How I treat autoimmune hemolytic anemias in adults

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Autoimmune hemolytic anemia (AIHA) is a rare disease. In a recent population-based study, the incidence was 0.8/100,000/year, but the prevalence is 17/100,000.1 Primary (idiopathic) AIHA is less frequent than secondary AIHA. Secondary cases are often challenging because not only AIHA but also the underlying disease(s) must be diagnosed and treated. AIHA is essentially diagnosed in the laboratory, and considerable improvement has been made in this field. However, progress in treatment has been much slower.2,3 Therapy has been reviewed by several investigators,3,4,5 but no treatment guidelines have yet been published.

Introduction

Autoimmune hemolytic anemia (AIHA) is a rare disease. In a recent population-based study,1 the incidence was 0.8/100,000/year, but the prevalence is 17/100,000.2 Primary (idiopathic) AIHA is less frequent than secondary AIHA. Secondary cases are often challenging because not only AIHA but also the underlying disease(s) must be diagnosed and treated. AIHA is essentially diagnosed in the laboratory, and considerable improvement has been made in this field. However, progress in treatment has been much slower.3,4 Therapy has been reviewed by several investigators,3,4,5 but no treatment guidelines have yet been published.

Autoimmune hemolytic anemia is a heterogeneous disease with respect to the type of the antibody involved and the absence or presence of an underlying condition. Treatment decisions should be based on careful diagnostic evaluation. Primary warm antibody autoimmune hemolytic anemias respond well to steroids, but most patients remain steroid-dependent, and many require second-line treatment. Currently, splenectomy can be regarded as the most effective and best-evaluated second-line therapy, but there are still only limited data on long-term efficacy and adverse effects. The monoclonal anti-CD20 antibody rituximab is another second-line therapy with documented short-term efficacy, but there is limited information on long-term efficacy and side effects. The efficacy of immunosuppressants is poorly evaluated. Primary cold antibody autoimmune hemolytic anemias respond well to rituximab but are resistant to steroids and splenectomy. The most common causes of secondary autoimmune hemolytic anemias are malignancies, immune diseases, or drugs. They may be treated in a way similar to primary autoimmune hemolytic anemias, by immunosuppressants or by treatment of the underlying disease.

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10 different definitions of CR and PR in various studies. In this review, we have used the definitions of CR and PR as defined by the individual authors. There are only a few long-term follow-up studies. With a few exceptions, no Kaplan-Meier analyses were performed (this method was published after the publication of most larger treatment series of AIHA). Therefore, all statements on treatment recommendations in the literature, including this review, have to be regarded with caution. In practice, most treatment decisions must be made individually. In our department, treatment decisions are always made on an individual basis after discussion of experienced hematologists and then with the patient.

AIHA frequently has an acute onset, but in most cases it must be considered as a chronic disease with few exceptions. In primary WAIHA, there is only a low chance of spontaneous or drug-induced long-term remission or cure. Thus, the primary goal of treatment is to keep the patient comfortably with few effects. The patient with acute, newly diagnosed, or recurrent AIHA

The onset of AIHA is frequently acute and sometimes life-threatening, with weakness and shortness of breath. Hospitalization is often required. The first decision to be made is whether the patient immediately needs transfusions. This is an individual decision and depends on the speed of development and severity of anemia, the type and cause of hemolytic anemia (the highest acute death rates were observed in patients with fludarabine-associated AIHA and IgM WAIHA), and the age and clinical condition of the patient. Because in WAIHA the antibody is directed against blood group antigens, no truly matched blood transfusions are possible, but red cells can be safely given if alloantibodies are excluded. In our university hospital, the following rules are established: In women without history of pregnancy and/or previous transfusions and in nontransfused men, the risk of alloantibody is considered as almost absent, allowing for transfusion of only ABO- and RhD-matched red cells in urgent cases. In other patients an extended phenotyping with respect to Rh subgroups (C, c, E, e), Kell, Kidd, and S/s with the use of monoclonal IgM antibodies is performed, and compatible red cell concentrates are selected for transfusion. Warm autoadsorption or allogeneic adsorption procedures for detection of alloantibodies are used only in exceptional cases. In any case, a biologic in vivo compatibility test is done at the

**Table 1. Prevalence and type of antibodies in secondary AIHA in adults**

<table>
<thead>
<tr>
<th>Underlying disease or condition</th>
<th>Prevalence of AIHA, %*</th>
<th>WAIHA</th>
<th>CAIHA</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>2.3-4.3</td>
<td>87%</td>
<td>7%</td>
<td>16,17</td>
</tr>
<tr>
<td>NHL (except CLL)</td>
<td>2.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM gammopathy</td>
<td>1.1</td>
<td>No</td>
<td>All</td>
<td>19</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>0.19-1.7</td>
<td>Almost all</td>
<td>Less common</td>
<td>20</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>Very rare</td>
<td>2/3</td>
<td>1/3</td>
<td>21</td>
</tr>
<tr>
<td>Ovarian dermoid cyst</td>
<td>Very rare</td>
<td>All</td>
<td>No</td>
<td>22</td>
</tr>
<tr>
<td>SLE</td>
<td>6.1</td>
<td>Almost all</td>
<td>Rare</td>
<td>23</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>1.7</td>
<td>All</td>
<td>No</td>
<td>24</td>
</tr>
<tr>
<td>CVID</td>
<td>5.5</td>
<td>All</td>
<td>No</td>
<td>25</td>
</tr>
<tr>
<td>ALPD</td>
<td>50</td>
<td>All</td>
<td>No</td>
<td>26</td>
</tr>
<tr>
<td>After autologous SCT</td>
<td>4.4</td>
<td>Yes</td>
<td>Yes</td>
<td>27</td>
</tr>
<tr>
<td>After organ transplantation</td>
<td>5.6 (pancreas)</td>
<td>Yes</td>
<td>No</td>
<td>28</td>
</tr>
<tr>
<td>Drug-induced in CLL</td>
<td>2.9-10.5</td>
<td>Almost all</td>
<td>Rare</td>
<td>29</td>
</tr>
<tr>
<td>Interferon α</td>
<td>Incidence: 11.5/100 000 patient-years</td>
<td>All</td>
<td>0</td>
<td>30</td>
</tr>
</tbody>
</table>

NHL indicates non-Hodgkin lymphoma; SLE, systemic lupus erythematosus; CVID, common variable immune deficiency; ALPD, autoimmune lymphoproliferative disease; and SCT, stem cell transplantation.

*Data from recent and/or larger studies.
Patients who are refractory to initial steroid therapy are easily convinced of the need for a second-line therapy, because they usually have severe side effects of steroid therapy. Patients of the second category are often subjectively satisfied with corticosteroid therapy and often want to proceed with this treatment. However, they are usually not aware of the risks of long-term corticosteroid treatment. They probably hope for a late remission that may occur but is not very likely (in contrast to autoimmune thrombocytopenia).

If the decision for a second-line treatment has been made, there are several options. For each option the benefit/risk ratio should be individually assessed.

Splenectomy and rituximab are the only second-line treatments with a proven short-term efficacy. We recommend splenectomy to all patients without contraindications as the best second-line therapy for the following reasons. (1) The short-term efficacy is high. After splenectomy short-term CR or PR can be expected in two-thirds of patients with a range of 38% to 82%, depending on the percentage of secondary cases. (2) Although no high-quality data on long-term success are available (a Kaplan-Meier analysis of disease- and drug-free survival after splenectomy has never been done in AIHA), there is good evidence that a substantial number of patients will remain in remission without need of medical intervention for years. Chertkow and Dacie were the first to describe the effects of splenectomy in WAIHA in a series of 28 patients. Half of the patients had a CR or PR. Only 2 patients were in remission for more than 5 years, but 6 patients remained in a stable PR for up to 7 years. The best data on follow-up were provided by Coon. In 52 patients who had undergone splenectomy (percentage of primary AIHA unknown) they found that 63% of patients had a hematocrit level greater than 30% without steroids after a mean follow-up of 33 months, and 21% had a hematocrit level greater than 30% with a PDN requirement of 15 mg/d or less after a mean follow-up of 73 months. In the study of Allgood and Chaplin, 44% of patients were in CR after more than 1 year after splenectomy. It is also the experience of many hematologists that patients with recurrence after splenectomy require lower doses of steroids to maintain acceptable hemoglobin levels. (3) The perioperative risk of splenectomy is low. Splenectomy can safely be performed laparoscopically in almost all cases of primary AIHA, because the spleen is usually of normal size. The mortality of laparoscopic splenectomy (all indications) was 0.5% in a large national study. All patients should receive postoperative thromboprophylaxis with low-molecular-weight heparin, probably even beyond hospital discharge. The withdrawal of steroids after splenectomy should be done slowly (as described for primary treatment) to prevent hemolytic crises in case of recurrence. (4) The only relevant long-term risk is a lifelong persisting higher rate of infections (the most feared is overwhelming pneumococcal sepsisemia). The infection risk is probably overstated for patients with adult AIHA, because the highest risk is in children and patients with hematologic malignancies. In AIHA the risk must be balanced against the risk of other second-line treatments. In a recent large population-based study an increased risk of infections in patients who had undergone splenectomy (vaccination rate approximately 60%) has been confirmed. Although data were not provided for AIHA but rather for idiopathic autoimmune thrombocytopenia (ITP), they may be relevant for AIHA. The adjusted relative risk in the matched-indication comparison (comparison of patients with splenectomy vs no splenectomy with the same disease) of hospital contacts for infections was 1.4 beyond 365 days after splenectomy, but mortality was not increased. There is good, but not definite, evidence that preoperative vaccination reduces the risk of severe
infections. Other long-term risks are an increased risk of venous thromboembolism and a (very small) risk of pulmonary hypertension.

If splenectomy is performed, all measures must be taken to prevent complications. We recommend that all our patients have preoperative vaccination against pneumococci, meningococci, and hemophilus and that vaccination for pneumococci should then be repeated every 5 years. Patients must be informed about the risk of infections and should be advised to take antibiotics in case of fever. They should also be informed about the higher risk of venous thromboembolism.

Unfortunately, a prediction for response to splenectomy is not possible in an individual patient. Response to steroids, duration of disease, or predominant red cell sequestration in the spleen is not predictive.

So far splenectomy is the only treatment that may provide freedom from treatment in a substantial number of patients for more than 2 years and possibly cure in approximately 20%. We believe that splenectomy is underused and should be offered as the preferred second-line treatment. In rituximab studies only one-third of patients who had undergone splenectomy before administration of this off-label drug.

The other reasonable option for second-line treatment is the anti-CD20 antibody rituximab. The discovery that this drug is effective in AIHA and ITP was an advance in the treatment of these diseases after almost 50 years with little progress. Rituximab has a well-documented short-term efficacy but currently can be prescribed only off-label for this indication. The standard regimen is 375 mg/m² on days 1, 8, 15, 22 for 4 doses. Patients on steroids before initiation of rituximab therapy should continue steroids until the first signs of response to rituximab. In a retrospective study, rituximab in standard dose was given to 11 patients with refractory primary WAIHA. Four patients received additional therapies. Eight patients achieved a CR and 3 a PR, but 6 patients still had discrete laboratory signs of hemolysis. At a mean follow-up of 604 days all patients were still in CR/PR. The longest remission duration was 2884 days. The efficacy and toxicity of rituximab monotherapy was tested in 5 additional retrospective studies in a mixed population of refractory primary or secondary AIHA. Overall response rate was 82% (half CR and PR). Safety data were available in 3 studies. In one study 2 patients had severe infections and 1 patient had a myocardial infarction; otherwise, there were no major safety problems. The most severe potential long-term complication of rituximab treatment is progressive multifocal leukoencephalopathy (PML), which, however, has been observed in only 2 patients with AIHA (C.L. Bennett, Siteman Comprehensive Cancer Center, Washington University School of Medicine, personal written communication, January 2010).

There is no doubt that the short-term benefit/risk ratio for rituximab is high and that rituximab is certainly the best option for patients who are not eligible for or who refuse splenectomy. The problem is the small number of selected patients, the heterogeneity of patient population, and the lack of systematic long-term data on efficacy and safety in the published reports. In ITP it has been shown that patients with a CR after rituximab can have long remission durations and that splenectomy can be avoided or postponed. Such data are not available for rituximab in AIHA. It appears that rituximab therapy has to be repeated every 1 to 3 years, and this may increase the risk of infections, including PML. We also do not know whether patients will become refractory after repeated treatments.

In practice, it is frequently the informed patient who decides on the second-line treatment modality. After consulting the internet (which usually promotes the most recent, but not the best, established treatments) patients often refuse splenectomy (they often do not understand why a healthy organ should be removed) and request treatment with the newest drug, which is currently rituximab.

Medical reasons in favor of rituximab are relative contraindications for splenectomy such as massive obesity, technical problems, and a high risk of venous thromboembolism. A contraindication to rituximab treatment is an untreated hepatitis B virus infection.

High-dose immunoglobulin has often been used as second-line therapy after or concurrent with PDN because of the presumed efficacy and low risk of side effects. However, efficacy is low. We have used high-dose immunoglobulin rarely for treatment of AIHA. In a recent guideline high-dose immunoglobulin was not recommended for routine use in AIHA. A potentially interesting second-line (or even first-line) treatment may be danazol, a synthetic anabolic steroid with pleiotropic effects. A success rate of 60% to 77% has been reported with danazol concurrent with or after steroids, but these data have not been confirmed. We have used danazol only in a few instances in the past, albeit without effect.

**Treatment of patients with refractory or recurrent disease after splenectomy or rituximab.** For patients who are refractory to splenectomy or those with recurrence after splenectomy (after exclusion of an accessory spleen), there are 2 options (Figure 2). One option is retreatment with steroids with the hope that the disease is now more responsive to steroids, which sometimes happens. We would try this in patients who had a relatively low steroid requirement (≤ 15 mg/d PDN) before splenectomy. Otherwise we would proceed directly to rituximab.

Patients who do not respond to rituximab should urgently be advised to undergo splenectomy. In patients who relapse after an initial response to rituximab and who had an initial response duration of less than 1 year, we recommend splenectomy and reserve retreatment with rituximab for progression after splenectomy. For patients with long remission durations after first rituximab treatment, retreatment with rituximab may be a reasonable option. Data in a few patients indicate that a good response to
repetition with rituximab can be expected,\textsuperscript{51,52} but there are no data on the duration of a second remission.

**Treatment options beyond second-line therapy.** Immunosuppressive treatment was often recommended as preferred second-line treatment because response rates of 40% to 60% have been claimed in earlier reviews.\textsuperscript{3,10,61} There is no doubt that immunosuppressive treatment is effective in some cases, but there is doubt on the overall efficacy. The opinion that cyclophosphamide is highly effective appears to be based on data from 2 earlier articles.\textsuperscript{62,63} Those studies provided overall results but no specific patient details. A critical analysis of other published cases of patients treated with azathioprine or cyclophosphamide\textsuperscript{39,41,64} shows that probably fewer than one-third had any “response.” Many patients received concomitant treatment with steroids. The durability of responses is unknown in most studies. Dosing of azathioprine is difficult because of the narrow therapeutic window, hypersensitivity due to genetic defects, and interaction with other drugs. Cyclophosphamide has a substantial mutagenic potential on long-term treatment. We regard the benefit-risk of azathioprine/cyclophosphamide (50 mg/kg/d for 4 days) and 6 of 9 patients achieved a CR with a median duration of 15 months at the time of publication (2002). All of these patients are still in CR in 2010 (R.A. Brodsky, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, personal written communication, January 2010). The results of autologous stem cell transplantation were disappointing.\textsuperscript{66} Alemtuzumab has been effective in a few patients, but toxicity is high.\textsuperscript{70}

On the basis of published data on benefits and risks (independent of individual factors) in our opinion the sequence of second-line treatments in primary WAIHA should be splenectomy, rituximab, and thereafter any of the immunosuppressive drugs (Figure 2). In practice the choice of the sequence mainly depends on the personal experience of the physician, patient factors such as age and comorbidity, the availability and cost of drugs, and the preference of the patient. The main factor for the selection of any drug should be safety, because the curative potential of all these drugs is low, and treatment may be more dangerous for the patient than the disease to be treated.

**Treatment of secondary AIHA**

**WAIHA associated with systemic lupus erythematosus.** Systemic lupus erythematosus is a most common cause of secondary AIHA (Table 2). The preferred first-line therapies are steroids used in the same manner as in primary AIHA. The response rate is high. On a maintenance treatment of 5 to 20 mg of PDN (in some patients with additional azathioprine or cyclophosphamide) the recurrence rate was low (3-4/100 patient-years).\textsuperscript{81} The same second-line treatments as in primary AIHA have been effective in some cases.\textsuperscript{81} Rituximab has been effective in single cases, but there is a concern of an increased risk of PML in this particular disease. Splenectomy seems to have only a low long-term efficacy.

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**Table 2. Suggested sequence of treatments in primary and secondary WAIHA and CAIHA**

<table>
<thead>
<tr>
<th>Disease or condition</th>
<th>First line</th>
<th>Second line</th>
<th>Beyond second line</th>
<th>Last resort</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary AIHA</td>
<td>Steroids</td>
<td>Splenectomy rituximab</td>
<td>Azathioprine, MMF, cyclosporin, cyclophosphamide</td>
<td>High-dose cyclophosphamide, alemtuzumab</td>
<td>See text</td>
</tr>
<tr>
<td>B- and T-cell NHL</td>
<td>Steroids</td>
<td>Chemotherapy + rituximab (splenectomy in SMZL)</td>
<td></td>
<td></td>
<td>71,72</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>Steroids</td>
<td>Chemotherapy (radiotherapy)</td>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>Steroids, surgery</td>
<td></td>
<td></td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Ovarian dermoid cyst*</td>
<td>Ovariectomy</td>
<td></td>
<td></td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>SLE</td>
<td>Steroids</td>
<td>Azathioprine</td>
<td>MMF</td>
<td>Rituximab autologous SCT</td>
<td>See text</td>
</tr>
<tr>
<td>CVID</td>
<td>Steroids + IgG</td>
<td>Splenectomy</td>
<td>Total colectomy</td>
<td></td>
<td>24,73</td>
</tr>
<tr>
<td>ALPD*</td>
<td>Steroids</td>
<td>MMF</td>
<td>Sirolimus</td>
<td></td>
<td>74,75</td>
</tr>
<tr>
<td>Allogeneic SCT</td>
<td>Steroids</td>
<td>Rituximab</td>
<td>Splenectomy, T-cell infusions</td>
<td></td>
<td>76</td>
</tr>
<tr>
<td>Organ transplantation (pancreas)*</td>
<td>Discontinuation of immune suppression, steroids</td>
<td>Splenectomy</td>
<td></td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>Interferon α</td>
<td>Withdrawal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary CAD</td>
<td>Protection from cold exposure</td>
<td>Rituximab, chlorambucil</td>
<td>Eculizumab, bortezomib</td>
<td></td>
<td>64,77-79</td>
</tr>
<tr>
<td>Paroxysmal cold hemoglobinuria</td>
<td>Supportive treatment</td>
<td>Rituximab</td>
<td></td>
<td></td>
<td>80</td>
</tr>
</tbody>
</table>

MMF indicates mycophenolate mofetil; NHL, non-Hodgkin lymphoma; SMZL, splenic marginal zone lymphoma; SLE, systemic lupus erythematosus; SCT, stem cell transplantation; CVID, common variable immunodeficiency; ALPD, autoimmune lymphoproliferative disease; and CAD, cold agglutinin disease.

*No personal experience.
†Off-label use.
AIHA associated with malignancies

**CLL-associated WAIHA.** For the treatment of patients with chronic lymphocytic leukemia (CLL)–associated WAIHA, several aspects are important. Compared with patients with primary AIHA, they are at a higher risk of infections, are older, and have higher comorbidity. CLL-associated AIHA may be either “spontaneous” or drug-induced. For treatment decisions not only the AIHA but also stage and progression of CLL have to be taken into consideration. A number of relatively small studies in different populations of patients with various drugs have been performed. The type of patients and pretreatment were not uniform in those studies.

Our strategy for treatment of CLL-associated AIHA is shown in Table 3. It is based on published data and our practical experience.

The treatment of AIHA in non-Hodgkin lymphomas. The treatment of AIHA in non-Hodgkin lymphoma depends on the type of lymphoma. Generally, the AIHA of patients with non-Hodgkin lymphoma has a poor response to steroids. Splenectomy is effective only in splenic marginal zone lymphoma. The best responses in high-grade B-cell lymphomas, follicular lymphomas, angioimmunoblastic T-cell lymphoma, and other T-cell lymphomas have been obtained with intensive antilymphoma chemotherapy with or without rituximab. Most of the chemotherapy-induced CRs of AIHA were sustained.

**Drug-related WAIHA.** Currently, the most important drug-related AIHAs are due to drugs that are used for treatment of CLL, in particular fludarabine, but also after other antileukemic drugs. AIHA may occur during or after drug exposure. Fludarabine-triggered AIHA may be life-threatening. It responds to steroids, but only one-half of the patients are in remission off steroids. Another important cause of WAIHA is interferon α treatment, in particular in hepatitis C. These patients recover usually after cessation of interferon.

**Treatment of CAIHA.**

AIHA may occur after a variety of viral infections such as hepatitis C, A, and E and cytomegalovirus. CAIHA is a rare, but typical, complication of mycoplasma infection which resolves spontaneously, although resolution is probably accelerated by antibiotic treatment.

A special problem is the preparation of patients with high-titer cold antibodies for surgery. Cryofiltration apheresis was successful for cold antibodies for surgery. Cryofiltration apheresis was successful for CAIHA in some patients in this situation.

**Primary chronic cold agglutinin disease.** Primary cold agglutinin disease (CAD) is defined as a CAIHA in patients with IgM–monoclonal gammopathy of undetermined significance or in lymphoma without overt clinical signs but with bone marrow infiltration. The anemia is rarely acute, often mild, and drug treatment is required in only one-half of the patients. All patients should be advised to avoid cold exposure. In contrast to WAIHA, CAIHA does not respond to steroids and/or splenectomy. In patients with evidence of lymphoma who are not severely anemic, therapy with chlorambucil may be tried, but efficacy in terms of an increase in hemoglobin level is rather small. The most effective and best-evaluated treatment is rituximab in standard lymphoma dose. Berentsen et al performed an open, uncontrolled prospective phase 2 study of rituximab in CAD. Twenty of 27 patients responded, but almost all responses (n = 19) were PRs. The median duration of response was 11 months, and most of the relapsed patients responded to retreatment with rituximab. Similar results were obtained by Schöllkopf et al. We treat all our patients with symptomatic CAD (hemoglobin level below 9-10 g/dL and/or vascular symptoms) with rituximab. Remarkable responses have recently been obtained with eculizumab and bortezomib in rituximab-refractory patients.

**Secondary CAIHA.** Chronic cold agglutinin AIHA also occurs in indolent and aggressive B- and T-cell lymphomas. The CAIHA of these patients responds well to antilymphoma chemotherapy. In rare cases a CAIHA associated with a solid tumor was controlled by curative resection of the primary tumor.

**Infection-related AIHA.**

WAIHA may occur after a variety of viral infections such as hepatitis C, A, and E and cytomegalovirus. CAIHA is a rare, but typical, complication of mycoplasma infection which resolves spontaneously, although resolution is probably accelerated by antibiotic treatment.

A special problem is the preparation of patients with high-titer cold antibodies for surgery. Cryofiltration apheresis was successful in some patients in this situation.

**Future directions**

An urgent need exists for better data and new treatments for WAIHA. Before new or old drugs or procedures are evaluated retrospectively or prospectively, a consensus on the definitions of responses is required. This could be achieved by an expert panel of hematologists as it has been done for ITP. For first-line therapy, steroids will remain the preferred treatment. In the era of comparative-effectiveness research we need to determine whether splenectomy or rituximab is the best second-line therapy in terms of efficacy, adverse events, and cost efficiency. Any potential new drugs that will emerge must then be compared with the established best current second-line therapy. Scientifically, the best way would be to do a randomized study comparing the best second-line treatments, splenectomy and rituximab, after a standardized first-line treatment. It is, however, doubtful whether such as study will be conducted.

### Table 3. Suggested treatments of CLL-associated AIHA

<table>
<thead>
<tr>
<th>Condition</th>
<th>First-line treatments</th>
<th>Second-line treatments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated drug-related AIHA, untreated AIHA in early stage CLL</td>
<td>Steroids</td>
<td>RCD</td>
<td>82,83</td>
</tr>
<tr>
<td>Untreated AIHA in active CLL</td>
<td>Steroids + chlorambucil</td>
<td>RCD; R-CVP</td>
<td>16,84,85</td>
</tr>
<tr>
<td>Steroid-refractory, nonprogressive CLL</td>
<td>Rituximab; cyclosporin; splenectomy</td>
<td>RCD; R-CVP</td>
<td>86-88</td>
</tr>
<tr>
<td>Multiply refractory AIHA, advanced or progressive CLL</td>
<td>Alectuzumab</td>
<td></td>
<td>89</td>
</tr>
</tbody>
</table>

RCD indicates rituximab, cyclophosphamide, and dexamethasone; and R-CVP, rituximab, cyclophosphamide, vincristine, prednisone.
recruit enough patients. A solution could be a cooperative world-wide effort of hematologists to set up a registry of patients with AIHA who had undergone splenectomy or rituximab treatment for retrospective analysis of these cases. The results would of course not be evidence-based medicine of highest standard, but certainly they would much better than the current state of knowledge. These data could be the basis for future prospective comparative studies with known or new drugs.

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Authorship

Contribution: K.L. and U.J. retrieved data and wrote the paper.

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How I treat autoimmune hemolytic anemias in adults

Klaus Lechner and Ulrich Jäger