Review: Pharmacologic treatment of warm autoimmune hemolytic anemia

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The clinical course of warm autoimmune hemolytic anemia (WAIHA) can be perplexing and frustrating. Although many patients respond to standard therapy in a predictable and timely fashion, some patients are refractory to standard therapy and may require several attempts of therapies that are less well established. The focus of this review is to discuss the various pharmacologic approaches and options for the treatment of WAIHA.

Corticosteroids

Corticosteroids are the initial therapy of choice for WAIHA. A standard approach is to treat adults with prednisone, 1 to 1.5 mg/kg per day (or 60 to 100 mg/day) for 1 to 3 weeks. Clinical response with improvement in hematologic variables may be seen within several days to 1 week. Approximately 80 percent of patients have a good initial response to this therapy.[1–3] Most patients who are going to respond will respond within 2 weeks. If no response is noted within 3 weeks, steroid therapy has failed and alternative therapeutic options should be considered.

For patients who improve with corticosteroid therapy, the dosage of corticosteroids can be gradually reduced only after stabilization of hematologic variables. It is generally recommended to continue the initial higher dose of steroids for 1 to 2 weeks after achieving a response, weighing the benefits of continued steroid therapy against the risks of this therapy. After this period of stabilization, the steroid dose should gradually be tapered. Sudden decreases in dosage or rapidly progressive tapers can lead to relapse. If relapse does occur, the dose should be increased. Most clinicians consider a daily maintenance dose of prednisone greater than 15 mg to achieve a Hct of at least 30% a therapeutic failure, requiring other interventions.

The adverse effects of corticosteroid therapy are well established, and their severity should not be underestimated. Initial complications may include insomnia, weight gain associated with increased appetite, and emotional lability. Conditions such as diabetes and hypertension may present or worsen, if preexisting. Long-term corticosteroid therapy is complicated by the development of a cushingoid habitus, osteoporosis, and avascular necrosis. Ophthalmologic complications include posterior subcapsular cataracts and glaucoma. Patients are at increased risk of infection owing to steroid-related immunosuppression. The complications of steroid therapy can be quite severe; consequently, steroids must be used judiciously and doses should be tapered as quickly as possible.[2,4]

The explanation for clinical response to corticosteroids is likely multifactorial. Steroids have been shown to have an early effect on tissue macrophages, which become less efficient at clearing IgG- and C3-coated RBCs within the first 8 days of therapy.[5] Steroids may also affect antibody avidity.[6] Only after several weeks of therapy is there a significant decrease in antibody production.[6]

Permanent remission of WAIHA occurs in only approximately 20 to 35 percent of adult patients.[7,8] Consequently, additional therapy is generally planned because clinical relapse is likely.

Splenectomy

Although the focus of this review is to provide an overview of the pharmacologic options for the treatment of autoimmune hemolytic anemia (AIHA), it is difficult to discuss treatment options without mentioning the role of splenectomy. Splenectomy has traditionally been the second-line therapeutic approach, after corticosteroid therapy; this may be in transition as pharmacologic options are improving.

Approximately 50 percent of patients with WAIHA will have an excellent initial response to splenectomy, although low doses of prednisone (< 15 mg/day) may still be needed to maintain adequate hemoglobin levels.[9] Late relapses do occur, presumably as a result of enhanced antibody synthesis and increased hepatic sequestration.[1,8]

Although there is surgical morbidity and mortality associated with splenectomy, the most significant risk of adverse event related to splenectomy is overwhelming postsplenectomy sepsis syndrome. Infections with encapsulated bacteria represent a medical emergency because there may be rapid progression from an apparent flulike illness to bacteremic shock, with hypotension and disseminated intravascular coagulation. The risk of overwhelming postsplenectomy sepsis syndrome has been quantitated as 3.2 percent with a mortality rate of 1.4 percent.[10] The risks of both infection and mortality can be reduced by the use of pneumococcal and meningococcal vaccines. Prophylactic antibiotic regimens are controversial; however, many advocate the use of penicillin (250 mg twice a day); amoxicillin or Bactrim can be used as alternatives. Febrile illnesses in splenectomized patients must be given prompt attention and antibiotics administered expeditiously.

Because of this life-threatening risk associated with splenectomy and because of the increasing pharmacologic options, many clinicians are no longer routinely using splenectomy as a second approach after corticosteroid therapy.

Immunosuppressive Agents

Several immunosuppressive agents have been reported to be successful in the treatment of WAIHA, but predominantly in case reports and small series. In the past, these more intensive immunosuppressive regimens were only considered when there is lack of response to corticosteroids and splenectomy, when there is relapse after corticosteroids and splenectomy, when splenectomy is an unacceptable medical risk, or when corticosteroid therapy cannot be tolerated.

Azathioprine

Azathioprine, an immunosuppressive antimetabolite, is an imidazolyl derivative of 6-mercaptopurine. It is used for the prevention of renal allograft rejection, as well as the treatment of autoimmune disorders, such as rheumatoid arthritis (RA) and inflammatory bowel disease.

Azathioprine has been used with reported success in WAIHA. One study described 14 patients with idiopathic WAIHA who were treated with azathioprine; 6 of the patients (43%) achieved good response with normal hemoglobin levels.[11] In a report of 26 patients with AIHA in the setting of systemic lupus erythematosus (SLE), 2 patients received azathioprine for relapse after successful initial response to corticosteroids.[12] Both patients achieved chronic remission, and one of these patients was able to stop steroid therapy after initiating azathioprine.

The generally recommended dose of azathioprine for this indication is 1 to 2 mg/kg per day, or 75 to 200 mg/day in adults. If the patient is already taking steroids and has a partial remission, the steroids should be continued and tapered after a clinical response is achieved. If after 3 to 4 weeks the patient has not responded, the dosage may be increased (usually in increments of 25 mg/day); however, the adverse effects of azathioprine can be limiting.

The use of azathioprine is associated with gastrointestinal intolerance, including nausea, vomiting, and diarrhea, and dose-related bone marrow suppression with leukopenia and thrombocytopenia. Because azathioprine is cytotoxic, its prolonged administration is not advised because of the risk of development of a neoplasm.

Cyclosporine

This lipophilic cyclic protein binds to cytoplasmic proteins, called cyclophilins, and the resulting complex inhibits calcineurin. Consequently, cyclosporine inhibits selected cytokine transcription, down-regulating the transcription of some proinflammatory cytokines, and it also inhibits T-lymphocyte activation. Cyclosporine is used in the prophylaxis and treatment of solid-organ transplant rejection and in the management of several autoimmune disorders, including RA, ulcerative colitis, and psoriasis.

Cyclosporine has been used with reported success in the treatment of refractory WAIHA. Emilia and associates[13] described the successful use of cyclosporine in the treatment of three patients with AIHA and one patient with Evans' syndrome. All patients were refractory to multiple previous therapies including steroids, splenectomy, and immunosuppressive agents. The patients were treated at an initial total dose of 5 mg/kg per day given twice daily for 6 days with subsequent dose reduction to 3 mg/kg per day, maintaining a serum cyclosporine level between

200 and 400 ng/mL. Low-dose prednisone (5 mg/day) was given to increase cyclosporine blood concentrations. Dundar and colleagues[14] reported similar successful hematologic response in a patient with Evans' syndrome. The patient was refractory to standard dose and high-dose corticosteroid therapy and splenectomy, but responded to a cyclosporine regimen with an initial dose of 10 mg/kg per day gradually tapering to 4 mg/kg per day.

Others have successfully used cyclosporine in combination with corticosteroid therapy. Hershko and coworkers[15] presented three patients, two with AIHA and one with Evans' syndrome, who relapsed despite initial clinical response to steroids. All three patients showed clinical improvement with cyclosporine therapy (4 to 6 mg/kg per day) in addition to continued corticosteroid therapy. A child with refractory Evans' syndrome, who had failed corticosteroids and splenectomy, was successfully treated with cyclosporine and prednisone.[16] Initially, the cyclosporine was given at 10 mg/kg per day and prednisone, at 2 mg/kg per day. Each drug was gradually tapered, ultimately going to alternate day cyclosporine and prednisone dosing. One remarkable case is that of a 51-year-old woman with SLE who had AIHA that was refractory to steroids, splenectomy, cyclophosphamide, and azathioprine, but who responded to cyclosporine therapy, allowing for the corticosteroid tapering.[17]

Despite these reports of success, other authors have reported failure in treating AIHA with cyclosporine. Ferrara et al.[18] reported a 27-year-old man with AIHA in the setting of myelodysplastic syndrome (MDS). In addition to being refractory to cyclosporine, this patient did not respond to corticosteroids or immunoglobulin. He was successfully treated with a single high dose of cyclophosphamide (4 g/m^2).

The most common and significant adverse effect of cyclosporine therapy is nephrotoxicity. Although reversible acute azotemia can occur, irreversible progressive renal disease may also occur. Because of this significant risk of nephrotoxicity, patients taking cyclosporine must be monitored closely. Other adverse effects include hypertension, often related to renal vasoconstriction, gastrointestinal intolerance, and neurologic complications.

Mycophenolate Mofetil

After adsorption, mycophenolate mofetil is hydrolyzed to its active metabolite, mycophenolic acid, which has potent cytostatic effects on lymphocytes. It inhibits proliferation of T and B lymphocytes, and it suppresses antibody production. This immunosuppressive agent is routinely used with cyclosporine and corticosteroids for the prevention of renal, cardiac, and hepatic allograft rejection. It may also be used to treat psoriasis and proliferative lupus nephritis.

A few case reports suggest efficacy in the treatment of WAIHA. Howard et al.[19] reported treating four adult patients with AIHA with mycophenolate mofetil. All patients had failed previous therapy; two patients had been treated with prednisone, splenectomy, azathioprine, and cyclosporine, and two patients were previously treated with prednisone and cyclosporine. Mycophenolate mofetil was dosed as follows: 500 mg/day increasing to 1 g/day after 2 weeks. All four patients achieved a complete or good partial response to therapy. Kotb and colleagues[20] reported the use of mycophenolate mofetil in the treatment of 13 patients with autoimmune cytopenias, including 3 patients with AIHA and 1 patient with Evans' syndrome. The patients with AIHA were refractory to steroids, immunoglobulin, and cyclophosphamide. The same treatment protocol was used for all patients; an initial dose of mycophenolate mofetil 500 mg/day increasing to 1 to 3 g/day during the course of 1 to 2 weeks, depending on the patient's weight. Once therapeutic goals were reached, other associated treatments were tapered and stopped, followed by tapering of the mycophenolate mofetil. Within 4 to 6 months, all 3 patients with AIHA were independent of RBC transfusion. The patient with Evans' syndrome, who had been refractory to high-dose steroids and immunoglobulin therapy, responded within 6 weeks.

Mycophenolate mofetil has also been used to successfully treat AIHA in the setting of several underlying conditions. Zimmer-Molsberger and colleagues[21] treated two patients who had received 2-chlorodesoxyadenosine for underlying B-cell lymphocytic leukemia. Both patients had previously failed corticosteroid treatment. One patient achieved transfusion independence after mycophenolate mofetil therapy. The other patient had a partial response but was able to decrease his RBC requirement by more than half. In the setting of MDS, Lin et al.[22] reported the successful use of mycophenolate mofetil. The patient had failed corticosteroid therapy alone. Although cyclosporine was tried, it was discontinued owing to neurotoxicity. After starting mycophenolate therapy at 1 g/day with prednisolone (15 mg/day), prednisolone was tapered and stopped within the following 3

weeks. Four weeks after the initiation of mycophenolate mofetil, the patient was transfusion independent. Alba and colleagues[23] described the successful use of mycophenolate in the treatment of two patients with AIHA in the setting of SLE and antiphospholipid syndrome. Both patients were given mycophenolate mofetil (1 to 2 g/day) for the treatment of lupus nephritis, but the authors noted an improvement in hematologic variables temporally associated with the mycophenolate mofetil therapy.

The adverse effects of mycophenolate mofetil tend not to be as severe compared with other immunosuppressive drugs. Some patients may experience gastrointestinal intolerance, and myelosuppression may be associated with this drug.

Cyclophosphamide

Cyclophosphamide is a cytotoxic, alkylating agent that is rapidly absorbed and converted by the liver to its active metabolite. It impairs DNA replication and transcription, ultimately resulting in cell death. All metabolites of the drug are excreted in the urine. The degree of immunosuppression and cytotoxic effects are related to the dose and duration of treatment.

Cyclophosphamide has been used in a variety of dose regimens for the treatment of AIHA. One suggested dosage is 1.5 to 2 mg/kg per day. If the patient is already taking corticosteroids, the steroids should be continued. If there is no hematologic improvement after 4 weeks, the dose can be increased in increments of 25 mg/day every 2 weeks.

Cyclophosphamide was successful in the treatment of a 12-year-old girl with AIHA in the setting of giant cell hepatitis.[24] Although the etiology of giant cell hepatitis has not been entirely elucidated, an immunologic pathogenesis has been proposed. This patient failed conventional dose and high-dose prednisone, azathioprine, and IVIG. After the addition of cyclophosphamide at a dose of 1.5 mg/kg per day to her baseline prednisone and azathioprine, the patient experienced resolution of both hematologic and hepatic variables.

A report by Panceri et al.[25] described a 5-month-old boy who had life-threatening AIHA. This child was refractory to steroids, high-dose immunoglobulin, azathioprine, and splenectomy. The patient required intensive transfusion support, receiving two to three RBC transfusions per day. Because of the severity of the clinical situation, the child was given high-dose methylprednisolone (40 mg/kg per day) followed by high-dose cyclophosphamide (10 mg/kg per day for 10 days). The child experienced striking, sudden improvement, ultimately achieving complete recovery without any major long-term complications.

Ferrara and colleagues[18] described the successful treatment of a 27-year-old man with refractory AIHA in the setting of refractory anemia, a subtype of MDS. The patient had failed the following treatments: high-dose methylprednisolone, high-dose immunoglobulin, and cyclosporine. The patient was treated with a single, high dose of cyclophosphamide (4 g/m^2) followed by daily filgrastim in an effort to mobilize CD34+ cells. On days 12 and 13, apheresis was performed to harvest peripheral stem cells in anticipation of an autologous peripheral stem cell transplant. The patient's hematologic counts recovered, and at 11 months' follow-up, his counts continued to be normal and he did not require a stem cell transplant.

High-dose cyclophosphamide without stem cell rescue was purposefully used by Moyo et al.[26] They report a series of nine patients with severe refractory hemolytic anemia. All patients had failed a median of three prior treatments (range, 1 to 7). Patients received cyclophosphamide 50 mg/kg per day for 4 days followed on day 6 by daily granulocyte colony-stimulating factor (5 μg/kg). This therapy successfully reversed refractory disease, achieving complete remission in six patients and partial remission in three patients of the nine treated. These investigators have subsequently reported successful use of this regimen for the treatment of other refractory autoimmune diseases, including SLE,[27] myasthenia gravis,[28] severe aplastic anemia,[29] and hepatitis-associated aplastic anemia.[30]

The severity of the adverse effects related to cyclophosphamide is dependent on the dose and duration of therapy. The toxicities include bone marrow suppression, increased susceptibility to infection, infertility as a result of gonadal toxicity, risk of malignancy, and bladder toxicities including cystitis and risk of bladder cancer. When high-dose cyclophosphamide is used, it is recommended to also give mesna to prevent hemorrhagic cystitis. High-dose regimens are also associated with nausea, alopecia, and cardiac toxicity.

Danazol

Danazol is a semisynthetic, attenuated androgen that was initially used for the treatment of endometriosis. Subsequently, it was found to be effective in the

treatment of fibrocystic breast disease and hereditary angioedema. Danazol has been helpful in a few cases of WAIHA. Its mechanism of action is uncertain in this clinical setting, although it has been suggested that it is an immunomodulatory drug that may decrease IgG production and reduce RBC-bound IgG and complement.

In the largest report, Ahn[31] described 28 patients with AIHA who were treated with prednisone 20 to 60 mg/day and danazol 600 mg/day. Once the hemolysis stopped, prednisone was tapered and ultimately discontinued. Of the 13 patients with idiopathic AIHA, 77 percent of patients had an excellent or good response. Fifteen of the patients had secondary AIHA caused by an underlying condition, including 12 patients with SLE. Sixty percent of the patients with secondary AIHA had an excellent or good response. The author noted that the side effects of danazol therapy were less than those of the steroids.

Pignon et al.[32] reported on the use of danazol in 17 adults with AIHA. Ten patients were newly diagnosed, and 7 patients were refractory to multiple therapies or had relapsed after initial steroid therapy. Patients were treated with prednisone (1 mg/kg per day) and danazol (600 to 800 mg). Once hemolysis was controlled, the prednisone was tapered or stopped. Long-lasting responses were noted in 80 percent of the newly diagnosed patients and in 60 percent of the previously treated patients. Only minimal side effects occurred.

Chan and Sack[33] reported a successful response to danazol in one patient with SLE and severe AIHA. This patient had been refractory to numerous therapies, including corticosteroids, splenectomy, azathioprine, chlorambucil, and IVIG.

In a series of 16 consecutive patients with SLE and AIHA or Evans' syndrome, danazol was given at an initial dose of 200 mg/day and was increased stepwise to a maximum dose of 1200 mg/day.[34] All 16 patients achieved a complete remission within 2 months after starting danazol. Most patients tolerated the drug well; however, some patients had undesirable side effects including weight gain, dizziness, rash, hepatic adenoma, cholestatic hepatitis, and pseudotumor cerebri.

Adverse effects include androgenic effects such as acne, hair loss, hirsutism, and amenorrhea. More severe effects also may be seen. Hepatic effects of danazol include increased transaminases, cholestatic jaundice, and hepatic adenoma. Changes in lipids may occur with increased risk of atherosclerosis. There is also an increased risk of thromboembolism and thrombotic complications.

Antibody Preparations

Intravenous Immunoglobulin

IVIG is manufactured from the pooled plasma of healthy donors. After a fractionation process, the product consists primarily of concentrated immunoglobulin, largely IgG. It is well established as an effective treatment for immune thrombocytopenic purpura (ITP). Despite its efficacy in a seemingly related disease, IVIG has not been shown to have comparable efficacy in WAIHA. IVIG is recommended for the treatment of AIHA only when patients are refractory or cannot tolerate first-line therapy. In a recent review of the use of IVIG in a large tertiary hospital, a total of 194 patients were treated with IVIG in 2004; only 6 of these patients (3%) were treated for AIHA.[35]

One study reported 37 patients in combination with 36 patients from the literature; all 73 patients had AIHA and were treated with IVIG.[36] Overall, 29 of 73 patients (39.7%) responded to IVIG therapy. The patients who responded were more likely to have hepatomegaly (with and without splenomegaly) and low initial hemoglobin. The authors suggest that IVIG is not optimal as standard therapy for AIHA, but has a role as adjunctive therapy especially for patients with low initial hemoglobin or hepatomegaly, or for those patients who cannot tolerate the toxicities of standard therapy.

A subsequent case report described a man with refractory and life-threatening AIHA in the setting of primary antiphospholipid syndrome.[37] He ultimately responded to a 5-day course of IVIG at a dose of 400 mg/kg per day. At the completion of the initial course of IVIG, hemolysis recurred and failed to respond to subsequent steroids, azathioprine, and cyclosporine. A second course of IVIG was successful in controlling his hemolysis followed by weekly maintenance of 800 mg/kg IVIG.

The adverse effects of IVIG are predominantly related to reactions occurring during infusion. Many of these reactions, which are generally self-limited, can be avoided by using a slower infusion rate. Consequently, it is usually recommended to infuse the initial dose at a slow rate, and, if well tolerated, the rate of infusion can be increased for subsequent doses. Aside from infusion-related adverse effects, the side effects of IVIG therapy are usually well tolerated.

Rituximab

Rituximab is a genetically engineered chimeric murine/human monoclonal anti-CD20 antibody that targets B-cell precursors and mature B cells; plasma cells do not carry the CD20 antigen. Rituximab is approved for the treatment of B-cell non-Hodgkin's lymphoma and B-cell chronic lymphocytic leukemia (CLL). Surprisingly, success of rituximab has not been limited to WAIHA secondary to B-cell neoplasms. The typical dosing regimen of rituximab for the treatment of WAIHA is 375 mg/m^2, weekly for 2 to 4 weeks, with some patients being treated for up to 12 weeks.[38]

Children with idiopathic WAIHA have responded to rituximab therapy. Quartier and colleagues[39] treated five children with refractory idiopathic AIHA and one child with AIHA after bone marrow transplantation. All children were refractory to prednisone and other therapies. The children ranged in age from 7 to 35 months. All patients achieved complete remission and remained in remission with 15 to 22 months' follow-up. Of note, patients experienced prolonged absence of B cells and hypogammaglobulinemia, such that five patients received prophylactic IVIG replacement for 9 to 10 months after completing rituximab therapy.

Zecca et al.[40] prospectively treated 15 children with refractory AIHA. All patients had previously failed two or more immunosuppressive therapies, and two of the children had undergone splenectomy. Four of the patients had underlying clinical conditions, including SLE, RA, vitiligo, and prior bone marrow transplantation. After completion of rituximab therapy, all patients received IVIG for 6 months. With a median follow-up of 13 months, 87 percent of patients (13 of 15) responded; 2 patients did not respond. Of the 13 patients who initially responded, 3 patients relapsed 7 to 10 months after therapy; all 3 patients responded to a second course of rituximab therapy.

Numerous single case reports and small series of adult patients report the successful use of rituximab in the treatment of refractory AIHA. Ahrens and colleagues[41] report a 68-year-old man with refractory disease who had failed previous therapies including steroids, azathioprine, cyclophosphamide, and mycophenolate mofetil. The patient experienced minimal side effects with chills associated with the first infusion. The patient's hemoglobin increased to 12.3 g/dL, and he became asymptomatic.

One of the larger series is reported by D'Arena and coauthors.[42] They report 11 adult patients with idiopathic WAIHA. Their retrospective analysis includes refractory patients who had failed corticosteroids, azathioprine, and high-dose immunoglobulins. At a mean follow-up of 604 days, 8 patients (73%) had achieved complete remission, and 3 patients (27%) had a partial remission. All patients were transfusion independent. The authors support the use of rituximab for steroid-refractory disease.

Shanafelt and colleagues[43] retrospectively reviewed the experience of five patients with AIHA and four patients with Evans' syndrome. Complete response occurred in two of the five patients (40%) with refractory AIHA. One patient with Evans' syndrome had resolution of ITP, and one patient had a complete response in AIHA; none of the patients with Evans' syndrome had resolution of both.

In the setting of CLL, rituximab has been successful in the treatment of AIHA. Narat et al.[44] presented 11 patients with chronic WAIHA refractory to numerous prior therapies. Of the 11 patients, 4 had underlying CLL and 1 patient had Waldenström's macroglobulinemia. Seven of the 11 patients (63.6%) responded to rituximab therapy, with 3 patients in complete remission and 4 patients in partial remission. The authors noted that the median duration of response was 11 months (range, 2.5 to 20 months).

D'Arena and coauthors[45] reported 14 patients with AIHA with underlying CLL. Three patients did not complete the full course of four doses; 2 patients died and 1 HCV-positive patient experienced a rise in amino transferases. An increase in hemoglobin was seen in all but 2 patients after rituximab therapy. Three patients (22%) were considered to have a full response, and 7 patients (50%) had a partial response.

The adverse effects of rituximab include infusion-related reactions, which may be quite severe. Patients may experience fevers, chills, and rigors, and in more severe cases, hypotension and even bronchospasm. The drug is associated with prolonged B-cell depletion, and, consequently, the risk of infection is long-lasting.

Alemtuzumab

Alemtuzumab, or Campath-1H, is a humanized rat IgG1 monoclonal antibody directed against CD52, which binds the cell membrane of lymphocytes, both B cells and T cells. This drug can induce a prolonged lymphopenia leading to extensive and long-lasting immunosuppression. The drug is used in the treatment of CLL, and it has been incorporated into stem cell transplant regimens.

There are far fewer reports on the use of alemtuzumab for the treatment of AIHA, most likely reflecting a relative lack of experience with this drug. Willis and colleagues[46] report 21 patients with refractory autoimmune cytopenias, including 2 patients with WAIHA and 3 patients with Evans' syndrome. Campath-1H was given as a 10-mg daily dose for 10 days. The patients with WAIHA both responded to therapy, one with a complete response and the other with a partial response. Two of the patients with Evans' syndrome responded, but both subsequently relapsed.

In a particularly dramatic case, a 58-year-old man with refractory AIHA failed numerous therapies, including steroids, azathioprine, splenectomy, and even rituximab.[47] This patient successfully responded after a regimen of alemtuzumab of 3 mg on day 1, 10 mg on day 3, and 30 mg on day 5, followed by 30 mg three times per week for 8 weeks. After this regimen, the patient's transfusion requirements decreased dramatically, and the alemtuzumab was gradually tapered. The patient experienced infusion-related chills and reactivation of CMV, requiring ganciclovir treatment.

Several small reports discuss the successful treatment of refractory AIHA in the setting of CLL. Karlsson and colleagues[48] reported five patients with B-cell CLL complicated by AIHA. The patients were transfusion dependent and refractory to previous therapy for AIHA including steroids and, in select patients, immunoglobulins, cyclosporine, cyclophosphamide, and rituximab in two patients. Patients were treated with an initial dose of 3 mg or 10 mg of alemtuzumab administered either subcutaneously or as an intravenous infusion. The doses were gradually increased to 30 mg, given three times per week for 12 weeks. All five patients responded with an increase in hemoglobin of more than 2 g/dL, no longer requiring transfusion support. At the end of treatment, the mean hemoglobin was 11.9 g/dL, and after 12 months' follow-up, the mean hemoglobin was 12.5 mg/dL.

The side effects related to alemtuzumab are predominantly infusion related, including fevers and chills. The most significant adverse effect of the treatment is prolonged lymphopenia and immunosuppression.

Eculizumab

This humanized monoclonal antibody is directed against the terminal complement protein C5. The antibody prevents cleavage of C5 into its proinflammatory components, inhibiting terminal complement activation. The drug has recently been approved for use in patients with paroxysmal nocturnal hemoglobinuria (PNH). In the initial study, 11 patients with PNH were treated with eculizumab using a regimen of 600 mg/week for 4 weeks, followed by 900 mg/week every other week through week 12. This study found eculizumab to be effective in reducing intravascular hemolysis, hemoglobinuria, and the need for transfusion in patients with PNH.[49] In an extension of the initial trial, the authors evaluated the long-term safety and response of eculizumab in the same 11 patients; the drug was found to have continued long-term efficacy and safety.[50] In a subsequent double-blind, multicenter trial, 87 patients were randomized to receive either placebo or eculizumab. This definitive trial confirmed the prior findings, with eculizumab reducing intravascular hemolysis and transfusion requirements with improvement in quality of life for patients with PNH.[51]

Although there are no reports to date in which eculizumab has been used in the treatment of AIHA, one must ask whether this drug would be useful particularly in refractory, life-threatening cases in which intravascular hemolysis is a key feature. In most cases of WAIHA, the hemolytic process is predominantly extravascular. But we have all been haunted by the unusual, troublesome patient who has a significant component of intravascular hemolysis. Perhaps it is in this setting of uncontrollable, refractory, and life-threatening intravascular hemolysis that eculizumab, or another complement inhibitory drug, may play a role in stabilizing the intravascular hemolysis, allowing the time for other therapeutics to be effective.

Conclusion

In an attempt to focus on the pharmacologic treatments of WAIHA, this review deliberately omits the role of transfusion therapy. Appropriate transfusion management is critical in the treatment of patients with life-threatening anemia, particularly those with a brisk hemolytic rate or reticulocytopenia. Transfusions may be needed for initial stabilization and should be anticipated during the patient's clinical course, such that appropriate serologic evaluations can be completed and optimal RBCs can be selected.

The therapeutic options for treating WAIHA are increasing with new immunosuppressive agents, monoclonal antibody preparations, and potentially complement inhibitory drugs. Despite these increasing therapeutic options, recommended initial

treatment remains corticosteroid therapy followed by a second-line approach of splenectomy. Because of the invasive nature of splenectomy and the lifelong risk of overwhelming postsplenectomy sepsis syndrome, in practice many clinicians are currently opting for pharmacologic agents, especially rituximab, as a second-line approach instead of splenectomy. One must be well aware that there are few definitive trials to support the use of these pharmacologic therapies as a second-line approach. The majority of the supportive evidence is based on case reports and small series of patients.

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