A US Retrospective Observational Study of Rituximab Initial and Retreatment in Patients With Warm Autoimmune Hemolytic Anemia

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Key Takeaways

- **Applying the definition of durable hemoglobin response from clinical trials to the outcomes following rituximab treatment allows for more specific characterization**
- **In a real-world setting, the 6-month durable hemoglobin response rate, median time to loss of hemoglobin response, and median time to treatment-based relapse were all greater with the first course of rituximab (65%, 400 days, and 234 days, respectively) compared with the second course (52%, 204 days, and 178 days, respectively)**
- **Six months after the initial dose, patients who received rituximab regimens with <4 infusions within 42 days had lower rates of durable hemoglobin response (49.3%) compared with those who received ≥4 infusions within 42 days (70.7%); however, receiving >4 infusions was associated with more AEs**
- **Together, these results highlight the potential limitations of repeat treatment with rituximab and support the need for novel therapies for wAIHA with a more rapid onset of action**

Background

- Warm autoimmune hemolytic anemia (wAIHA) is the most common form of autoimmune hemolytic anemia (AIHA), accounting for 60% to 70% of cases, and is characterized by autoantibody-mediated red blood cell destruction at body temperature[1-3]
- Oral corticosteroids (OCSs) are typically first-line therapy, although only 30% of patients achieve sustained remission[3-5]
- Many patients require rescue therapy, such as blood transfusions and intravenous (IV) corticosteroids, despite treatment[2,6]
- Rituximab is frequently used as a second-line agent as monotherapy or in combination with OCSs[5]
  - Although treatment with rituximab is often repeated following relapse, real-world evidence regarding outcomes of patients who were retreated with rituximab following relapse remains limited[7,8]
  - The definition of hemoglobin response differs between real-world evidence studies of rituximab and recent clinical trials of other therapies, which limits the ability to assess relative outcomes[7-10]

Objectives

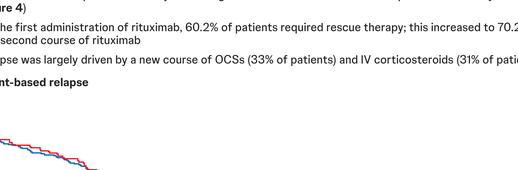
- Describe initial rituximab treatment outcomes
- Evaluate the durable hemoglobin response based on the criteria used in clinical trials[9,10]
- Characterize the occurrence of treatment-based relapse and complications related to rituximab infusion
- Analyze efficacy after the second course of rituximab

Methods

Study Design

- Adults with newly diagnosed wAIHA were identified from electronic health records (OptumPanTher EHR) between 2010 and 2024 (**Figure 1**)
  - Patients with a diagnosis of AIHA (*International Classification of Diseases, Ninth Revision* [ICD-9] code 283.0*; *International Classification of Diseases, Tenth Revision* [ICD-10] code D59.1*); hemoglobin <10 g/dL; direct antiglobulin test that is positive for immunoglobulin G antibodies; and an abnormal measurement of haptoglobin, lactate dehydrogenase, or direct bilirubin were eligible for inclusion. Patients with a diagnosis of cold or mixed-type AIHA or a cold agglutinin titer ≥64 were excluded
  - Patients who were treated with OCSs or nonsteroidal immunosuppressants prior to the initiation of rituximab were included in the analyses
  - Eligible patients were required to have records ≥6 months before and ≥6 months after the diagnosis of wAIHA
- Rituximab regimens were classified as 4 weekly doses within 42 days, 2 to 3 doses within 42 days, a single infusion, or >4 infusions

FIGURE 1: Study design



Assessments

- Durable hemoglobin response was defined as an increase of ≥2 g/dL and an absolute hemoglobin ≥10 g/dL that is sustained for ≥28 days, consistent with definitions used in the fostamatinib (FORWARD; NCT03764618) and nipocalimab (ENERGY; NCT04119050) clinical trials[9,10]
  - Response duration was calculated as the first measurement that met the criteria to the first hemoglobin measurement below the threshold
- Hemoglobin-based loss of response was defined as:
  - Hemoglobin less than the response threshold defined above after attaining durable response
- Treatment-based relapse was defined as any of the following:
  - Second course of rituximab observed (if >90 days since the last course)
  - Initiation of rescue therapy (ie, blood transfusion, erythropoiesis-stimulating agents, IV immunoglobulin, plasma exchange, splenectomy, or IV corticosteroids not administered with rituximab)
  - Splenectomy
  - Initiation of new non-rituximab, nonsteroid therapy for the treatment of wAIHA
  - New steroid course after a 60-day gap
- Known severe rituximab-related adverse events (AEs) were assessed during the follow-up period[11]

Results

Study Population

- Of 503 patients with wAIHA who were treated with rituximab, 403 patients with sufficient hemoglobin measurements were included in the analyses (**Table 1**)
- Median age was 68.0 years, and 55% of patients were female

TABLE 1: Patient characteristics

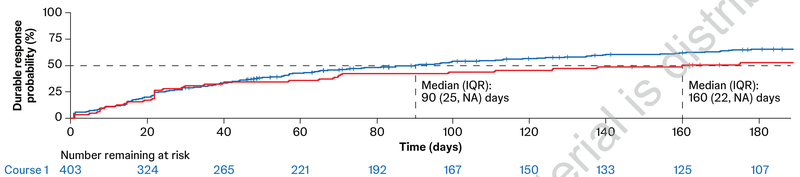
Characteristic	Eligible patients (n = 403)	Patients with repeat rituximab treatment (n = 65)
Median (IQR) age at diagnosis date, years	68.0 (54.0, 76.0)	64.0 (49.0, 77.0)
Female, n (%)	221 (54.8)	41 (63.1)
Calendar year of wAIHA diagnosis, n (%)		
2010-2014	81 (20.1)	20 (30.8)
2015-2019	216 (53.6)	35 (53.8)
2020-2023	106 (26.3)	10 (15.4)
Median (IQR) duration of follow-up, years	3.4 (1.6, 5.7)	3.0 (1.8, 5.0)
Primary wAIHA, n (%)[a]	209 (51.9)	38 (58.5)
Secondary wAIHA, n (%)	194 (48.1)	27 (41.5)
Hematologic malignancy	128 (31.8)	17 (26.2)
Solid tumors	53 (13.2)	6 (9.2)
Immunodeficiency	35 (8.7)	5 (7.7)
Autoimmune disease	46 (11.4)	7 (10.8)
Charlson Comorbidity Index score, n (%)		
0	150 (37.2)	23 (35.4)
1-2	144 (35.7)	29 (44.6)
≥3	109 (27.0)	13 (20.0)
Median (IQR) weight at index treatment, kg	80.8 (69.4, 97.4)	82.6 (63.6, 94.5)
Median (IQR) hemoglobin, g/dL	6.45 (5.40, 7.50)	7.00 (6.09, 8.19)
Anemia severity, n (%)		
Moderate (hemoglobin 8-9.9 g/dL)	80 (19.9)	20 (30.8)
Severe (hemoglobin 6.5-7.9 g/dL)	115 (28.5)	19 (29.2)
Very severe (hemoglobin <6.5 g/dL)	208 (51.6)	26 (40.0)
Median (IQR) LDH, units/L	478 (331, 724)	350 (285, 647)
Median (IQR) haptoglobin, mg/dL	10.0 (8.0, 30.0)	10.0 (8.0, 53.5)
Median (IQR) indirect bilirubin, mg/dL	2.25 (1.30, 3.93)	2.35 (1.08, 3.95)

[a]Primary wAIHA was defined as patients with the absence of a related underlying condition shown in this table under "Secondary wAIHA." **IQR**=interquartile range, **LDH**=lactate dehydrogenase, **wAIHA**=warm autoimmune hemolytic anemia.

Response and Relapse

- Within 6 months of the first course of rituximab, 65% of patients achieved a durable response, with a median time to response of 90 days (**Figure 2**)
  - Among the 65 patients who received a second course of rituximab, the durable response rate decreased to 52%, with a longer median time to response of 160 days

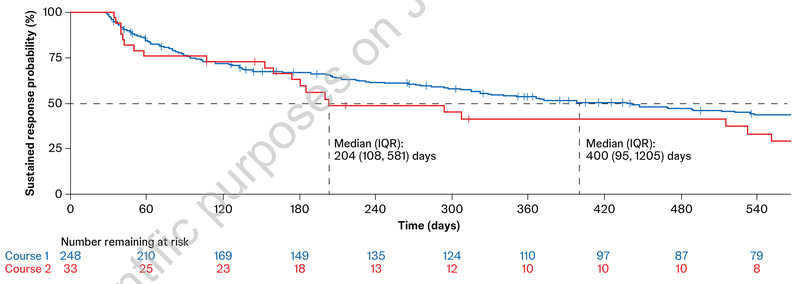
FIGURE 2: Time to durable hemoglobin response



IQR=interquartile range, **NA**=not available.

- The median time to hemoglobin-based loss of response was approximately 200 days shorter following a second versus first course of rituximab (**Figure 3**)
  - Loss of response occurred in 33.8% of patients within 6 months and in 47.2% (cumulative) within 12 months following the first course of rituximab, while it occurred in 44.3% and 62.9% (cumulative) of patients within 6 and 12 months following a second course of rituximab, respectively

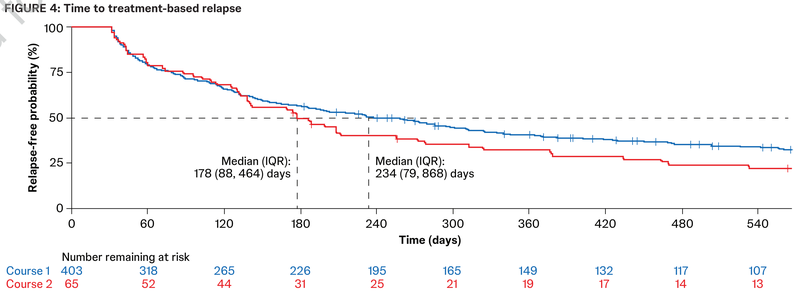
FIGURE 3: Time of loss of durable hemoglobin response



IQR=interquartile range.

- The median time to treatment-based relapse was 234 days following the first course of rituximab compared with 178 days following the second course of rituximab (**Figure 4**)
  - Within 12 months of the first administration of rituximab, 60.2% of patients required rescue therapy; this increased to 70.2% within 12 months after the start of the second course of rituximab
  - Treatment-based relapse was largely driven by a new course of OCSs (33% of patients) and IV corticosteroids (31% of patients)

FIGURE 4: Time to treatment-based relapse



IQR=interquartile range.

- Overall, only 40.9% of patients received 4 infusions of rituximab within 42 days (the most commonly employed regimen); 16.1% received only a single infusion
  - Regardless of the regimen, durable hemoglobin response at 6 months was higher for patients who received ≥4 infusions within 42 days compared with those who did not (**Table 2**)

TABLE 2: Achievement of a durable hemoglobin response by rituximab treatment regimen

	Regimens with ≥4 infusions			Regimens with <4 infusions		
	4 infusions[a] (n = 165)	>4 infusions[b] (n = 103)	Total: ≥4 infusions (n = 268)	2-3 infusions[a] (n = 53)	Single infusion (n = 65)	Total: <4 infusions (n = 118)
Percentage of population	40.9	25.6		13.2	16.1	
Months from initial administration, %						
1	33.9	31.1	32.8	24.5	17.0	20.4
2	49.1	54.4	51.1	32.2	17.0	23.8
3	57.1	62.5	59.2	38.3	27.8	32.5
4	62.1	68.9	64.7	49.1	31.5	39.4
5	65.2	71.1	67.5	51.3	35.6	42.7
6	68.3	74.6	70.7	56.0	43.9	49.3

[a]Within 42 days. [b]Without a gap of >90 days between doses.

AEs

- Regardless of the dosing schedule, more than 20% of patients experienced an AE following rituximab treatment, most commonly infections, with the highest percentage of AEs among the 103 patients who received >4 infusions (36.9%; **Table 3**)
  - This increased frequency was driven by a greater incidence of cardiovascular AEs and bowel obstruction or perforation
- The median time from rituximab initiation to first AE was 60 days in patients who received >4 infusions compared with 32 days for patients who received 4 infusions and 13 days for those who received a single infusion (**Table 3**)

TABLE 3: First observed AEs following rituximab initiation by treatment regimen

	Regimens with ≥4 infusions			Regimens with <4 infusions		
	4 infusions[a] (n = 165)	>4 infusions[b] (n = 103)	Total: ≥4 infusions (n = 268)	2-3 infusions[a] (n = 53)	Single infusion (n = 65)	Total: <4 infusions (n = 118)
Any AE, n (%)	33 (20.0)	38 (36.9)	71 (26.5)	15 (28.3)	15 (23.1)	30 (25.4)
Death	2 (1.2)	0	2 (0.7)	0	0	0
Infection	13 (7.9)	14 (13.6)	27 (10.1)	8 (15.1)	7 (10.8)	15 (12.7)
Cardiovascular	7 (4.2)	10 (9.7)	17 (6.3)	2 (3.8)	4 (6.2)	6 (5.1)
Bowel obstruction and perforation	7 (4.2)	9 (8.7)	16 (6.0)	2 (3.8)	2 (3.1)	4 (3.4)
Infusion reactions	2 (1.2)	4 (3.9)	6 (2.2)	3 (5.7)	0	3 (2.5)
Tumor lysis syndrome	2 (1.2)	1 (1.0)	3 (1.1)	0	2 (3.1)	2 (1.7)
Median (IQR) time from initiation to first AE, days	32 (9, 48)	60 (14, 153)	39 (12, 86)	22 (8, 54)	13 (9, 71)	18 (4, 47)

[a]Within 42 days. [b]Without a gap of >90 days between doses. **AE**=adverse event, **IQR**=interquartile range.

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