*Review Article*

# Rituximab use in warm and cold autoimmune hemolytic anemia

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**Abstract:** Autoimmune hemolytic anemia is a rare condition characterized by destruction of red blood cells with and without involvement of complement.  It is associated with significant morbidity and mortality.   In warm autoimmune hemolytic anemia less than 50% of patients remain in a long-term remission following initial steroid therapy and subsequent therapies are required.  Cold agglutinin disease is a clonal hematologic disorder which requires therapy in majority of patients and responds poorly to steroids and alkylators.   Rituximab has a favorable toxicity profile and has demonstrated efficacy in autoimmune hemolytic anemia in first line as well as relapsed setting.   Rituximab is the preferred therapy for steroid refractory wAIHA and as part of the   first- and second-line treatment of cold agglutinin disease. This article reviews the mechanism of action of the rituximab and current literature its role in management of primary and secondary warm autoimmune hemolytic anemia and cold agglutinin disease.

Keywords: Autoimmune Hemolytic Anemia Treatment; Warm Autoimmune Hemolytic Anemia; Rituximab; Cold Agglutinin Disease

## 1. Introduction

Autoimmune hemolytic anemia (AIHA) is a rare disorder with an estimated incidence of 0.8–3 per $10^5$/year in adults, and prevalence of 17 per 100,000 [1-3].   AIHA can present at any age but it is more common in adults with a peak incidence between 50-70 years [1]. AIHA is characterized by production of antibodies directed against red cell antigens with consequent red blood cell destruction with or without involvement of complement [4].

Autoimmune hemolytic anemia is classified as warm or cold (cold autoimmune hemolytic anemia and paroxysmal cold hemoglobinuria) based on the antibody class and thermal amplitude of the pathogenic antibodies.   Warm autoimmune hemolytic anemia (wAIHA) accounts for 80% of the cases of AIHA in adults [5]. The pathogenic antibody is usually IgG, and direct antiglobulin test (DAT) is positive for presence of IgG and in some cases C3d on the red cell surface, although it can be negative in 5% of cases [4,6].   Destruction of IgG coated red blood cells (RBC) takes place in the spleen via Fcγ receptor mediated phagocytosis by splenic macrophages, ADCC, or complement-mediated hemolysis [7].

In cold AIHA the pathogenic antibody is usually IgM with I antigen specificity. IgM is a cold agglutinin, which fixes complement (C1q) below core body temperature and dissociates from the red cells as they move centrally.  This leads to activation of the classical complement pathway and deposition of C3b on the RBC surface [8].   DAT is positive for C3d.   Complement coated red cells are subject to extravascular hemolysis in via C3b receptors in the hepatic reticuloendothelial system. If large amount of complement is generated, formation of the membrane attack complex leads to in intravascular hemolysis. In some cases of AIHA, both pathogenic IgG antibody and clinically significant cold agglutinin are present.   Those are referred as "mixed" AIHA. Paroxysmal Cold Hemoglobinuria is characterized by a biphasic cold reacting IgG which binds to patient RBCs in the cold, fixes complement and dissociates at body temperature causing hemolysis [9,10].

In approximately 50% cases AIHA is secondary to an underlying collagen vascular disease, lymphoproliferative disorder, infection, solid tumors, or medication, and in the other 50% are idiopathic [11]. Autologous and allogeneic transplant [12-14], and immune checkpoint inhibitor therapy for solid tumors [15,16] are emerging etiologies for AIHA.

Clinical course can be variable and severe with mortality rate of 11% [17]. Degree of anemia depends on antibody characteristics, activity of the reticuloendothelial system, and bone marrow compensatory response [1,18]. Patients can experience acute or chronic hemolytic anemia; hemoglobinuria can be seen with significant complement involvement and intravascular hemolysis. The risk of thrombosis in increased in warm AIHA, particularly during active phase of the disease [17,19], as well as in cold agglutinin disease [20,21]. In cold agglutinin disease, cold induced intravascular agglutination results in circulatory symptoms such as acrocyanosis and/or Raynaud phenomena which occur in 50-90% of the patients [22,23].

## 2. AIHA pathophysiology

Multiple mechanisms are involved in the pathogenesis of AIHA. In warm autoimmune hemolytic anemia, B cell mediated immune dysregulation results in production of pathogenic autoantibodies, cytokines, as well as T cell activation [4, 24]. In addition, T cell dysregulation results in loss of immune tolerance. Decreased levels of regulatory T cells (Tregs), which play a key role in the immunologic self-tolerance, are associated with autoreactivity in AIHA [25,26]. Altered Th1/Th2 balance in favor of Th1 lymphocytes has been demonstrated in patients with autoimmune hemolytic anemia. [27]. Th17 cells, a subset of CD4+ T helper cells which secrete IL-17, have also been implicated in pathogenesis of AIHA and other autoimmune diseases [28]. Increased IL-17 secretion has been shown to be correlated with the disease activity in AIHA patients. [29]. Increased ratio of T follicular helper cells to T follicular regulatory cells, which are essential in the regulation of germinal center reactions and antibody production, were shown to play important role for control and induction of AIHA [30].

Unlike warm autoimmune hemolytic anemia, cold agglutinin disease (CAD) is a clonal hematologic disorder. Primary CAD is a distinct low grade lymphoproliferave disorder [31-33], with discernible histologic [31] and flow cytometric characteristics [32], immunoglobulin heavy and light chain gene features [33], cytogenetic abnormalities [34], and recurrent somatic mutations on next generation sequencing [35]. The pathogenic IgM is monoclonal, with kappa light chain specificity in 85% cases [22,36,37]. Secondary cold agglutinin syndrome associated with B cell lymphoproliferative disorders is less common than primary CAD. In infection associated cAIHA, which is usually transient, IgM is polyclonal [38].

## 3. Rituximab mechanism of action

Rituximab is a chimeric anti-CD20 antibody which consists of human IgG1-kappa constant region and variable regions from the murine monoclonal anti-CD20 antibody [39]. The B-cell antigen CD20 is a transmembrane protein which is present on virtually all B cells from the stage of commitment to B-cell lineage to differentiation into plasma cells, at which point it is downregulated. [40].

Rituximab was initially developed as a therapy for CD20+ lymphoproliferative malignancies. Subsequently, efficacy weas also demonstrated in autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and several hematologic autoimmune diseases such as immune thrombocytopenic purpura (ITP), acquired hemophilia, thrombotic thrombocytopenic purpura, and AIHA [41-45]. In AIHA rituximab demonstrated efficacy in the first line as well as relapsed setting [43,46-52] in primary as well as secondary forms [49,53] of wAHA, cold agglutinin disease, and secondary cold agglutinin syndrome.

Rituximab binding to CD20 on the B cell surface induces B cell apoptosis via direct signaling, activation of complement, and engagement of the cell-mediated cytotoxicity [39,54].   The resultant B cell depletion, which can persist for 6-12 months [40,55], leads to suppression of B-cell mediated production of auto-Abs, cytokine secretion, and their APC function [55]. In addition to B cell depletion, rituximab has an immunomodulatory effect on cellular and innate immunity in autoimmune diseases. In ITP therapy with rituximab has been associated with upregulation of the T reg cells and restoration of Th1/Th2 ratio [57-59].   In nephrotic syndrome Rituximab therapy was associated with decrease in Th17, Th2, and memory T cells, and increased Treg cells [60]. In AIHA clinical response to rituximab therapy was found to be associated with decrease in Th1 cytokines interferon-$\gamma$, interleukin-12, and tumor necrosis factor-$\alpha$, and IL-17, suggesting immunomodulatory activity of rituximab on Th1/Th2 balance [61].

### 4.    Treatment of warm autoimmune hemolytic anemia

Management of wAIHA has been historically empirically derived or based on retrospective studies with paucity of randomized and prospective clinical trials [1,62]. Steroids have been used as a first line therapy with initial response rate of 70-80% [17,50,63].   Up to 20-40% of patients have a durable remission after initial therapy, but the rest have a chronic, relapsing course [2,17,64], requiring subsequent therapy [50].

Splenectomy has been used traditionally as a second line therapy for wAIHA with initial response rates of 60–70% [65-67], and surgical mortality rate of 0.8% in the recent studies [68]. However long-term cure rates are only approximately 20% [2] with associated risk of infections due to encapsulated bacteria of 3.3–5% [69,70]. Thrombotic complications [71] and pulmonary hypertension [72] are also increased in splenectomized patients. More recently Rituximab has emerged as an effective therapy of wAIHA, replacing splenectomy as preferred modality in the second line setting [7, 73-77].

Additional therapeutic options in wAIHA include immunosuppressive agents.   Azathioprine and cyclophosphamide have been used in relapsed setting with overall responses seen in one-third of patients [2,78]. Responses to therapy with other immunosuppressive agents such as cyclosporine and mycophenolate mofetil have been reported as well, although data are limited [2]. Danazol was reported to produce responses both as a single agent and in combination with prednisone [79] in retrospective studies. Administration of erythropoietin has been successfully used in patients with refractory AIHA, particularly in the presence of reticulocytopenia [18].   Several novel agents are currently under investigation including Syk inhibitor Fostamatinib [80], FcRn receptor inhibitors [81,82], and Bruton tyrosine kinase (BTK) inhibitors [83,84]. Figure 1 summarizes current therapeutic algorithm for wAIHA.
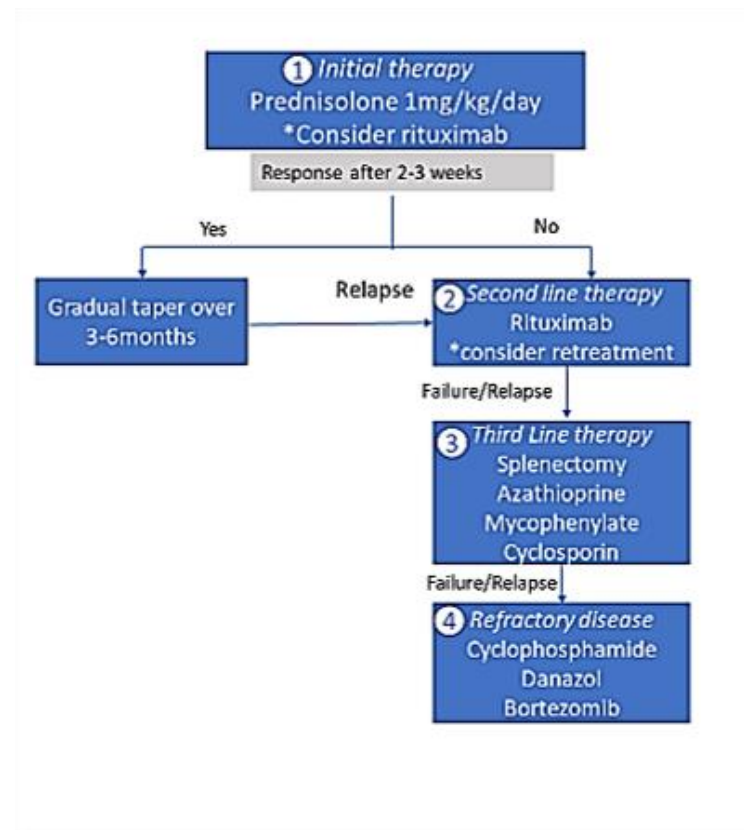
**Figure 1.** Treatment algorithm for warm autoimmune hemolytic anemia.

## 5.    Rituximab in warm autoimmune hemolytic anemia

### 5.1. Relapsed/Refractory wAIHA

In a small prospective pediatric study in 15 children with relapsed/refractory wAIHA, rituximab therapy was associated with an 87% response rate [85].   Several retrospective observational studies reported efficacy of Rituximab in treatment of relapsed/refractory wAIHA.   The largest studies which include primary wAIHA are summarized in Table 1.     Rituximab demonstrated efficacy in patients with both primary and secondary AIHA with overall response rates (ORR) of 70 - 80% in relapsed/refractory setting and a median duration of response of 1 - 2 years.   Median time to response was 4 to 6 weeks after the first rituximab dose, with majority of patients responding within 4 weeks after the first dose [48,86].   Responses within the first week [49] and up to 3 months [86] were also seen.   Complete response (CR) rates were more variable, ranging from 25 to 75%.   Relapse rate at 1 -2 years was 25 - 50% [43,86], with retreatment associated with responses [49,85,86].

A meta-analysis of 21 observational studies that included adults or children with primary or secondary cold and warm AIHA treated with rituximab reported similar results with overall response rate (ORR) of 79% and CR rate of 42% for wAIHA. CR rate was the highest within 2 to 4 months after rituximab initiation. Younger patients, and shorter duration of wAIHA had a better response to Rituximab treatment [87].

**Table 1.** Retrospective trials of Rituximab in relapsed/refractory wAIHA.

| First Author (Year) | Number of patients | Splenectomy (N) | ORR/CR (%) | Duration of response (mo) | Comment |
|---|---|---|---|---|---|
| Narat (2005) | 11 | 5 | 64/27 | 2-20(median 11) | |
| D'Arena (2007) | 11 | 1 | 100/73 | 1-96+ | All primary AIHA, 2 patients received 3 additional monthly doses of maintenance R; additional patient had Rituxan retreatment for ITP |
| Bussone (2009) | 27 | 6 | 93/30 | NR | 5 (18% relapses) after median f/u 20.9 mo, 3 retreated with R and responded |
| Dierickx (2009) | 36 | 10 | 83/50 | 1yr PFS 72% 2yr PFS 56% | |
| Peñalver (2010) | 27 | 13 | 77/61 | Duration of response > 6mo in patients in CR | |
| Maung (2013) | 34 | 3 | 71/27 | 9-60 | 50% relapse; median time to next treatment 16.5mo 28.5% maintained response at 3 years |
| Roumier (2014) | 25 | 2 | 80/NR | 50% relapse after a mean of $14 \pm 8$ | 62% secondary wAIHA |
| Barcellini (2014) | 32 | NR | 81/56 | | Primary AIHA only Low dose R |
| Jaime-Pérez (2019) First-line Relapsed | 18 8 | N/A 7 | 100/83 100/63 | Median 16.5 Mean maintained response $82\pm18$ | Low dose R + High dose Dexamethasone (40 mg/day) for 4 days |

R = Rituximab.

Low dose Rituximab: Rituximab at 100 mg/week for 4 weeks.

*5.2. Rituximab as first line therapy of wAIHA*

Two prospective randomized phase III studies [88,89] evaluated addition of Rituximab to front line therapy with steroids. A Danish open label randomized study compared rituximab with prednisolone with prednisolone monotherapy in 64 newly diagnosed primary wAIHA patients. Conventional lymphoma schedule of 4 weekly intravenous rituximab 375 mg/m2 infusions was utilized.   Addition of rituximab to prednisone resulted in significantly higher response rates at 12 months (75% vs 36%) and improved relapse free survival at 36 months (70% vs 45%) compared to prednisone alone [88].

A more recent randomized double-blind placebo-controlled trial in 32 adults with newly diagnosed primary wAIHA demonstrated similar results with higher efficacy (ORR 75%/34% CR) with Rituximab compared to placebo (ORR 31%/16% CR).   Two infusions of rituximab or placebo at a fixed dose of 1,000 mg were administered 2 weeks apart. Patients in both arms received steroids 1 mg/kg day in the first 2 weeks [89].    Response duration was longer with rituximab compared to placebo with 10/16 patients treated with rituximab compared to 3/16 in the placebo arm remaining in CR at 2 years.

*5.3.Rituximab Combination Therapy*

Rituximab combination therapy with cyclophosphamide and dexamethasone (RCD) in chronic lymphocytic leukemia (CLL)-associated wAIHA demonstrated significant efficacy [90,91].   This combination has also been evaluated in primary wAIHA. Response rate of 97% with CR 42% was reported by Bocian et al. in 19 wAIHA cases (12 primary AIHA and 6 treatment naïve) treated with RCD in the first line and relapsed setting [92].    Similar response rates were seen in 16 relapsed/refractory wAIHA with OR 94% and CR of 69% [93]. Among patients who achieved CRs, majority (64%) had secondary WAIHA.   The median duration of response was 9.8 months.   Two patients required hospitalization for infection.   Taking into consideration single agent rituximab activity in WAIHA, further studies are needed to evaluate the role of RCD in wAIHA therapy.

*5.4. Rituximab in secondary wAIHA*

Most common etiologies for secondary wAIHA include hematological malignancy, infection, immunodeficiency, and autoimmune disorders [50]. A general principle for therapy of secondary wAIHA is if the underlying disorder is clinically active, initial therapy should include treatment of underlying cause [74,77].   If underlying disease is adequately controlled, treatment of secondary wAIHA is generally similar to that of primary wAIHA.

 Rituximab has shown efficacy in relapsed setting in CLL as a single agent [53] and in combination with cyclophosphamide and dexamethasone (RCD) [90,91], cyclophosphamide, vincristine and prednisone (CVP) [94], and with Bendamustine [95] with response rates of 80-100% and response duration of 22–24 months with combination therapy (Table 2).   In AIHA associated with SLE [96] and CVID [97] responses are around 80%, with majority being complete responses.

AIHA associated with non-CLL lymphoproliferative disorders has lower response rate to steroids, higher rates of steroid dependency and higher likelihood to require second line therapy [50,51].   Despite limited data, rituximab containing lymphoma directed regimens are associated with higher probability of response [51]. Similarly, in AIHA associated with transplantation responses to steroids are poor, and front-line rituximab therapy is associated with better outcomes [98,99].

**Table 2.** Rituximab in secondary wAIHA

| Underlying Condition | First Author (Year) | Regimen | Number of patients | ORR/CR (%) | Duration of response (mo) | Line of therapy |
|---|---|---|---|---|---|---|
| CLL | D'Arena (2006) | R 375mg/m2 x 4 | 14 | 72/22 | NR | R/R |
| CLL | Rossignol (2011) | Rituximab, cyclophosphamide, and dexamethasone (RCD) | 26 | 89.5 /81 | 24 | R/R (including R-refractory |
| CLL | Kaufman (2009) | RCD | 20 | 100/85 | 22 | 7 front line, 13 R/R |
| CLL | Bowen (2010) | R-CVP | 17 | 100/82 | 21.7 | R/R (including R-refractory |
| CLL | Quinquenel (2015) | R-Bendamustine | 26 | 81/31 | 28 | 1 front line 25 R/R |
| non-CLL LPD | Hauswirth (2007) | R, R-chemo | 7 | 100/100 | NR | R/R |
| SLE | Serris (2018) | R, R-immunosuppression | 16 | 87.5/75 | RFS 62.5% at 2 years | R/R |
| CVID | Gobert (2011) | R | 5 AIHA 5 AIHA/ITP | 80/80 80/40 | NR | R/R |
| Transplant associated | Farachi (2014) | R, immunosuppression | 7 | 100/100 | NR | 2nd/3rd line |
| Transplant associated First-line R/R | Sanz (2014) | R, immunosuppression | 4 4 | 75/50% 50%/0 | NR | 1st line R/R |

R = Rituximab; R-CVP - Rituximab, cyclophosphamide, vincristine and prednisone, R/R - Relapsed/Refractory.

6.   **Treatment of Cold Agglutinin Disease**

Corticosteroids have limited efficacy in treating CAD with response rates of 14-35% [17,22], and need for high doses to maintain the remission [1,38,100]. Cytototoxic immunosuppressive drugs such as chlorambucil or cyclophosphamide have been tried with limited efficacy with partial responses seen in 16% patients [22;101].   Splenectomy is not effective since clearance of c3b-opsonized red blood cells occurs primarily in the liver [1,22].

Single agent Rituximab as well as Rituximab containing immunochemotherapy have significant activity and are currently recommended as first- and second-line therapy [78,102] in CAD (Figure 2).   Bortezomib has shown promising activity in a small prospective, non-randomized study of 19 patients with CAD.   Responses were seen in 31.6% patients after a single cycle of therapy 31.6%, with 15.8% complete responses [103].

Complement inhibition with antibody directed therapy against C5 with eculizumab [104], C3 with pegcetacoplan [105], and most recently C1s sutimlimab [106], have shown efficacy and are further being explored in clinical trials [107,108]. PI3K kinase inhibitors [109] are in trials as well, and BTK inhibitor ibrutinib has also shown promising results [110]. Figure 2 summarizes current treatment algorithm for cold agglutinin disease.
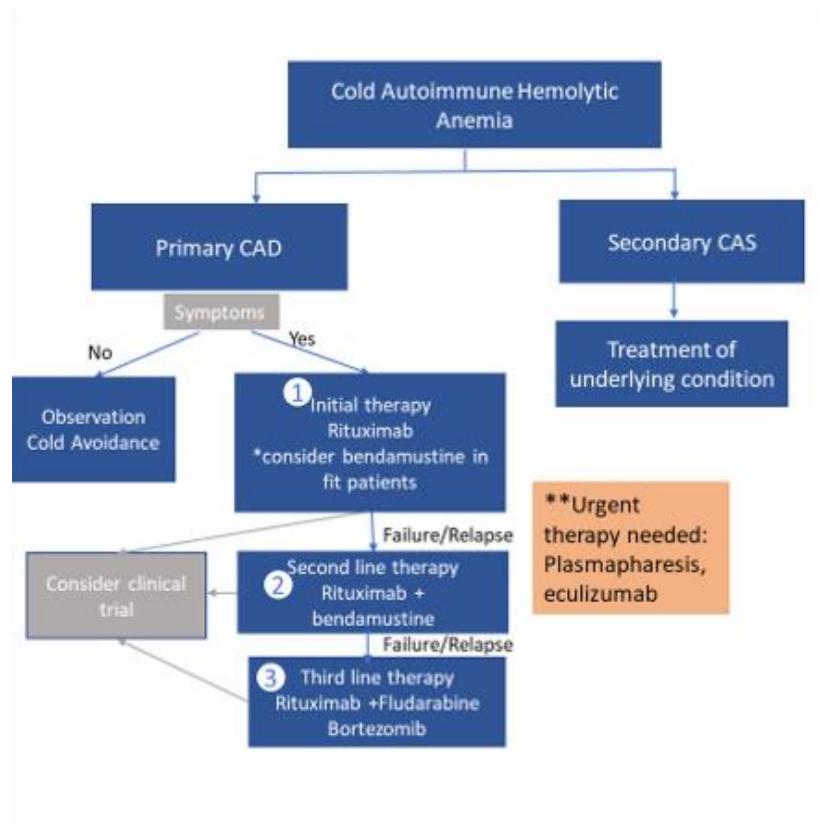


**Figure 2.** Treatment algorithm for cold agglutinin disease.

*6.1. Rituximab in primary CAD*

Several retrospective studies reported efficacy of Rituximab in cold autoimmune hemolytic anemia, including secondary cold agglutinin syndrome and primary cold agglutinin disease with

response rates of 60% [43,49]. In two prospective studies in CAD single agent Rituximab therapy was associated with overall response rate of ~50% [111,112].   Complete responses were rare and median duration of response was short at only 6 - 11 months.

Recognition of presence of an underlying lymphoproliferative disorder in CAD prompted consideration for incorporation of the cytotoxic lymphoma directed therapy in rituximab-based therapy. A Norwegian multicenter trial prospectively evaluated a combination of Rituximab and Fludarabine in 29 patients with CAD.   Four 28-day cycles of oral fludarabine 40 mg/m$^2$ on days 1–5 with standard dose rituximab 375mg/m$^2$ were administered.   Responses were seen in 76% of patients with complete response rate of 21%, including patients previously treated with rituximab. Estimated median response duration was greater than 66 months.   Toxicity was considerable with 41% grade 3-4 hematologic toxicity, 59% G1-3 infections, including recurrent infections, and 10% herpes zoster reactivation [113]. A 10 year update of this study reported OR 62%, CR 38% with median estimated response duration of 77 months [23].   The rate of late onset second malignancies was 31%, which was numerically higher compared all CAD patients and those treated with rituximab/bendamustine combination (13% and 9%, respectively), although it did not reach statistical significance.

A more recent study investigated combination of rituximab with bendamustine in a prospective, nonrandomized multicenter trial of 45 patients with CAD. Rituximab 375 mg/m2 day 1 and bendamustine 90 mg/m2 days 1 and 2 were administered for 4 28-day cycles.   Overall response rate was 71% with 40% complete response.   Responses were observed in 50% of cases previously treated with rituximab or rituximab-fludarabine therapy. Acrocyanosis and Raynaud symptoms resolved completely in 50% of patients and improved in additional 32%.   Grade 3-4 neutropenia was seen in 33% of patients; 11% of patients experienced infections and 29% of patients required hospitalization for a median of 8 days [114].   In a recent update [23] the authors reported higher response rates with ORR 78% and CR of 53%, suggesting that responses deepen over time. This was attributed to the prolonged time to response seen in many patients. In patients responding to rituximab-bendamustine, median response duration was not reached after 88 months, and estimated 5-year sustained remission was 77%.   A combination of rituximab with or without bendamustine is currently recommended in the first line for patients with cold agglutinin disease requiring therapy and in second line therapy [77].

## 7. Rituximab dose

Most studies of rituximab in autoimmune hemolytic anemia utilized conventional dose of 375mg/m2 weekly for 4 weeks used in treatment of lymphoproliferative diseases. Recognition that lymphocyte burden in autoimmune diseases is lower than the tumor mass in lymphoproliferative disorders led to consideration of lower dose rituximab with potential benefit of lower cost and toxicity.   Lower doses of rituximab (100 mg fixed dose) have been studied in various autoimmune settings such as rheumatoid arthritis, vasculitis, thrombotic thrombocytopenic purpura, and immune thrombocytopenic purpura [57,115-117].

In steroid refractory patients with autoimmune cytopenia low dose rituximab in combination with anti-CD52 MoAb alemtuzumab produced responses in 100% of patients with complete response in 58% [118]. In wAIHA, a retrospective analysis of 64 adults reported response rates of 76.7% to steroids alone and 100% to rituximab at 100 mg/wk for 4 weeks in combination with high-dose dexamethasone [52].

A prospective Italian multicenter study of low dose rituximab in warm primary AIHA and CAD demonstrated responses comparable to standard dose rituximab which were sustained. [61,119].   In wAIHA overall response rate was 80-100% with CR of 60-80% at 12 months.   Response rate in CAD was inferior at around 50%, with higher relapse rates. Ten year follow up of this data [120] confirmed the efficacy of lower rituximab in primary AIHA. Overall median duration of response was 1 year and 3 months, with 62% of the patients relapsing. In wAIHA responses deepened overtime,

supporting postulated immunomodulatory effect of rituximab. Relapse-free survival (RFS) was significantly longer in wAIHA compared with other forms (mixed, atypical forms and CAD) at 64 months vs 25 months and correlated with the depth of the response. Responses were seen with retreatment with both conventional dose and low dose rituximab.

## 8. Rituximab Toxicity

Rituximab has been used extensively in hematologic malignancies where has demonstrated a well-established safety profile [121]. Approximately 40% patients experience mild to moderate infusion-related reactions, mostly fever and chills, during the first administration of rituximab [87]. The incidence decreases markedly with subsequent infusions. Rheumatoid arthritis patients receiving rituximab exhibited adverse effect profile similar to patients with lymhoproliferative disorders, but the overall incidence and severity were considerably lower, possibly due to lack of cytokine release associated with lysis of tumor cells. Neutropenia is seen in 2% patients and hypogammaglobinemia is seen occasionally, but infections are not common [122].

Rare cases of serious viral infections such as JC polyomavirus (JCV) reactivation leading to progressive multifocal encephalopathy, hepatitis B reactivation, as well as other infections have been reported [122-126]. Majority (65%) of PML cases are diagnosed in the first 2 years after the first rituximab dose (median time 16 months) and are fatal in 90% [123]. In a recent review of PML cases reported in a FAERS and EudraVigilance databases approximate incidence rate of progressive multifocal encephalopathy (PML) ranged from 1.39 to 1.87 per 10 000 exposed patients [124]. Potential synergies, particularly with the purine analog fludarabine, alkylating agent bendamustine, and hematopoietic stem cell transplantation have been observed, with higher incidence rates of PML in CLL and NHL compared to RA patients.

Association of rituximab therapy with hepatitis B viral reactivation has been first observed in lymphoma patients [125]. In rheumatoid arthritis the incidence of reactivation was reported to be 9.1% among the HBsAg–/anti-HBc+ patients within the mean duration of 25.4 months from the first rituximab [126]. Pre-treatment screening with hepatitis B serologies and prophylactic antiviral therapy for carriers is recommended in patients who are treated with anti-CD20 therapy [77].

A meta-analysis of 21 studies comprising 154 patients with AIHA treated with rituximab reported toxicities in 14% patients. Of those, infusion-related side effects, mostly fever and chills, were seen in for 42%. The remaining 58% were more severe, with 2.6% neutropenias, 12% severe infections and Pneumocystis jiroveci pneumonia in one patient [87]

## 9. Discussion

Rituximab therapy demonstrated significant efficacy in autoimmune hemolytic anemia. In wAIHA, rituximab has an established role in relapsed disease and can be considered in certain cases in the first line setting where prolonged corticosteroid therapy is not desirable. Rituximab has a favorable safety profile with limited treatment duration. Although relapses are common, retreatment with rituximab is generally effective in reestablishing remission. Further studies are needed to evaluate role of potential rituximab maintenance in multiply relapsing patients. Role of low dose rituximab in therapy and potential maintenance of wAIHA should be explored as well. In CAD rituximab-based therapy is effective in the first line as well as relapsed setting. Infectious complications are a concern with chemotherapy-based regimens. Further studies are needed to investigate role of combination of rituximab with novel therapies for a potentially chemotherapy free combinations.

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