Sutimlimab After Prior Rituximab Use in Patients with Cold Agglutinin Disease (CAD): Pooled Post-hoc Analyses from the CARDINAL and CADENZA Trials

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INTRODUCTION

- Cold agglutinin disease (CAD) is a serious, rare, autoimmune hemolytic anemia (AIHA), characterized by the autoantibody-mediated destruction of erythrocytes, and mediated by activation of the classical complement pathway.[1–4]
- Patients with CAD experience a variety of physical and mental manifestations, including fatigue, acrocyanosis, dyspnea, hemoglobinuria, weakness, and weight loss[5]
- Sutimlimab is a humanized monoclonal anti-C1s antibody approved for the treatment of adults with CAD in the United States, following the results of the Phase 3 CARDINAL (NCT03347396) trial.[6]
- Prior to the approval of sutimlimab, off-label rituximab was the best-documented first-line therapy for CAD.[7,8]

OBJECTIVE

- This post-hoc analysis aimed to describe the characteristics of patients with CAD who received prior off-label rituximab treatment versus rituximab-naïve patients and present the efficacy of sutimlimab in these subgroups, using pooled data from the Phase 3 CARDINAL and CADENZA (NCT03347422) trials.

METHODS

Study design

- CARDINAL was an open-label, single-arm, multicenter (North America, Europe, Japan, and Australia) study for patients with CAD with a recent blood transfusion
  - Patients received intravenous infusions of sutimlimab for 6 months.
- CADENZA was a randomized, double-blind, placebo-controlled, multicenter (North America, Europe, Israel, Japan, and Australia) study in patients with CAD without a recent blood transfusion.
  - Patients were randomized 1:1 to receive either intravenous infusions of sutimlimab or placebo for 6 months.
- Data from the first 6 months of the CARDINAL and CADENZA trials (Part A) were included in this analysis.
  - Only patients treated with sutimlimab in the CADENZA trial were included in these analyses.

Eligibility criteria

- Included patients were ≥18 years of age, with a confirmed diagnosis of CAD, and had a hemoglobin level of ≤10 g/dL.
  - In CARDINAL, patients with ≥1 documented blood transfusion within the 6 months prior to enrollment were included.
  - In CADENZA, patients had no blood transfusions within the 6 months prior to enrollment, and ≤1 in the 6 months prior to that.
- Patients were excluded if they received rituximab monotherapy within 3 months, or combination therapy (e.g., with bendamustine, fludarabine, ibrutinib, or cytotoxic drugs) within 6 months, prior to the start of sutimlimab treatment.

Study endpoints

- Endpoints were analyzed descriptively according to prior rituximab use, including previous monotherapy, combination therapy, or both.

Primary endpoint

- For this analysis, the composite efficacy endpoint was response, defined as follows. Patients:
  - Received no blood transfusions or prohibited medications from Week 5 to 26
    and
  - Had an improvement in hemoglobin from baseline of ≥2.0 g/dL (the most stringent criterion between both trials was chosen for this post-hoc analysis) **or**
    Had a hemoglobin level of ≥12.0 g/dL in CARDINAL, at the treatment assessment timepoint (TAT), which was an average of Weeks 23, 25, and 26.

Secondary endpoints

- Secondary endpoints included mean change from baseline to TAT in hemoglobin, bilirubin, lactate dehydrogenase (LDH), and the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) score.

RESULTS

Study participants

- Overall, 46 patients receiving sutimlimab were included in this analysis (CARDINAL, n=24; CADENZA, n=22).
  - At baseline, 54.3% of patients had prior rituximab use (n=25) and 45.7% were rituximab-naïve (n=21).
- Baseline demographics were similar between subgroups; mean (SD) age was 67.8 (9.7) for patients with prior rituximab and 69.2 (10.4) years for rituximab-naïve patients (**Table 1**).
- Mean (SD) time between last rituximab intake and sutimlimab treatment start date was 26.4 (24.0) months.

Baseline clinical and laboratory characteristics

- At baseline, levels of hemoglobin, bilirubin, and LDH, and the FACIT-Fatigue score were similar between subgroups (**Table 1**).
  - In CADENZA, immunoglobulin M (IgM) level and cold hemagglutinin titer were greater in the rituximab-naïve subgroup compared with prior use; however, subgroups were not compared statistically.
- Accounting for differences in blood transfusion inclusion criteria between CARDINAL and CADENZA, in both trials at baseline there were a greater number of blood transfusions in patients with prior rituximab versus without (**Table 1**).
  - In the CARDINAL trial, mean (SD) number of transfusions per patient within 1 year prior to enrollment was 6.0 (7.5) for patients with prior rituximab use versus 3.4 (4.1) without.
  - In CADENZA, the number of patients with one blood transfusion within 1 year prior to enrollment was greater for patients with prior rituximab use (n=3), compared with without (n=0).
- Mean (SD) CAD disease duration was longer for patients with (9.4 [8.2] years) versus without (4.9 [5.0] years) prior rituximab use (**Table 1**).
- In CARDINAL, prior CAD-related hospitalizations were greater in prior rituximab users (84.6%) versus those without (45.5%).

Medical history and prior corticosteroid use

- A greater proportion of patients in with prior rituximab use had a vascular disorder history (28.0%; n=7), compared with those without (19.1%; n=4) (**Table 1**).
- Two patients (8.0%) in the prior rituximab group had thromboembolic events within the last year, versus 0 patients (0.0%) without (**Table 1**).
- Intravenous corticosteroid use was greater in patients with prior rituximab use (52.0%; n=13) versus those without (23.8%; n=5) (**Table 1**).
- Mean (SD) time in months from last rituximab intake to sutimlimab start date was 23.94 (20.65) months for patients in the CARDINAL trial (n=12), and 29.05 (27.89) months for patients in the CADENZA trial (n=11), despite the lower cold agglutinin titer and IgM level in patients in CARDINAL compared with CADENZA (**Table 1**).

RESULTS

Table 1. Baseline demographics and clinical characteristics for patients with CAD receiving sutimlimab according to prior off-label rituximab use

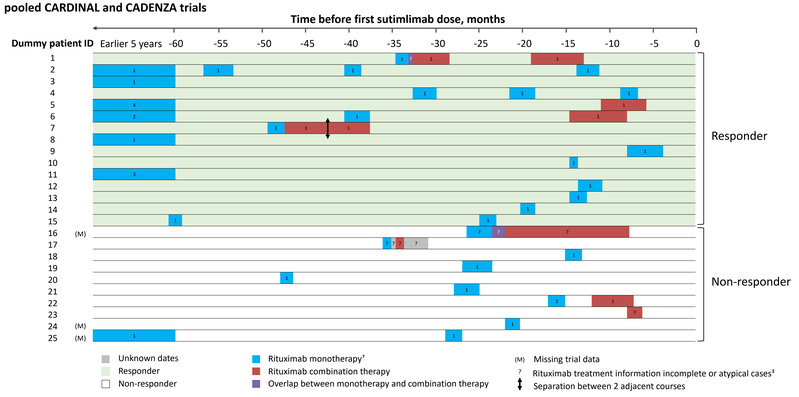
Characteristic	CARDINAL (N=24)		CADENZA[a] (N=22)		Pooled data (N=46)	
	Prior rituximab (n=13)	No prior rituximab (n=11)	Prior rituximab (n=12)	No prior rituximab (n=10)	Prior rituximab (n=25)	No prior rituximab (n=21)
Demographics						
Mean age (SD), years	70.8 (9.1)	71.8 (7.4)	64.5 (9.6)	66.3 (12.7)	67.8 (9.7)	69.2 (10.4)
Female, n (%)	7 (53.8)	8 (72.7)	10 (83.3)	7 (70.0)	17 (68.0)	15 (71.4)
Geographic location, n (%)						
Europe	11 (84.6)	6 (54.5)	10 (83.3)	5 (50.0)	21 (84.0)	11 (52.4)
North America	2 (15.4)	1 (9.1)	2 (16.7)	1 (10.0)	4 (16.0)	2 (9.5)
Asia (Japan)	0 (0.0)	3 (27.3)	0 (0.0)	3 (30.0)	0 (0.0)	6 (28.6)
Other (Australia & Israel)	0 (0.0)	1 (9.1)	0 (0.0)	1 (10.0)	0 (0.0)	2 (9.5)
Medical history						
CAD disease duration						
Mean (SD) years	11.1 (8.4)	5.3 (4.4)	7.6 (8.0)	4.4 (5.8)	9.4 (8.2)	4.9 (5.0)
Median [range] years	10 [0–33]	5.0 [0–14]	4 [1–23]	2.0 [0–16]	7 [0–33]	4 [0–16]
Any hospitalizations related to CAD[b], n (%)	11 (84.6)	5 (45.5)	1 (8.3)	1 (10.0)	12 (48.0)	6 (28.6)
Number of blood transfusions per patient within one year prior to enrollment[c], mean (SD)	6.0 (7.5)	3.4 (4.1)	N/A	N/A	N/A	N/A
Number of patients with 1 blood transfusion within one year prior to enrollment[d], n (%)	N/A	N/A	3 (25)	0 (0)	N/A	N/A
Patients with prior thromboembolic history within the last year[e], n (%)	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.0)	0 (0.0)
Patients with vascular disorders, n (%)	2 (15.4)	0 (0.0)	5 (42.7)[f]	4 (40.0)[g]	7 (28.0)	4 (19.1)
Medication use						
Any corticosteroid use (intravenous), n (%)	6 (46.2)	2 (18.2)	7 (58.3)	3 (30.0)	13 (52.0)	5 (23.8)
Use of anti-anemic preparations, n (%)	8 (61.5)	6 (54.5)	9 (75.0)	6 (60.0)	17 (68.0)	12 (57.1)
Time from last rituximab intake to treatment start, mean (SD) months [n]	-23.94 (20.65) [12]	N/A	-29.05 (27.89) [11]	N/A	-26.38 (23.95) [23]	N/A
Laboratory measures, mean (SD)						
Hemoglobin (g/dL)	8.5 (1.5)	8.7 (1.9)	9.6 (1.0)	8.6 (0.9)	9.0 (1.3)	8.7 (1.4)
Bilirubin (µmol/L)	55.8 (28.5)	45.2 (14.8)	38.6 (14.6)	43.8 (36.1)	47.5 (24.1)	44.5 (26.4)
LDH (U/L)	516.2 (328.8)	345.8 (198.1)	384.3 (187.6)	466.1 (203.4)	452.9 (273.3)	403.1 (205.0)
Immunoglobulin M, (g/L)	3.5 (3.7)	3.8 (2.1)	2.3 (1.6)	9.9 (10.1)	2.9 (2.9)	6.7 (7.6)
Cold hemagglutinins (titer), in 1,000s	548.2 (1525.5)	540.2 (1571.9)	16.3 (49.0)	649.1 (1088.2)	293.8 (1112.9)	592.0 (1330.9)
PRO measures, mean (SD)						
FACIT-Fatigue score[h]	32.2 (11.3)	32.8 (10.5)	32.7 (12.5)	30.4 (13.7)	32.5 (11.7)	31.7 (11.9)

Baseline (Day 0) is defined as the last non-missing value before the first administration of study drug; Prior rituximab includes rituximab monotherapy, combination therapy (e.g., with bendamustine, fludarabine, ibrutinib, or cytotoxic drugs), or both. [a]Patients treated with placebo in the CADENZA trial were not included in the current analysis. [b]Within the last 2 years, not including blood transfusions unless overnight stay. [c]In CARDINAL, included patients received ≥1 blood transfusion within 6 months prior to enrollment. [d]In CADENZA, included patients did not receive a blood transfusion in the 6 months prior to enrollment and ≤1 blood transfusion in the previous 6 months. [e]Deep vein thrombosis (n=1), pulmonary embolism (n=1); [f]Arteriosclerosis (n=1), hypertension (n=2), Raynaud's syndrome (n=2); [g]Deep vein thrombosis (n=1), hypertension (n=2), and peripheral vascular disorder (n=1); [h]FACIT-Fatigue scores range from 0–52, with a higher score indicating lower fatigue. CAD, cold agglutinin disease; LDH, lactate dehydrogenase; N/A, not applicable; SD, standard deviation.

Rituximab treatment patterns

- Eight (32%) patients had received at least one course of rituximab combination therapy and 17 (68%) received monotherapy only (**Figure 1**).
- The number of rituximab courses received prior to trial enrollment ranged from 1 to 5 with a mean number of 1.92, considering all rituximab use (monotherapy and combination therapy).
- Thirteen patients (52%) received their last rituximab treatment in the 3 to 15 months prior to sutimlimab start date; while six patients (24%) received their last treatment in the 16 to 27 months prior; and finally, six patients (24%) received their last treatment 27 months or more prior to sutimlimab (**Figure 1**).
  - Per the inclusion criteria, rituximab treatment was ceased at least 3 months (rituximab monotherapy) or 6 months (combination therapy) prior to the first dose of sutimlimab.

Figure 1. By-patient history of treatment with rituximab monotherapy and/or combination therapy in for patients receiving sutimlimab in the pooled CARDINAL and CADENZA trials



Day/Month 0 was the date of the first dose of sutimlimab treatment. †Rituximab and corticosteroid use was considered equivalent to rituximab monotherapy. ‡Atypical cases were those with either incomplete rituximab treatment information, or a quick succession of multiple treatment approaches.

RESULTS

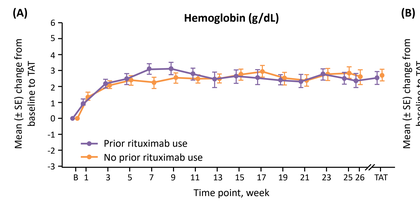
Primary endpoint

- Response rates were similar between subgroups, 60.0% in patients with prior rituximab use (n=15/25), and 66.7% in rituximab-naïve patients (n=14/21).

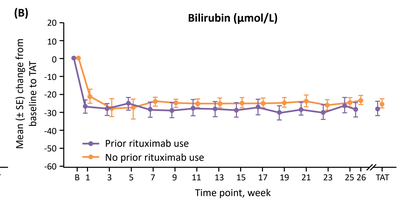
Secondary endpoints

- Change from baseline to TAT was similar between subgroups for hemoglobin, bilirubin, and FACIT-Fatigue score (**Figure 2A, B**, and **D**, respectively).
  - Mean (SE) change from baseline to TAT in hemoglobin level was 2.6 (0.4) and 2.7 (0.4) g/dL for patients with versus without prior rituximab use, respectively.
  - Corresponding values for bilirubin were -28.5 (4.1) versus -25.6 (2.7) µmol/L.
  - Mean (SE) change in FACIT-Fatigue score was similar in both subgroups (9.9 [58.4] and 9.8 [39.8], respectively).
- In patients with data available at baseline and TAT, mean (SE) change in LDH level was greater for patients with (-183.8 [58.4] U/L), versus without (-58.9 [39.8] U/L) prior rituximab use (**Figure 2C**).

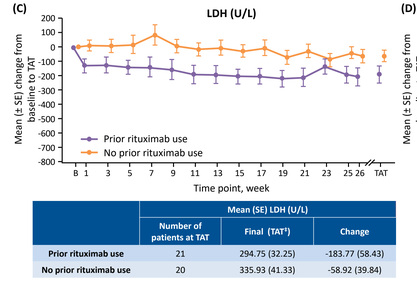
Figure 2. Change from baseline to TAT in (A) hemoglobin (g/dL), (B) bilirubin (µmol/L) and (C) LDH level and (D) FACIT-Fatigue score in patients receiving sutimlimab according to prior rituximab use, using pooled CARDINAL and CADENZA studies



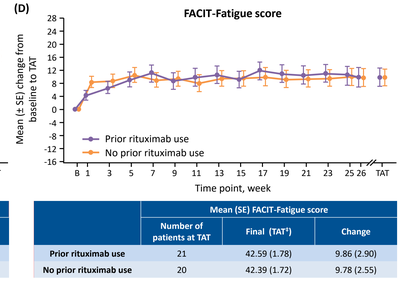
	Mean (SE) Hemoglobin (g/dL)		
	Number of patients at TAT	Final (TAT[1])	Change
Prior rituximab use	21	11.59 (0.46)	2.56 (0.40)
No prior rituximab use	20	11.49 (0.33)	2.74 (0.39)



	Mean (SE) Bilirubin (µmol/L)		
	Number of patients at TAT	Final (TAT[1])	Change
Prior rituximab use	21	17.38 (2.66)	-28.48 (4.13)
No prior rituximab use	20	13.85 (1.43)	-25.62 (2.66)



	Mean (SE) LDH (U/L)		
	Number of patients at TAT	Final (TAT[1])	Change
Prior rituximab use	21	294.75 (32.25)	-183.77 (58.43)
No prior rituximab use	20	335.93 (41.33)	-58.92 (39.84)



	Mean (SE) FACIT-Fatigue score		
	Number of patients at TAT	Final (TAT[1])	Change
Prior rituximab use	21	42.59 (1.78)	9.86 (2.90)
No prior rituximab use	20	42.39 (1.72)	9.78 (2.55)

*In this analysis, included patients had data available at baseline and TAT; *TAT was an average of weeks 23, 25, and 26. B, baseline; CAD, cold agglutinin disease; FACIT-Fatigue, The Functional Assessment of Chronic Illness Therapy (Fatigue); LDH, lactate dehydrogenase; SD, standard deviation; SE, standard error; TAT, treatment assessment timepoint.*

CONCLUSIONS

- The burden of disease for patients with CAD treated with sutimlimab in CARDINAL and CADENZA was greater for those with prior rituximab use compared with rituximab-naïve patients.
  - Changes from baseline in clinical and laboratory parameters were mostly similar between subgroups.
- Response rates were similar between patients with and without prior off-label rituximab treatment.
- These results suggest that sutimlimab is effective in patients with CAD, irrespective of prior off-label rituximab use.
  - A prospective validation is warranted to confirm the results of these post-hoc analyses.

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DISCLOSURES

AR is a consultant to Alexion, Apellis, Novartis, Roche, Sanofi and Bioverativ; received research funding from Roche; and received honoraria from Alexion. **AK** is a consultant for Sanofi. **JM, IH, FJ, FS**, and **TS** are employees and shareholders of Sanofi. **QAH** has received honoraria for lecturing or advisory work from Alexion, Amgen, Apellis, Argenx, Grifols, Novartis, ReAlta and Sanofi.

ACKNOWLEDGEMENTS

The authors would like to thank patients and site staff that took part in the CARDINAL and CADENZA trials. Medical writing support was provided by Emily Evans, BMedSc, of Ashfield MedComms, an Ashfield Health company, and funded by Sanofi in accordance with Good Publication Practice guidelines. This study was sponsored by Sanofi.