction, g/L		IgM level reduction, %	
	n	%	Median	Range	Median	Range	Median	Range
CR	1	3	47	—	3.4	—	83	—
PR	19	51	39	7-71	5.1	0-26.3	54	0-79
NR	17	46	13	-14-+43	1.2	0-16.1	32	0-55
Total	37	100	—	—	—	—	—	—

— indicates not applicable.

Hemoglobin (Hgb) levels increased by a median of 40 g/L (4 g/dL) (mean, 41 g/L [4.1 g/dL]; range, 7-71 g/L [0.7-7.1 g/dL]) among the responders. In addition, 4 patients classified as nonresponders achieved increases in Hgb level from 20 to 43 g/L (2.0-4.3 g/dL). Peripheral circulatory symptoms improved by definition in all PRs and CRs and in 6 of 17 NRs. One partial responder had an increased Hgb level of only 7 g/L (0.7 g/dL). However, the initial Hgb level was within the normal range, and the clinical indication for therapy was circulatory symptoms. Another patient classified as PR showed no decrease in IgM. This patient had a baseline IgM concentration within the normal range but with a monoclonal band. Thus both patients met the criteria for PR.

Response duration was calculated in 17 responders observed until relapse or for more than 12 months after they achieved response. The median observed response duration was 11 months (mean, 13 months; range, 2-42 months). All responders observed for more than 12 months had relapses except 1, who is still in PR after 28 months. The only patient who achieved a CR retained the remission for 42 months.

Clinical-hematologic response compared with other parameters

There was complete or partial histologic regression of the bone marrow findings in 12 cases after rituximab therapy and no or uncertain histologic responses in 11. In the remaining 14 cases, such assessment was not relevant, not made, or unsuccessful. Table 4 shows the frequencies of histologic regression in relation to clinical-hematologic response.

Flow cytometric assessment of bone marrow aspirates for elimination of CD20⁺ cells was performed successfully after 26 courses of rituximab. Reduced percentages of CD20⁺ cells were achieved in all patients (responders and nonresponders). This decrease was modest (approximately 50% from baseline) in 2 patients and near complete (reduction to 0%-4% of the lymphocytes) in the remaining 24 patients. After 5 courses of rituximab, a CD19/CD20 discrepancy was found 3 months after therapy. After the remaining 21 courses, the reduction of CD20⁺ lymphocytes was paralleled by a reduction of CD19⁺ lymphocytes.

The following baseline parameters were compared between responders and nonresponders: age (mean, 72 and 71 years,

respectively), Hgb concentration in blood (mean, 83 and 88 g/L [8.3 and 8.8 g/dL]), serum levels of IgM (median, 5.2 and 4.4 g/L), complement protein C3 (median, 0.78 and 0.72 g/L), C4 (median, less than 0.06 g/L in each group), CD20⁺ cell percentage in bone marrow aspirates (median, 24% and 25%), and κ/λ ratio (median, 9.3 and 7.8). None of these differences were significant (Mann-Whitney *U* test).

Tolerance

No serious infusion-related adverse effects occurred with rituximab, but 1 patient reported muscular pain during the first infusion. Hematologic toxicity related to rituximab was observed in 1 patient (transient neutropenia WHO grade 4, fever grade 2, and infection grade 1). During IFN therapy we recorded flulike symptoms in 4 patients and hematologic toxicity grade 1 in 2 patients and grade 2 in 1 patient. We observed no exacerbation of hemolysis after IFN administration. In 3 of 5 patients, the IFN dose was reduced or its administration discontinued before week 20.

Two nonresponders, 76 and 89 years old, who were treated with single-agent rituximab died of unrelated diseases after 12 and 4 months, respectively. The other patients are alive at 3 to 43 months after therapy.

Discussion

In this work we extended our experience with rituximab therapy for primary CAD to 37 courses in 27 patients. Six patients previously reported by us⁴ were included in this study in an appropriate way because the inclusion and exclusion criteria and response definitions were identical in the 2 trials.

Results confirmed our previous findings that rituximab is effective in primary CAD.⁴ Response rates were 52% following rituximab single-agent therapy in 27 patients who had not previously received rituximab and 60% after 10 courses of re-treatment with or without the addition of IFN. In both groups combined, 20 responses were achieved after 37 courses, giving an overall response rate of 54%. Hemoglobin data may indicate a benefit even in some patients classified as nonresponders.

Response rates are similar to those reported in follicular lymphoma and other indolent CD20⁺ B-cell lymphomas.^{25,30-32} The observed response duration (median, 11 months; mean, 13 months) is similar to that observed after rituximab therapy for follicular lymphoma.³¹

Re-treatment at relapse was feasible, and the response rate after re-treatment was in the same order of magnitude as the overall response rate. Furthermore, 2 PRs were achieved after rituximab therapy for second relapse.

Except for our previous study of 6 patients,⁴ all original publications on rituximab therapy in CAD are case reports or retrospective observations of a few patients.^{12-16,26} According to review articles,^{17,26} 23 cases have been published, and responses

Table 4. Clinical-hematologic response and histologic response

Regression of histologic bone marrow findings	Clinical-hematologic response frequencies		Total
	CR or PR	NR	
Partial or complete	8	4	12
None or uncertain	4	7	11
Not determined, unsuccessful, or not relevant	8	6	14
Total	20	17	37

Differences were not statistically significant (χ^2 analysis with Yates correction).

have been observed in 21; both nonresponders were reported in the only prospective study.⁴ A high proportion of the responses described in case reports have been classified by the authors as complete, but there is no indication of well-defined response criteria.²⁶ Our data are not in accordance with the combined results from the case reports. This discrepancy can easily be explained because response rates estimated from case reports are likely to have been influenced by publication bias, lack of strict disease definitions, and heterogeneous response criteria.

Rituximab therapy was well tolerated, apparently better than in patients treated for other B-cell lymphomas.^{31,32} This finding is not unexpected because tumor burden is low in patients with primary CAD.¹

It was our intention to evaluate whether combining rituximab with IFN could improve efficacy, but patient and physician acceptability resulted in only 5 patients receiving the combination therapy. This small number makes us unable to put forward any firm statements. It may be interesting, however, that 1 patient who had no response to single-agent rituximab therapy achieved PR after second-line therapy with rituximab plus IFN. No conclusion can be drawn from the 2 PRs after relapse in 3 patients treated with rituximab plus IFN because the response rate after rituximab single-agent therapy for relapse was 63%.

In our series, a clinical response was usually accompanied by a histologic response. However, we observed some patients achieving PR without significant histologic regression of the bone marrow disorder and other patients achieving significant improve-

ment of bone marrow histology without any clinical improvement. Furthermore, we observed a near complete elimination of CD20⁺ cells from bone marrow aspirates after most courses of rituximab therapy in responders and nonresponders. In most cases this effect was not caused by receptor blocking because such blocking should result in CD19/CD20 discrepancy. The histologic and flow cytometric findings, therefore, suggest that some mechanism other than elimination of clonal CD20⁺ cells may be partly responsible for the therapeutic effect of rituximab in CAD. Responses could not be predicted from the baseline levels of Hgb, IgM, C3, or C4 or from the κ/λ ratio or the percentage of CD20⁺ cells in the bone marrow.

In conclusion, this prospective study documents the favorable effect of rituximab in primary CAD. Further studies should be undertaken for insight into the characteristics of the nonresponders so that therapies can be proposed for this subgroup. The potential for increasing the response duration should also be investigated.

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