Primary chronic cold agglutinin disease: a population based clinical study of 86 patients

Background and Objectives. Our knowledge of primary chronic cold agglutinin disease (CAD) is incomplete. The aim of this study was to collect comprehensive and precise data on epidemiological, clinical and pathological features, course, and therapy of CAD.

Design and Methods. We performed a population-based retrospective follow-up study of as many as possible of all CAD patients in Norway. Eighty-six patients were studied.

Results. The prevalence of primary CAD was 16 cases per million inhabitants. The incidence rate was 1 per million per year. The median age at onset was 67 years (range, 30-92) and the male to female ratio was 0.55. The median survival was 12.5 years from onset. Autoimmune diseases other than CAD were reported in 8% of patients, cold-induced circulatory symptoms in 91%, and exacerbation of hemolytic anemia during febrile illness in 74%. At least 51% had received red blood cell transfusions. The mean initial hemoglobin level was 9.2 g/dL (range, 4.5-15.6) and the median monoclonal immunoglobulin level 4.0 g/L (range, 0.0-47.3). Most laboratory findings did not change significantly during a median follow-up of 5 years. Monoclonal IgM was detected in 90%; IgG and IgA in 3.5% each; with κ light chains in 94%. An abnormal κ/λ ratio in bone marrow was found in 90%, lymphoma in 76%, and lymphoplasmacytic lymphoma in 50%. Transformation to aggressive lymphoma occurred in 3.5% during 10 years. Rituximab therapy was the only treatment showing acceptable response rates (60%).

Interpretations and Conclusions. Primary CAD represents a spectrum of clonal lymphoproliferative bone marrow disorders, in most cases with morphological signs of lymphoma. Despite a favorable prognosis for survival, the disease is not indolent in terms of clinical manifestations.

Key words: anemia, hemolytic, cold agglutinin, cold agglutinin disease, lymphoproliferative diseases

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addition to the well-known worsening caused by low ambient temperatures, exacerbations may be precipitated by febrile illnesses. Low levels of complement proteins C3 and C4 limit the hemolysis during or steady-state, whereas hemolysis increases when complement becomes available during acute phase reactions. Primary CAD has been considered a stable or very slowly progressive disease with a fairly good prognosis. Single agent therapies with corticosteroids, alkylating agents, immunosuppressive drugs, interferon-α or cladribine have failed to demonstrate any significant clinical effect. Case observations and theoretical considerations do not support the use of splenectomy as a therapeutic measure. More recently, therapy with the chimeric monoclonal anti-CD20 antibody rituximab has been shown to induce remission in more than 50% of CAD patients.

Given the limitations in our knowledge of the clinical details and course of primary CAD, we undertook a retrospective follow-up study, intended to be population-based. The aim was to collect comprehensive and precise information on the epidemiology, clinical presentation, course, frequency of bone marrow findings, response to treatment, prognosis, and possible differences between subgroups of patients with CAD.

**Design and Methods**

**Study design**

Between January and June 2005 we performed a retrospective multicenter study of as many as possible of all CAD patients in Norway. For each patient we collected and analyzed clinical and hematologic baseline and follow-up data from the first relevant examination in a hospital until the time of the study or the patient’s death. CAD patients were identified by asking all hematologists and other physicians responsible for hematologic services to notify cases. This was done initially by contacting all members of the Norwegian Society of Hematology and then by repeated inquiries to relevant hospital physicians not responding to previous requests. Data were collected from the patients’ records, in most cases by the investigators and in some cases by local hematologists, using a standardized form. The patients’ data were registered anonymously, but a code was allocated in order to prevent double registration. The Regional Medical Research Ethics Committee of Southern Norway approved the study.

**Patients**

To be eligible for the study, patients were required to have CAD, as defined by the combination of chronic hemolysis, cold agglutinin titer at 4°C of 64 or higher, and a typical pattern for the direct antiglobulin test (DAT). Typical DAT findings were a positive test when performed with polyclonal antiserum and a strongly positive test with anti-complement protein C3d (anti-C3d). One patient with otherwise very typical clinical disease and hematological and immunologic findings was included in spite of having a cold agglutinin titer below 64. CAD patients who were known to local hematologists but had died before the time of the study were included if sufficient data could be provided. Patients with classical secondary CAD (e.g. overt lymphoma diagnosed at or before their first examination for CAD) were excluded.

**Clinical and laboratory data**

Clinical data were recorded, including any chronic or serious disease other than CAD, first year of clinical CAD symptoms or hemolytic anemia, year of death when relevant, the occurrence of cold-induced circulatory symptoms, transfusion dependency, and any history of exacerbation during febrile illness. We collected data on blood hemoglobin (Hb) level, serum concentrations of lactate dehydrogenase (LDH), bilirubin and monoclonal immunoglobulins, and serum cold agglutinin titer measured at 4°C. Whenever possible we registered two initial and two end-point measurements for laboratory data. In case of discrepancy we used the mean baseline and mean end-point value, respectively. We also recorded the findings from serum agarose electrophoresis with immunofixation for the detection and classification of monoclonal proteins; results of DAT using polyspecific antiserum, anti-IgG and anti-C3d; κ/λ-ratio as assessed by flow-cytometric analysis in bone marrow aspirates if done; and data from bone marrow biopsy if performed. All patients’ records were examined for evidence of transformation of an indolent lymphoproliferative disorder into aggressive non-Hodgkin’s lymphoma. Because of the retrospective design it was not possible to implement standardized sampling techniques, centralized laboratory analyses, or parallel titration of cold agglutinins in serum samples collected at different times. Nearly half of the patients had previously participated in prospective therapeutic trials or descriptive studies. For these patients we had data on immunological analyses from blood samples kept at 37°C from drawing to separation of serum, as well as centralized serology, flow cytometry and histology assessments.

In June 2003, clinical chemistry laboratories in Norway changed their method of LDH measurement; levels measured after that time corresponded to approximately one half of previously measured values. For comparison, therefore we calculated corrected LDH levels by dividing concentrations measured before June 2003 by two.

**Treatment**

Essential treatment data were registered, i.e. whether or not the patient had received therapy (transfusions and other purely supportive measures not included), and year and type of each therapy modality. Responses were evaluated according to previously published standard criteria whenever possible. Complete response was defined as absence of anemia, no signs of hemolysis, no clinical symptoms of CAD, undetectable serum monoclonal protein, and no signs of clonal lymphoproliferation by bone marrow histology, immunohistochemistry and flow cytometry. Partial response was defined as a stable increase in Hb levels by at least 2.0 g/dL or to the normal range, combined with a reduction...
of serum IgM concentrations by at least 50% or to the normal range, improvement of clinical symptoms, and transfusion independency. Patients were classified as non-responders if they failed to achieve a complete or partial response.

Statistics
Mean values were calculated for normally distributed data and median values for data that were not normally distributed. Differences between groups of continuous data were tested with Student’s t-test if the values were approximately normally distributed and with the Mann-Whitney U test in the case of very small groups or markedly skewed distribution. Paired t-test and Wilcoxon paired test were used for significance testing of paired data with normal or skewed distribution, respectively. Correlations between continuous variables were tested by calculating Pearson’s r correlation coefficient, while Spearman’s test was used if one variable was ordinal. In order to test associations between nominal variables we used cross tables and the χ² test. Statistical calculations were performed on a personal computer using SPSS version 12.0.1 software (SPSS Inc., Chicago, IL, USA). Population data were obtained from Statistics Norway. 1,2,3

Results
Epidemiology and clinical data
Eighty-six patients were registered, of whom 30 were men and 56 women, giving a male/female ratio of 0.54. Eighteen patients had died before 1 Jan 2005 and 68 were alive. The median age at the onset of clinical symptoms or hemolytic anemia was 67 years (range 30-92) in the whole group, whereas the median age at the time of the study was 76 years (51-96) among those still alive. Taking regional differences in population density into account, patients were approximately evenly distributed throughout Norway (4,606,560 inhabitants on 1 Jan 2005) except for the northernmost counties (Nordland, Troms and Finnmark; 462,640 inhabitants altogether), where only two patients were registered. Patients as well as the total population in these three counties were excluded from calculations of prevalence and incidence. In the remaining counties, 67 CAD patients were alive in a population of 4,143,720 inhabitants (462,640 inhabitants altogether), where only two patients were registered. Patients as well as the total population in these three counties were excluded from calculations of prevalence and incidence. In the remaining counties, 67 CAD patients were alive in a population of 4,143,720 inhabitants, giving a prevalence of 16.2 cases per million. From 1995 through 2004 there were 42 new patients altogether. Assuming that registration was nearly complete for deceased patients, the median survival was 12.5 years (range, 0-45). For the deceased patients, the median survival was 12.5 years (range, 1-21) from the onset of clinical CAD and 9 years (range, 1-21) from the initial examination, and they died at a median age of 82 years (range, 68-96). Clinical features are listed in Table 1. Cold-induced circulatory symptoms were reported in 63 patients (91% of those with data available on such symptoms) during all or part of the disease duration, and exacerbation of hemolytic anemia during febrile illness occurred in 50 (74% of those with available data). At least 44 patients (51%) had received red blood cell transfusions, but only six (7%) were transfusion-dependent both at presentation and last follow-up evaluation. Twenty patients (25%) were transfusion-dependent at presentation, but not at the last follow-up, while another 18 (21%) were transfusion-independent initially, but transfusion-dependent at the last follow-up.

Basic laboratory findings
Table 2 shows baseline findings and changes over time in concentrations of Hb, bilirubin, LDH, monoclonal immunoglobulins and cold agglutinins. The mean Hb level at presentation was 9.2 g/dL (median 8.9; ter- ties, 8.0 and 10.4). The mean initial serum bilirubin level was 41.0 µmol/L and the corrected LDH level 487 U/L. The median serum concentration of monoclonal immunoglobulin at presentation was 4.0 g/L and median cold agglutinin titer 2048. Apart from an increase in median monoclonal immunoglobulin level from 4.0 to 5.6 g/L, we found no significant overall changes in these parameters during follow-up. However, there were large individual differences with regard to changes, as indicated in Table 2. Patients treated with rituximab had a mean increase in Hb concentration of 1.5 g/dL from initial measurement to last follow-up (p=0.002, paired t-test). Hb levels were not significantly correlated to monoclonal immunoglobulin concentrations or cold agglutinin titers at presentation or last follow-up. Cold agglu-

<table>
<thead>
<tr>
<th>Table 1. Clinical features of patients with CAD.</th>
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<tr>
<td>Cold-induced circulatory symptoms</td>
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<tr>
<td>Both at baseline and last follow-up examination</td>
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<tr>
<td>At baseline or last follow-up, but not both</td>
</tr>
<tr>
<td>Not reported at any time</td>
</tr>
<tr>
<td>Patients with available data</td>
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</table>

*Percentages of patients with available data.*
Immunoglobulin classes

Results of serum electrophoresis with immunofixation were available for 84 patients and a monoclonal band had been detected in 79 (94%), while five (6%) had no verified monoclonal serum protein. The monoclonal immunoglobulin was of the IgM class in 71 patients (90% of 79 patients with available information), IgG in three (3.5%), IgA in three (3.5%), while two patients (2.5%) had biclonal IgM and IgG. The light chain restriction was κ in 74 patients (94%), λ in two (2.5%), and unknown in three (3.5%). All findings of λ monoclonal light chains occurred with the IgG and IgA classes. Comparing patients who had monoclonal IgM in serum with those who had only IgG or IgA showed median initial Hb levels of 8.8 g/dL and 10.3 g/dL, respectively, but the difference was not statistically significant (p=0.3; Mann-Whitney U test). The median initial cold agglutinin titer in the IgM group was 4096 as compared to 96 in the IgG/IgA group (p=0.007; Mann-Whitney U test). Data on specific D A T were available for 81 patients. Sixty-four (79%) had no detectable IgG on their erythrocytes, while cell-bound IgG had been detected in the remaining 17 (21%). All five patients with monoclonal IgG or biclonal IgM and IgG in serum displayed erythrocyte-bound IgG. DAT performed with polyspecific antiserum and anti-C3d was positive in all cases by definition.

Histology and flow cytometry data

Flow cytometric analysis of bone marrow aspirates had been performed successfully in 40 patients. The median κ/λ ratio was 7.8 (range 0.9-186), and a κ/λ ratio > 3.5 was found in 36 patients (90%). Information on bone marrow histology was available for 66 patients (Table 3), and morphological and immunohistochemical signs of non-Hodgkin’s B-cell lymphoma were found in 50 (76%). Thirty-three patients had lymphoplasmacytic lymphoma (50% of patients with available histology data and 66% of those with a demonstrable clonal lymphoproliferative bone marrow disorder). There were few differences in descriptive data between patients with morphological bone marrow lymphoma (n=50) and those with normal or benign histology (n=16). The mean initial and final Hb levels and change in Hb over time did not differ significantly between the groups (Student’s t-test). There was no statistically significant difference with regard to monoclonal immunoglobulin concentration, cold agglutinin titer, or change in these variables during follow-up (Mann-Whitney U test). The median κ/λ ratio as assessed by flow cytometry was 8.2 in patients with morphological bone marrow lymphoma, as compared to 4.8 in those without (p=0.05; Mann-Whitney U test). Three patients (3.5%) initially diagnosed with an indolent lymphoproliferative bone marrow disorder developed diffuse large B-cell lymphoma (DLBCL). Transformation occurred in lymph nodes in two patients and at multiple extranodal sites in one. The initial presentation in one male was chronic lymphocytic leukemia with monoclonal IgGλ cold agglutinin. Transformation occurred at the age of 54 after 6 years’ disease, and lymph node histology revealed a pleomorphic variant of DLBCL. After immuno-chemotherapy (rituximab plus CHOP) he achieved complete remission of DLBCL and partial remission of CAD. He is alive one year after transforma-

Cold agglutinin disease: a population-based clinical study

Table 2. Laboratory data.

<table>
<thead>
<tr>
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<th>Initial level</th>
<th>Level at last follow-up</th>
<th>Change after a median follow-up of 5 years</th>
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<tr>
<td></td>
<td>Difference</td>
<td>Factor</td>
<td>Significance</td>
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<tr>
<td>Hemoglobin (g/dL), mean (SD; range)</td>
<td>9.2 (±2.3; 4.5 - 15.6)</td>
<td>9.8 (±2.5; 3.6 - 14.9)</td>
<td>+0.6 (±3.0; -7.7 - +5.8)</td>
</tr>
<tr>
<td>Bilirubin (μmol/L), mean (SD; range)</td>
<td>41.0 (±231; 11 - 162)</td>
<td>42.9 (±342; 6 - 228)</td>
<td>+1.9 (±36; -124 - +187)</td>
</tr>
<tr>
<td>Lactate dehydrogenase, corrected (U/L), mean (SD; range)</td>
<td>437 (±172; 194 - 998)</td>
<td>448 (±222; 195 - 1508)</td>
<td>+11 (±237; -556 - +817)</td>
</tr>
<tr>
<td>Monoclonal immunoglobulin (g/L), median (range)</td>
<td>4.0 (0.0 - 47.3)</td>
<td>5.6 (0.0 - 88.3)</td>
<td>+1.6 (29 - +86)</td>
</tr>
<tr>
<td>Cold agglutinin titer, median (range)</td>
<td>2048 (&lt;32 - 819200)</td>
<td>2048 (&lt;32 - 409600)</td>
<td>n.a.</td>
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Table 3. Bone marrow histology.

<table>
<thead>
<tr>
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<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>Normal/reactive lymphocytosis</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Irregular lymphoid hyperplasia</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Non-Hodgkin’s B-cell lymphoma</td>
<td>50</td>
<td>76</td>
</tr>
<tr>
<td>Lymphoplasmacytic lymphoma</td>
<td>33</td>
<td>50</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Small lymphocytic B-cell lymphoma/ Chronic lymphocytic leukemia</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Clonal lymphocytosis/ other small B-cell lymphoma</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>100</td>
</tr>
</tbody>
</table>

n.a., not applicable; *paired t-test (Hb, bilirubin and LDH); Wilcoxon’s paired test (immunoglobulin levels and cold agglutinin titers); n.s., not significant.
tion with stable CAD and no signs of DLBCL. In two males aged 68 and 85, initially diagnosed with lymphoplasmacytic bone marrow lymphoma producing monoclonal IgMκ, transformation occurred after clinical disease lasting 14 and 21 years, respectively. Both died within 6 months of transformation.

Therapy

Twenty-three patients (27%) had not received any treatment apart from supportive measures such as counseling and transfusions, while each of the remaining 63 (75%) had received one to eight courses of one to five different therapies. Treatment modalities and response data are listed in Table 4. Four of the five corticosteroid-responsive patients had been diagnosed with bone marrow lymphoma, whereas biopsy had not been performed in the fifth. Bone marrow lymphoma had been detected in all three patients who responded to alkylating agents. Thirty-one patients responded to rituximab as a single agent or in combination therapy (60% of those who had received rituximab%). There was no significant difference in response rate between those with bone marrow lymphoma and those with normal, benign or unknown histology (χ² test). These subgroups were, however, small. Comparing responders with non-responders, there was no statistically significant difference with regard to initial Hb concentration, serum monoclonal immunoglobulin level, cold agglutinin titer, or bone marrow k/λ ratio as assessed by flow cytometry (Mann-Whitney U test).

Discussion

To our knowledge, this is the first population-based and the largest clinical study of CAD ever published. The results provide new epidemiologic data and allow quantitative estimations of clinical, hematologic and pathologic features of this disease. The prevalence of primary CAD in Norway is 16 per million, i.e. higher than previously reported, and the incidence rate is approximately 1 per million per year. These figures are probably underestimated due to the design of the study. On the other hand, given the cold climate in Norway during the winter, it is to be expected that most CAD patients will be symptomatic and come to diagnosis. The male/female ratio of about 0.5-0.6 confirms the female preponderance reported in smaller surveys. Most autoimmune disorders are more common in women than in men. However, the male/female ratio in the general Norwegian population aged 67 and above is 0.72. The old age of most CAD patients is sufficient, therefore, to account for most of the female preponderance. Furthermore, the frequency of autoimmune disease other than CAD does not differ from what is to be expected in an elderly population with some female predominance. Thus, CAD differs from most polyclonal autoimmune diseases by its lack of association with other autoimmune disorders. This confirms our previous report on low frequencies of autoantibodies other than cold agglutinins in CAD. A plausible explanation is that CAD, unlike most autoimmune diseases, is characterized by autonomous production of a monoclonal antibody in a patient with an otherwise competent regulation of the immune system.

The median survival from the onset of CAD (12.5 years) and the median age at death (82 years) imply a good prognosis with respect to survival. One-third of the patients, however, had initial Hb levels ranging from 4.5 through 8.0 g/dL, and more than 50% were transfusion-dependent at some time during the course of the disease. We found cold-related circulatory symptoms in 91%, often with severe Raynaud’s phenomena even at exposure to slight cold, and exacerbation resulting in profound anemia during febrile illness in 74%. These high figures clearly document that CAD is not an indolent disease in terms of major clinical symptoms and quality of life.

There was no overall change over time in Hb, bilirubin and LDH levels, or in cold agglutinin titers. However, care should be taken when interpreting LDH levels and cold agglutinin titers. Our results confirm previous assumptions that CAD does not follow a progressive clinical course, although hemolysis and Hb levels may fluctuate considerably with exposure to cold and during acute phase reactions. The increase in monoclonal immunoglobulin levels over time still indicates some progression of the underlying pathologic process in most patients. As for variations in individual patients, Hb levels decreased by 7.7 g/dL in some patients and increased by 5.8 g/dL in others (Table 2). A high number of transfusion-independent patients later became transfusion-dependent, and vice versa. Thus, the clinical course of CAD is highly variable. Our findings of monoclonal IgMκ in 90% of the patients and the rare occurrence of a monoclonal serum immunoglobulin other than IgMκ confirm previously published data. As for erythrocyte surface-bound immunoglobulin, it is well-known that CAD patients have a positive DAT when this test is performed with polyclonal antisera or anti-C3d, and in most cases, the test is negative with anti-IgG. However, we detected IgG on erythrocytes in 17 patients (21%), and all five patients with clonal IgG in serum were in this group. In this retrospective
study it was not possible to determine the type of cell-bound IgG by performing elution of warm-type IgG from erythrocytes. We do not know, therefore, whether erythrocyte-bound IgG was clonal in the remaining 2 patients. Biclunality was documented by routine diagnostic work-up in only two patients. A possible explanation for the DAT findings is that biclonal immunoglobulin in low concentrations might occur more frequently than previously assumed. We found a tendency towards lower Hb levels in patients with monoclonal IgM in serum than in those with only IgG or IgA, although this was not statistically significant. Cold agglutinin titers were significantly higher in the IgM group than in the IgG/IgA group. These observations probably reflect the higher efficiency of IgM in agglutinating erythrocytes and initiating complement-mediated hemolysis.4,36 Assessment of cold hemolysis activity might also be of interest,36 but due to the retrospective design we were unable to obtain data on this from a sufficient number of patients’ sera.

This study provides comprehensive data on the occurrence of lymphoproliferative bone marrow disease in CAD patients. On flow cytometry, most healthy subjects have a k/\lamda ratio of 0.9-3.5,34 whereas this ratio was higher than 3.5 in 90% of our patients. The high frequency of B-cell lymphoma in bone marrow biopsies (overall non-Hodgkin’s lymphoma, 76%; lymphoplasmacytic lymphoma, 50%) show that CAD is a clonal lymphoproliferative bone marrow disorder in most, if not all cases. This conclusion is in accordance with the very frequent occurrence of monoclonal immunoglobulins reported in this work and previous studies.4,36 The lack of a monoclonal band on serum electrophoresis in 6% of patients may reflect problems of test sensitivity. Therefore, immunofixation should be done in the diagnostic work-up of CAD patients even when no monoclonal band is visible on agarose electrophoresis, and all protein analyses should be performed in specimens kept at 37°C from sampling to separation of serum. In conclusion, CAD represents a spectrum of clonal lymphoproliferative bone marrow disorders with most patients having indolent B-cell lymphoma and the others having monoclonal gammopathy of undetermined significance. According to recent criteria, Waldenström’s macroglobulinemia is defined as lymphoplasmacytic lymphoma of the bone marrow combined with monoclonal IgM at any serum concentration.37 Thus, 50% of our patients with available histology data met the diagnostic criteria for both CAD and Waldenström’s macroglobulinemia.

Based on the high frequency of bone marrow lymphoma and diagnostic overlap with Waldenström’s macroglobulinemia, one may argue that most cases of primary CAD should be re-classified as secondary or that the distinction between primary and secondary CAD should be abandoned. However, CAD patients diagnosed by us as having a low-grade lymphoproliferative bone marrow disorder undoubtedly represent the same majority that used to be classified as having primary CAD.4,34,35 Furthermore, most of the rather rare patients traditionally classified as having secondary CAD suffer from a readily demonstrable lymphoma, often of an aggressive type, that can be associated with IgM as well as IgMk cold agglutinins.36,37 We, therefore, will continue to apply the term primary CAD in patients not showing the classical features of the secondary form.

Transformation to an aggressive lymphoma in primary CAD has previously been reported in a single case.46 In a recent survey of 83 patients with monoclonal IgM-related clinical disorders other than Waldenström’s macroglobulinemia and without CAD, only one patient developed an aggressive non-Hodgkin’s lymphoma.46 The risk of transformation found in our study (3-4%; median duration of CAD was 10 years) is also low. Obviously, this risk has no major impact on the overall survival of CAD patients.

According to published information, counseling on cold avoidance should be the mainstay of treatment in primary CAD.19,24,42 In 73% of the patients described here, however, physicians and/or patients had not perceived such measures as sufficient. Our data confirm that corticosteroids and alkylating agents are usually ineffective as therapeutic measures. We were not able to identify subgroups in which these modalities should be tried in clinical practice. Furthermore, some of the few patients who improved during corticosteroid therapy only did so at high doses that were unacceptable for long-term use. The observation of high response rates to rituximab therapy is not new.48-50 Nevertheless, it is of interest that 60% of patients treated with rituximab alone or in combinations achieved partial or complete responses, adding support to previous findings from prospective, but not randomized trials. Response duration could not be assessed from the data presented here; however, in patients treated prospectively with rituximab the observed median response duration was 11 months.50 We could not identify predictors for the effect of rituximab therapy. Still, the relatively high proportion of non-responders highlights the need for further studies in order to improve therapy in this challenging condition.
References


