

How I treat autoimmune hemolytic anemias in adults

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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. (*Blood*. 2010;116(11):1831-1838)

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Introduction

Autoimmune hemolytic anemia (AIHA) is a rare disease. In a recent population-based study¹ 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.³⁻⁸ Therapy has been reviewed by several investigators,⁸⁻¹⁵ but no treatment guidelines have yet been published.

Diagnosis

The diagnosis of AIHA is usually straightforward and made on the basis of the following laboratory findings: normocytic or macrocytic anemia, reticulocytosis, low serum haptoglobin levels, elevated lactate dehydrogenase (LDH) level, increased indirect bilirubin level, and a positive direct antiglobulin test with a broad-spectrum antibody against immunoglobulin and complement (Figure 1). However, there are pitfalls, particularly in secondary cases, because not always are all of the typical laboratory findings of AIHA present.¹⁵ Two pieces of information are of utmost importance for the clinician to make an appropriate treatment decision: (1) What type of the antibody is involved? (2) Is the AIHA primary or secondary? The type of antibody can be identified with the use of monospecific antibodies to immunoglobulin G (IgG) and C3d. When the red cells are coated with IgG or IgG plus C3d, the antibody is usually a warm antibody (warm antibody AIHA [WAIHA]). When the red cells are coated with C3d only, the antibody is often but not always a cold antibody. For definite diagnosis of a cold antibody AIHA (CAIHA), the cold agglutinin titer should be markedly elevated (> 1:512). In some cases (direct antiglobulin test negativity, IgM warm antibodies, cold antibodies with low titers, or Donath-Landsteiner antibodies), diagnosis may be difficult, and the expertise of an immune-hematologic laboratory

is required. For the diagnosis of secondary AIHA a careful history, including information on the onset (acute or insidious), history of infections, information on recent transfusions, exposure to drugs or vaccination, signs of immune disease (arthritis), and general clinical condition are helpful. The exclusion of a drug-induced hemolytic anemia is particularly important, because stopping the drug is the most effective therapeutic measure in this situation. A clinical examination (to rule out lymphadenopathy, splenomegaly) is obligatory. The need for additional investigations must be determined by history, clinical findings, and the type of antibody. Routine work-up relevant for treatment decisions may include abdominal examination by computed tomographic scan (to search for splenomegaly, abdominal lymphomas, ovarian dermoid cysts, renal cell carcinoma), quantitative determination of immunoglobulins, a search for a lupus anticoagulant in case of warm antibodies, or a bone marrow examination and a search for clonal immunoglobulins (immune fixation) in case of cold antibodies.

The list of underlying diseases in which AIHA can occur is long. The most common underlying diseases are lymphoproliferative disorders and immune diseases. Among others, the type of AIHA is the most important clue to the most likely underlying disease (Table 1).

Treatment of AIHA

General remarks

This review deals only with the treatment of adult AIHA.

In the era of evidence-based medicine it is surprising and regrettable that treatment of AIHA is still not evidence-based, but essentially experience-based. There are no randomized studies and only a few prospective phase 2 trials. Otherwise, only retrospective studies, small series of (probably selected) patients or single cases have been reported (evidence level V). There is no formal consensus on the definition of complete (CR) or partial (PR) hematologic remission and refractoriness. We found more than

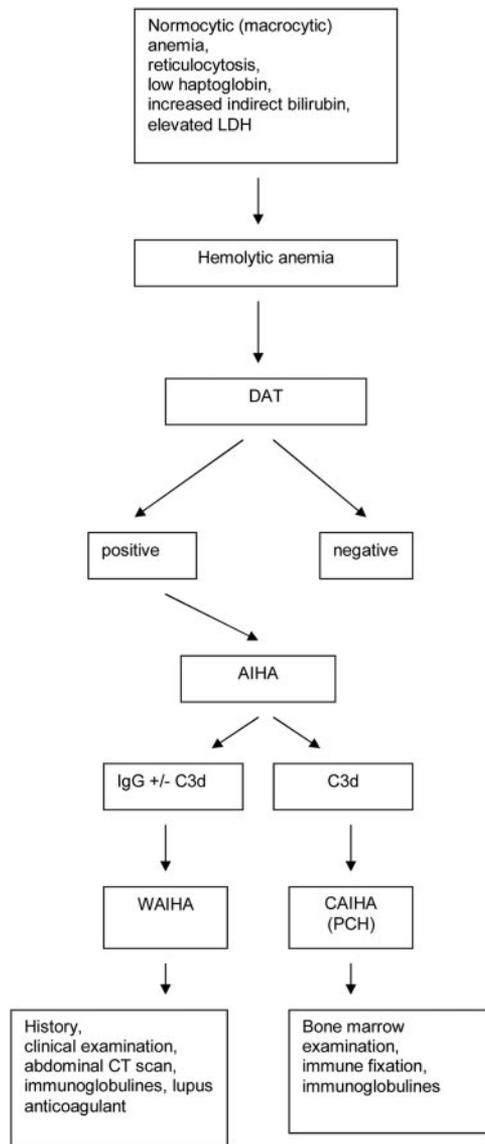


Figure 1. Diagnostic algorithm in AIHA. LDH indicates lactate dehydrogenase; DAT, direct antiglobulin test; and CT, computed tomography.

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 clinically comfortable and to prevent "hemolytic crises" with the use of medical interventions with the lowest possible short- and long-term side 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 AIHA³¹ and IgM WAIHA³²), 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 alloantibodies³³ 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

Underlying disease or condition	Prevalence of AIHA, %*	WAIHA	CAIHA	References
CLL	2.3-4.3	87%	7%	16,17
NHL (except CLL)	2.6	More common	Less common	18
IgM gammopathy	1.1	No	All	19
Hodgkin lymphoma	0.19-1.7	Almost all	Rare	20
Solid tumors	Very rare	2/3	1/3	21
Ovarian dermoid cyst	Very rare	All	No	22
SLE	6.1	Almost all	Rare	23
Ulcerative colitis	1.7	All	No	24
CVID	5.5	All	No	25
ALPD	50	All	No	26
After allogeneic SCT	4.4	Yes	Yes	27
After organ transplantation	5.6 (pancreas)	Yes	No	28
Drug-induced in CLL	2.9-10.5	Almost all	Rare	29
Interferon α	Incidence: 11.5/100 000 patient-years	All	0	30

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.

ward: rapid infusion of 20 mL of blood, 20 minutes' observation, and, if there is no reaction, further transfusion at the usual speed. In critical cases transfusions should not be avoided or delayed because of uncertainty in matching. Even a small amount of transfused blood can be life-saving. The value of plasmapheresis to reduce antibody titers is unproven.³⁴ In WAIHA treatment with steroids should begin immediately. In patients with CAIHA transfused blood must be prewarmed with the use of commercial warming coils.

Treatment of (primary) idiopathic WAIHA

First-line treatment. The mainstay of treatment of newly diagnosed primary WAIHA is glucocorticoids (steroids). According to accepted recommendations we start treatment immediately with an initial dose of 1 mg/kg/d prednisone (PDN) orally or methylprednisolone intravenously. This initial dose is administered until a hematocrit of greater than 30% or a hemoglobin level greater than 10 g/dL (thus, not necessarily a complete normalization of hemoglobin) is reached. If this goal is not achieved within 3 weeks, second-line treatment is started because further improvement with steroid treatment is unlikely.⁹ Once the treatment goal is achieved, the dose of PDN is reduced to 20 to 30 mg/d within a few weeks. Thereafter, the PDN dose is tapered slowly (by 2.5-5 mg/d per month) under careful monitoring of hemoglobin and reticulocyte counts. An alternate-day regimen (reducing the dose gradually to nil on alternate days) may reduce the side effects of steroids. If the patient is still in remission after 3 to 4 months at a dose of 5 mg of PDN/day, an attempt to withdraw steroids is made. All patients on steroid therapy will receive bisphosphonates, vitamin D, and calcium from the beginning according to the recommendation of the American College of Rheumatology. Supplementation with folic acid is recommended. We carefully monitor blood glucose and treat patients with diabetes aggressively because diabetes is a major risk factor for treatment-related deaths from infections.³⁵ We do not treat patients with acute hemolysis routinely with heparin,³⁶ but we always consider the possibility of pulmonary embolism, because symptoms could wrongly be ascribed solely to acute anemia. At particular high risk of thromboembolism are patients with AIHA and lupus anticoagulant³⁷ or recurrent AIHA after splenectomy.³⁸

Second-line treatment: when? what? and who decides? Approximately 80% of patients achieve a CR or PR with initial PDN treatment.⁹ However, the most responders require maintenance steroids to maintain an acceptable hemoglobin value (> 9-10 g/dL). Approximately 40% to 50% of patients need 15 mg/d or less PND (15 mg/d is regarded by many as the highest tolerable dose for long-term treatment), but 15% to 20% need higher maintenance PDN doses. It is not exactly known how many patients will remain in remission after withdrawal of steroids and are possibly cured. It is estimated that this occurs in less than 20% of patients.^{9,10,38}

If a patient is refractory to the initial corticosteroid treatment, a diagnostic reevaluation with regard to a possible underlying disease should be made. Patients with malignant tumors, benign ovarian teratomas, or with warm IgM antibodies³² are often steroid-refractory.

With regard to the decision for a second-line treatment we classify patients in 3 categories: (1) patients who are refractory to initial steroids and those who need more than 15 mg/d PDN as a maintenance dose are absolute candidates for a second-line therapy; (2) patients who need between 15 and 0.1 mg/kg/d PDN should be encouraged to proceed to a second-line treatment; whereas (3) patients with PDN requirement of 0.1 mg/kg/d or less may do well with long-term low-dose PDN.

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 patients¹³ with a range of 38% to 82%, depending on the percentage of secondary cases.^{9,38-43} (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 Dacie⁴⁰ 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.⁴³ 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,³⁸ 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.⁴¹ (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.⁴⁴ 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 septicemia). 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 study⁴⁵ 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.⁴⁶ There is good, but not definite, evidence that preoperative vaccination reduces the risk of severe

infections.⁴⁷ Other long-term risks are an increased risk of venous thromboembolism⁴⁸ 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,³⁸ duration of disease, or predominant red cell sequestration in the spleen is not predictive.⁴⁹

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 had undergone splenectomy before administration of this off-label drug.⁵⁰⁻⁵⁶

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.⁵⁰ 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.^{51-54,56} Overall response rate was 82% (half CR and PR). Safety data were available in 3 studies. In one study⁵¹ 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).⁵⁷ 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.⁵⁸ 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

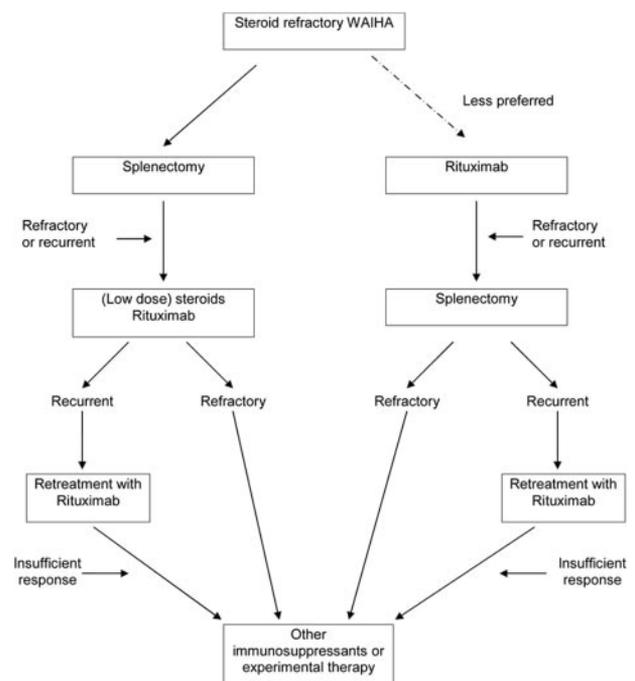


Figure 2. Treatment algorithm for steroid-refractory WAIHA.

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.⁵⁹ 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 reported⁶⁰ with danazol concurrent with or after steroids, but these data have not been confirmed.⁴¹ 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

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

Disease or condition	First line	Second line	Beyond second line	Last resort	References
Primary AIHA	Steroids	Splenectomy rituximab	Azathioprine, MMF, cyclosporin, cyclophosphamide	High-dose cyclophosphamide, alemtuzumab	See text
B- and T-cell NHL	Steroids	Chemotherapy ± rituximab (splenectomy in SMZL)			71,72
Hodgkin lymphoma	Steroids	Chemotherapy (radiotherapy)			20
Solid tumors	Steroids, surgery				21
Ovarian dermoid cyst*	Ovariectomy				22
SLE	Steroids	Azathioprine	MMF	Rituximab autologous SCT	See text
Ulcerative colitis	Steroids	Azathioprine		Total colectomy	24,73
CVID	Steroids + IgG	Splenectomy			25
ALPD*	Steroids	MMF	Sirolimus		74,75
Allogeneic SCT	Steroids	Rituximab	Splenectomy, T-cell infusion		76
Organ transplantation (pancreas)*	Discontinuation of immune suppression, steroids	Splenectomy			28
Interferon α	Withdrawal	Steroids			
Primary CAD	Protection from cold exposure	Rituximab, chlorambucil		Eculizumab,† bortezomib†	64,77-79
Paroxysmal cold hemoglobinuria	Supportive treatment	Rituximab			80

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.

retreatment with rituximab can be expected,^{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.^{9,10,61} 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.^{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^{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 only moderate at best. Skinner and Schwartz⁶⁵ wrote on immunosuppressive drugs in AIHA in his review in 1972: “Unfortunately, all that is known now is merely that immunosuppressive therapy of this condition is feasible.” This is still true today.

All other immunosuppressive treatments (mycophenolate mofetil, cyclosporine) have in common that only a very few patients were treated, but, surprisingly, in almost all cases favorable responses were achieved.^{66,67} This probably indicates that there was a strong selection bias. From the pretreatment data in rituximab trials it appears that, in the era before rituximab, azathioprine and cyclophosphamide were popular as second-line therapy, but we have used immunosuppressants rarely because of doubts about efficacy and the fear of side effects.

Treatment of last resort (severe anemia and none of the known drugs have worked). High-dose cyclophosphamide has been used as treatment for selected highly refractory patients. In the

study of Moyo et al,⁶⁸ 9 patients received several cycles of 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.⁶⁹ Alemtuzumab has been effective in a few patients, but toxicity is high.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).⁸¹ The same second-line treatments as in primary AIHA have been effective in some cases.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.

Table 3. Suggested treatments of CLL-associated AIHA

Condition	First-line treatments	Second-line treatments	References
Untreated drug-related AIHA, untreated AIHA in early stage CLL	Steroids	RCD	82,83
Untreated AIHA in active CLL	Steroids + chlorambucil	RCD; R-CVP	16,84,85
Steroid-refractory, nonprogressive CLL	Rituximab; cyclosporin; splenectomy	RCD; R-CVP	86-88
Multiply refractory AIHA, advanced or progressive CLL	Alemtuzumab		89

RCD indicates rituximab, cyclophosphamide, and dexamethasone; and R-CVP, rituximab, cyclophosphamide, vincristine, prednisone.

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 data⁹⁰ and our practical experience.

It seems reasonable to use steroids as first-line therapy in the same manner as in primary AIHA in patients with nonprogressive early CLL. However, there are no data on the efficacy and adverse effects of steroid monotherapy. In fludarabine-induced AIHA CLL steroid monotherapy is the best choice and often successful.⁸² In AIHA associated with untreated “active” CLL long-term steroid treatment (combined with chlorambucil) seems to be successful (84% CR/PR, 54% of the patients in CR are relapse-free after 5 years) with an acceptable toxicity.¹⁶ In steroid-refractory AIHA in CLL more aggressive treatments are indicated. An effective and surprisingly well-tolerated second-line treatment is the combination of rituximab, cyclophosphamide, and dexamethasone.⁸⁴ Favorable results in AIHA associated with progressive CLL were also obtained with rituximab combined with cyclophosphamide, vincristine, and PDN.⁸⁵ Other treatment options are cyclosporin, which has relatively good activity,⁸⁷ and rituximab. Rituximab monotherapy is less active than in primary AIHA and has a higher toxicity.⁸⁶

WAIHA 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.⁷¹ 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.⁸² Another important cause of WAIHA is interferon α treatment, in particular in hepatitis C.³⁰ These patients recover usually after cessation of interferon.

Treatment of CAIHA

Almost all CAIHAs seem to be secondary. The underlying conditions in most cases are lymphoproliferative diseases (including IgM-monoclonal gammopathy of undetermined significance), less commonly autoimmune diseases or infections, and rarely drugs.^{8,91}

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.⁹² 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,^{64,93} but the 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 al⁷⁹ 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.⁹⁴ 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 eculizumab⁷⁷ and bortezomib⁷⁸ 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.⁷¹ In rare cases a CAIHA associated with a solid tumor was controlled by curative resection of the primary tumor.²¹

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.⁹⁵

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.⁹⁶ 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 a study will

recruit enough patients. A solution could be a cooperative worldwide 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 be much better than the current state of knowledge. These data could be the basis for future prospective comparative studies with known or new drugs.⁹⁷

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