First-Line Therapy in Warm Autoimmune Haemolytic Anaemia: Real-world Outcomes with Oral Corticosteroids Alone or Combined with Rituximab

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Key Takeaways

- **This study provides an overview of 1L wAIHA treatment patterns and outcomes in Swedish patients.**
- **OCS was the mainstay of 1L therapy, but almost one third of patients received OCS+RTX.**
- **Regardless of treatment received, many patients failed 1L therapy (non-response or relapse) and required rescue therapy, indicating inadequate disease control and persistent anaemia with current treatment options.**
- **The results of this Swedish study suggest an ongoing need for additional treatment options to achieve sustained and durable control of primary and secondary wAIHA.**

Background

Autoimmune Haemolytic Anaemia (AIHA) is caused by autoantibodies attacking red blood cells leading to haemolysis.[1,2] Warm AIHA (wAIHA) is the most common subtype of AIHA (60–70% of cases).[1]

wAIHA can develop as a primary disease or secondary to other conditions, creating a heterogeneous patient population with variable disease course, treatment response, and clinical outcomes.[2,3]

Current international consensus recommend oral corticosteroids (OCS) alone as first-line (1L) therapy and reserve rituximab (RTX) for severe cases.[1]

However, real-world evidence on contemporary first-line treatment patterns and associated outcomes with OCS alone versus OCS combined with RTX remains limited in Sweden.

Objectives

To describe current 1L treatment patterns and outcomes among patients diagnosed with wAIHA in Sweden who initiated OCS or OCS+RTX.

Methods

Data Sources (data linkage using Personal Identification Numbers)

- Multiple nationwide healthcare registries, including the Patient Registry, the Prescribed Drug Registry, and the Cause of Death Registry.
- Electronic medical records (EMR) and lab information systems (LIS) at Karolinska University Hospital, St. Göran's Hospital, and Uppsala University Hospital.

Study Population

- **Inclusion criteria:** (i) ≥18 years diagnosed with wAIHA at three Swedish hospitals; (ii) ICD-10-SE codes D59.1, D59.1B, or D59.1X recorded between 1 July 2006 and 30 June 2023; (iii) Positive Direct Antiglobulin Test for IgG (negative for IgM and C3d only) within ±3 months of diagnosis; (iv) Haemoglobin (Hgb) <100 g/L at diagnosis; (v) Evidence of ongoing haemolysis within ±14 days of diagnosis, defined as increased LDH and/or decreased haptoglobin and/or increased bilirubin.
- **Exclusion criteria:** (i) Patients with Evans syndrome; (ii) less than 12 months of baseline observation due to, or incomplete electronic medical record/laboratory data.
- Classification as primary or secondary disease based on records of associated underlying diseases (defined as secondary if ≥1 diagnosis of haematologic malignancies, autoimmune diseases, primary immunodeficiencies, chronic viral infections, or transplantations within ±180 days of wAIHA diagnosis).

Study Outcomes (derived from linked register and EMR/LIS data)

- **Patient Characteristics:** Sex, age at diagnosis, underlying conditions, lab characteristics
- **Treatment Patterns**: Treatment regimen and duration.
  - First-line treatment (1L) was defined as the first wAIHA-related therapy initiated after diagnosis; if multiple drugs were initiated within 30 days of each other they were considered combination therapy.
- **Clinical Outcomes**: Response, relapse, and need for rescue therapy
  - Partial Response: Hgb ≥100 g/L and an increase of ≥20 g/L from baseline Hgb, without recent rescue therapy (no transfusion, plasmapheresis, injectable corticosteroids, intravenous immunoglobulin or erythropoiesis-stimulating agent in preceding 1-2 weeks depending on type).[4,5]
  - Complete Response: Hgb ≥120 g/L and normalized haemolytic markers (lactate dehydrogenase, haptoglobin and bilirubin), without recent rescue therapy.[4,5]
  - Relapse: Hgb <100 g/L or a drop of ≥ 20 g/L from the highest achieved Hgb after response.[4]
  - Relapse-free survival (RFS): Time from first response to relapse or death.
- Follow-up until treatment switch, death, hospital transfer, emigration or 30 June 2023; Outcomes were captured during both on- and off-treatment periods.
- Outcomes were compared between patients initiating 1L OCS and those on 1L OCS+RTX (concurrent use of other immunosuppressive therapies [IST] was allowed).
- **Statistical Analyses:** T-tests (means); Wilcoxon rank-sum tests (medians); categorical variables: chi-square tests or Fisher's exact tests (any cell <5); log-rank tests and Cox regression (time-to-event data).

Results

Patients initiating 1L OCS and those initiating 1L OCS+RTX displayed no major differences in their patient characteristics at diagnosis (Table 1).

- Of 137 patients diagnosed with wAIHA during 2006-2023, 130 initiated 1L treatment (OCS: 92; OCS+RTX: 38), 3 received no 1L treatment, and 4 received other 1L regimens.
- 1L outcomes could be reliably captured due to median observation time of 3.2 years (IQR: 0.8-5.8).
- Patients receiving OCS+RTX had a higher median age at diagnosis and slightly lower baseline Hgb than patients on OCS monotherapy. However, neither of these differences was statistically significant.
- Among patients with secondary wAIHA, haematological malignancies were the most common underlying diseases in both groups, but more frequent with OCS+RTX (87.5% vs 62.2%; *p*=0.03). Autoimmune / connective tissue diseases were the second most common underlying diseases (16.7% in OCS+RTX vs 35.1% in OCS, p=0.12). Other underlying conditions were rarely observed.

OCS remain the mainstay of 1L wAIHA treatment, but OCS+RTX was used in a notable subset of both patients with primary and secondary wAIHA (Table 2).

- Among patients with primary wAIHA, 55 (80%) received OCS, while 14 (20)% received OCS+RTX.
- Among patients with secondary wAIHA, 37 (61%) received OCS, while 14 (39%) received OCS+RTX; the higher proportion of patients receiving OCS+RTX combination therapy likely reflects the need to also treat their underlying conditions.
- Median 1L duration ranged from 5.9-6.9 months, indicating that many patients require long-term treatment.

Current 1L outcomes remain suboptimal with high non-response and relapse rates, as well as a frequent need for rescue therapy. (Table 2, Figure 1).

- Over the follow-up (median outcome assessment period: 0.8 years), non-response rates to 1L therapy were 13% (OCS) and 23% (OCS+RTX) in primary wAIHA, and 24% and 25% in secondary wAIHA, respectively.
- Even though overall response rates were not higher among patients on OCS+RTX, their complete response rates were higher. However, even in the OCS+RTX group, 46.2% (primary wAIHA) and 62.5% (secondary wAIHA) did not achieve complete response after 1L therapy.
- Relapse after 1L treatment was common in both primary and secondary wAIHA. Among responders with primary wAIHA, OCS+RTX was associated with lower relapse rates and longer RFS (2-year RFS rates: 67.5% for OCS+RTX [n=10] vs 35.5% for OCS [n=47]). Relapse rates and RFS did not differ significany between groups in secondary wAIHA.
- Rescue therapy was required by 28-63% of patients, depending on wAIHA subtype and 1L regimen received. This indicates insufficient treatment effectiveness resulting in persistent haemolysis and/or anaemia with current treatment options.

TABLE 1. Clinical and laboratory patient characteristics at wAIHA diagnosis

	Primary wAIHA			Secondary wAIHA		
	1L OCS[c] (n=55)	1L OCS+RTX[c] (n=14)	*p*-value	1L OCS[c] (n=37)	1L OCS+RTX[c] (n=24)	*p*-value
Sex, %			0.86			0.39
Male	45.5	42.9		51.4	62.5	
Female	54.5	57.1		48.6	37.5	
Median age at diagnosis (IQR), years	64 (49-78)	74 (66-80)	0.20	70 (52-78)	75 (69.5-80)	0.10
Direct Antiglobulin Test Pattern[a], %			0.05			0.62
IgG only	63.6	78.6		29.7	25.0	
IgG + C3d	>31.0[d]	<21.4[d]		64.9	75.0	
IgG + IgA	<5.4[d]	<21.4[d]		0	0	
IgG + C3d + IgA	0	0		<8.1[d]	0	
Severity of anaemia at diagnosis,%			0.07			0.67
Moderate (Hgb 70-100 g/L)	74.5	50.0		75.7	70.8	
Severe (Hgb <70 g/L)	25.5	50.0		24.3	29.2	
Median haemoglobin (IQR), g/L	80 (69-91)	72 (68-85)	0.08	79 (71-89)	75 (65.5-81.5)	0.26
Median haptoglobin (IQR), g/L	0.1 (0.1-0.1)	0.1 (0.1-0.1)	0.62	0.1 (0.1-0.1)	0.1 (0.1-0.1)	0.98
Median LDH (IQR), ukat/L	7.2 (4.8-9.3)	6.0 (5.4-8.1)	0.26	5.7 (4.8-7.5)	6.5 (5.7-7.6)	0.25
Median total bilirubin (IQR), umol/L	40 (23-59)	42 (27-149)	0.84	28 (17-44)	28 (20.5-38.5)	0.91
Median observation years[b] (IQR)	3.6 (1.2-5.9)	5.7 (2.6-7.1)	0.51	2.6 (0.8-4.9)	2.9 (0.7-4.6)	0.92

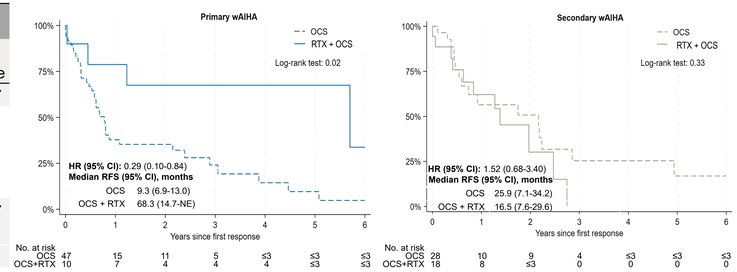
Abbreviations: LDH, Lactate Dehydrogenase; IQR: Interquartile Range; OCS, Oral Corticosteroid; RTX, Rituximab; IST, immunosuppressive therapies.
[a] Direct Antiglobulin Test Pattern positivity and Hgb <100 g/L were inclusion criteria; [b] Time from wAIHA diagnosis to death, hospital transfer, emigration or end of study period (June 30, 2023); [c] Concomitant IST was included in 6% of treatment lines among primary wAIHA patients; and in ≤8% of OCS treatment lines and 29% of OCS+RTX treatment lines in secondary wAIHA. [d] Results were masked to protect patient privacy due to cell counts below three or risk of back-calculation.

TABLE 2. Treatment pattern and clinical outcomes over the follow-up

	Primary wAIHA			Secondary wAIHA		
	1L OCS (n=55)	1L OCS+RTX (n=14)	*p*-value	1L OCS (n=37)	1L OCS+RTX (n=24)	*p*-value
Median treatment duration in months (95% CI)	5.9 (4.9-7.8)	6.3 (3.1-9.7)	0.94	6.9 (4.2-9.1)	5.9 (4.0-8.0)	0.07
Number of RTX administrations, %						
<4 administrations	-	35.7	-	-	33.3	-
4 administrations	-	57.1	-	-	29.2	-
>4 administrations	-	7.1	-	-	37.5	-
Overall response[a], % (95% CI)	87.1 (76.2-94.0)	76.9 (50.3-93.0)	0.17	75.6 (60.3-87.2)	75.0 (55.5-88.8)	0.77
Complete response	35.2 (21.7-51.5)	53.8 (25.1-80.3)		29.7 (15.5-49.4)	37.5 (18.5-61.3)	
Partial response	51.9 (36.2-67.2)	23.1 (6.6-56.0)		45.9 (28.2-64.7)	37.5 (18.5-61.3)	
Relapse[b], % (95% CI)	66.0 (51.8-78.2)	30.0 (9.3-60.6)	**0.04**	50.0 (32.2-67.8)	61.1 (38.3-80.6)	0.46
Any rescue therapy, % (95% CI)	32.7 (21.5-45.8)	28.6 (10.5-54.5)	0.77	37.8 (23.6-53.9)	62.5 (42.6-79.6)	0.06

[a] Analysis restricted to s with baseline and post-baseline Hgb assessment: primary wAIHA: OCS (n=54), OCS+RTX (n=13); secondary wAIHA: OCS (n=37), OCS+RTX (n=24). Median outcome assessment period for response from from 1L initiation until next treatment line, death, hospital transfer, emigration or June 2023, was 0.8 years (IQR: 0.2-2.5); [b] Analysis was restricted to s reaching at least partial response: primary wAIHA: OCS (n=47), OCS+RTX (n=10); secondary wAIHA: OCS (n=28), OCS+RTX (n=18).

FIGURE 1. Relapse-free survival by treatment groups



Note: Analysis restricted to s reaching at least partial response. OCS used as reference for hazard ratio (HR).

Limitations

- **Unreported treatment indication:** Data sources used for this study lack recorded treatment indication, making it unclear whether therapies were initiated for wAIHA or other conditions.
- **Non-standardized outcome assessment:** As laboratory testing used to define the clinical outcomes (response & relapse) was driven by routine clinical practice rather than a pre-specified schedule, response and relapse status were only observable at recorded visits. Consequeny, potential achievement or loss of response occurring between visits could not be assessed.
- **Limited outcome scope:** Outcomes assessed as part of this study do not encompass all patient-relevant outcomes; e.g., hospitalizations and adverse events related to broad immunosuppression are not captured.
- **Small sample size:** Small sample size per treatment group and sparse outcome counts precluded robust multivariable adjustment for confounders; it also limits generalisability to other regions/countries.

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