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BASELINE CHARACTERISTICS FROM THE FIRST INTERIM ANALYSIS OF CADENCE, THE COLD AGGLUTININ DISEASE (CAD)/COLD AGGLUTININ SYNDROME (CAS) REGISTRY

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Introduction

- Cold agglutinin disease (CAD) is a subtype of cold antibody-driven autoimmune hemolytic anemia, characterized by an immunoglobulin M-induced classical complement pathway-mediated hemolysis. When cold antibody-driven autoimmune hemolytic anemia is associated with an underlying condition, it is known as cold agglutinin syndrome (CAS)[1]
- CAD is associated with a substantial disease burden, including severe fatigue which negatively impacts patient quality of life (QoL), as well as an increased risk of thromboembolic events (TEs) and mortality[2,3]
- CADENCE is a multinational, multicenter, observational, prospective, longitudinal registry study of patients with CAD or CAS[4,5]
  - The study aims to better understand patient demographics, clinical characteristics, treatment patterns, healthcare resource utilization, the natural history of the disease, long-term clinical outcomes, and impact on patient QoL
  - The CADENCE registry is expected to enroll ~400 patients; the first patient was enrolled in Q2 2022 and the last patients' last visit is expected in 2028
- Here we report data from the first interim analysis of CADENCE, analyzing patient characteristics at the time of enrollment into the study

Aims

- To report the disease characteristics of patients enrolled in CADENCE at study enrollment (baseline)

Methods

- Key inclusion criteria: adults ≥18 years of age, diagnosed with CAD or CAS
  - CAD diagnostic criteria: Monospecific direct antiglobulin test strongly positive for C3d, negative or weakly positive for immunoglobulin G, and a cold agglutinin titer ≥1:64
    - Patients who do not meet these criteria may be enrolled at the treating physician's discretion
  - CAS diagnostic criteria: Meet CAD criteria, with causative infection, autoimmune disorder, or overt malignancy (including overt evidence of a B-cell lymphoproliferative disease)
- Key exclusion criteria: diagnosis of warm or mixed autoimmune hemolytic anemia, and active participation in a CAD or CAS interventional trial

Results

Patient Demographics and Characteristics at Diagnosis

- As of the data cut-off (October 6, 2023), 133 patients had been enrolled; 112 patients diagnosed with CAD and 21 patients diagnosed with CAS
  - Among patients with CAD, treatment status at enrollment was treatment-naïve (n=50), CAD treatment ongoing (non-sutimlimab) (n=33), sutimlimab ongoing (n=15), and previously on CAD therapy (n=14)
- Routine laboratory tests and symptoms of anemia were the most common circumstances for CAD or CAS presentation (**Table 1**)
- Lymphoma/malignancy was the underlying cause of CAS in 85.7% (18/21) of patients

Table 1 | CADENCE Registry patient demographics by diagnosis.

	CAD n=112	CAS n=21
Female sex, n (%)	**70 (62.5)**	**11 (52.4)**
Geographic region, n (%)		
Northern Europe	78 (69.6)	16 (76.2)
USA	34 (30.4)	5 (23.8)
Age at enrollment, mean (SD) years	72.0 (10.3)	74.5 (10.2)
Age at diagnosis, mean (SD) years	65.9 (11.1)	70.3 (10.8)
Circumstances of presentation, n (%)		
Routine laboratory tests	52 (46.4)	9 (42.9)
Symptoms of anemia	50 (44.6)	10 (47.6)
Symptoms of acrocyanosis	15 (13.4)	2 (9.5)
Acute hemolytic crisis evaluation	5 (4.5)	5 (23.8)
Acute TE event evaluation	2 (1.8)	0
Related to surgery	1 (0.9)	1 (4.8)
Other/Unknown	30 (26.8)	5 (23.8)

CAD, cold agglutinin disease; CAS, cold agglutinin syndrome; SD, standard deviation; TE, thromboembolic event.

Laboratory Values at Diagnosis and Enrollment

- Laboratory values for patients with CAD and CAS are detailed in **Table 2**
- The majority of patients had cold agglutinin titer data available at enrollment, and tested positive for the C3d direct antiglobulin test
  - Missing data highlight the regional differences in diagnosis and testing for CAD

Burden of Disease at Enrollment

- History of TE, symptoms of disease, and scores of patient-reported outcome (PRO) measurements for patients with CAD and CAS are presented in **Table 3**
- The most common TE event at enrollment was deep vein thrombosis
- The most common physician-reported symptom at enrollment was fatigue
  - FACIT-Fatigue scores are comparable to those experienced by patients with cancer-related anemia and paroxysmal nocturnal hemoglobinuria[6–8]
- SF-36 physical and mental component scores indicate a worse health status in patients with CAD compared with the general population[9]

Table 2 | Laboratory data at diagnosis and enrollment

	CAD n=112	CAS n=21
Hemoglobin, mean (SD) g/dL		
At diagnosis	9.61 (2.22), n=80	9.86 (1.96), n=16
At enrollment	11.25 (1.86), n=85	11.51 (1.44), n=15
Lowest hemoglobin level since diagnosis, g/dL		
Mean (SD)	8.22 (2.16), n=78	7.22 (1.45), n=20
<8.00 g/dL, n (%)	37 (47.4), n=78	8 (40.0), n=20
Bilirubin, mean (SD) mg/dL		
At diagnosis	1.95 (0.83), n=51	1.70 (1.05), n=11
At enrollment	1.64 (0.98), n=52	1.25 (0.82), n=9
Lactate dehydrogenase, mean (SD) U/L		
At diagnosis	459.10 (218.86), n=59	630.3 (391.6), n=10
At enrollment	391.7 (242.49), n=72	340.4 (150.1), n=13
Haptoglobin, mean (SD) mg/dL		
At diagnosis	20.2 (30.4), n=26	10.4 (7.3), n=9
At enrollment	36.1 (42.1), n=30	36.4 (39.0), n=9
Monoclonal gammopathy/immunoglobulin, n (%)[a]		
n	39	13
IgG	9 (23.1)	3 (23.1)
IgA	1 (2.6)	0
IgM	29 (74.4)	10 (76.9)
Missing	73	8
Monospecific direct antiglobulin test/ Coombs-anti-C3d, n (%)[a]		
n	109	20
Positive	109 (100)	20 (100)
Weak/+1[†]	8 (9.3)	0
Strong/≥+2[†]	78 (90.7)	17 (100)
Missing	23	3
Negative	0	0
Missing	3	1
Polyspecific direct antiglobulin test/ Coombs-anti-IgG, n (%)[a]		
n	107	20
Positive	26 (24.3)	3 (15.0)
Weak/+1[b]	20 (100)	3 (100)
Strong/≥+2[b]	0	0
Missing	6	0
Negative	81 (75.7)	17 (85.0)
Missing	5	1
Cold agglutinin titer, n (%)[a]		
n	99	17
<1:64	10 (10.1)	3 (17.6)
≥1:64	89 (89.9)	14 (82.4)
Missing	13	4
Bone marrow testing, n (%)[a]		
n	64	17
Normal	36 (56.3)	2 (11.8)
Abnormal	28 (43.8)	15 (88.2)
Missing	48	4

[a]Data collected at diagnosis; [b]Percentages are calculated using the number of subjects with positive result and available data as denominator.

CAD, cold agglutinin disease; CAS, cold agglutinin syndrome; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; SD, standard deviation.

Table 3 | CAD/CAS symptoms and burden of disease by diagnosis

Characteristic	CAD n=112	CAS n=21
Thromboembolic event, myocardial infarction, and/or stroke[a]		
Deep vein thrombosis	10 (8.9)	2 (9.5)
Pulmonary embolism	4 (3.6)	0
Transient cerebral ischemic attack	2 (1.8)	0
Cerebral infarction	1 (0.9)	0
Hemorrhagic stroke	1 (0.9)	0
Ischemic stroke	1 (0.9)	1 (4.8)
Venous thrombosis	1 (0.9)	0
Myocardial infarction	0	1 (4.8)
Other	2 (1.8)	2 (9.5)
Physician-reported symptom or complication[b]	64 (57.1)	9 (42.9)
Fatigue	43 (38.4)	4 (19.0)
Acrocyanosis	25 (22.3)	1 (4.8)
Raynaud's phenomenon	17 (15.2)	3 (14.3)
Weakness	16 (14.3)	1 (4.8)
Dyspnea	15 (13.4)	1 (4.8)
Jaundice	7 (6.3)	1 (4.8)
Hemoglobinuria	7 (6.3)	0
Dizziness	6 (5.4)	1 (4.8)
Acute hemolytic crisis	5 (4.5)	0
Other	30 (26.8)	4 (19.0)
FACIT-Fatigue subscale score at enrollment, mean (SD)	34.9 (12.8)	32.6 (11.9)
SF-36 subscale score at enrollment, mean (SD)		
Physical component score	42.9 (10.5)	43.1 (8.4)
Mental component score	48.0 (11.1)	43.0 (10.3)

[a]TE event, myocardial infarction, and/or stroke at any time prior to enrollment; [b]Physician-reported symptom or complication occurring within 6 months prior to enrollment. Headache, dysphagia, chest pain, erectile dysfunction, and peripheral gangrene each occurred in <5 patients.

CAD, cold agglutinin disease; CAS, cold agglutinin syndrome; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; SD, standard deviation; SF-36, 36-Item Short Form Health Survey.

Treatment History at Enrollment

- At the data cut-off, the median (Q1, Q3) time since diagnosis for patients with CAD and CAS was 57.8 (15.4, 104.3) and 27.3 (12.2, 92.7) months, respectively
- Prior to the data cut-off date, 50% (56/112) of patients with CAD and 47.6% (10/21) of patients with CAS had received no treatment for their disease
  - 28.6% (32/112) and 33.3% (7/21) of patients with CAD and CAS, respectively, had received 1 line of therapy, and 21.4% (24/112) and 19.0% (4/21) of patients had received ≥2 lines of therapy
- 34.8% (39/112) of patients with CAD and 28.6% (6/21) of patients with CAS had previously received rituximab
  - 37 patients with CAD received rituximab monotherapy and 2 patients with CAD received rituximab in combination with an antineoplastic agent
- Prior to enrollment, 49.1% (55/112) and 33.3% (7/21) of patients with CAD and CAS, respectively, had received ≥1 transfusion of blood

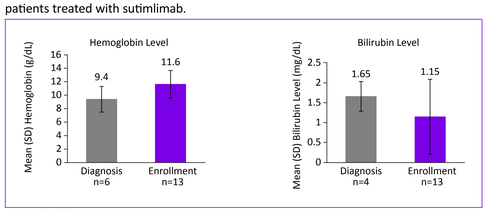
Conclusions

- This first report from the ongoing CADENCE registry shows that the demographics of enrolled patients with CAD were consistent with previous literature[10,11]
- The data on hemolytic markers, PROs, disease complications, and transfusion burden, highlight the disease burden in CAD[2]
- The characteristics of patients with CAS at enrollment into the registry are similar to those of patients with CAD
- Initial data on patients treated with sutimlimab are consistent with results from clinical trials, demonstrating the benefit of sutimlimab in managing anemia and hemolysis, and in addressing PROs[10,11]
- Further analyses will provide insights about the natural history of CAD and CAS and real-world, long-term safety and effectiveness of sutimlimab as a treatment for these patients

Sutimlimab-treated Patients at Diagnosis or Enrollment

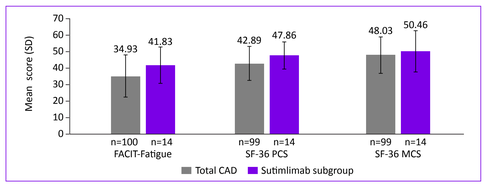
- Hemoglobin and bilirubin levels at diagnosis and at enrollment for patients treated with sutimlimab are shown in **Figure 1**
- At enrollment, for patients in the sutimlimab subgroup:
  - 66.7% (6/9) of patients reported that the lowest hemoglobin level since diagnosis was <8.0 g/dL
  - Mean (SD) lowest hemoglobin level since diagnosis was 8.5 (2.2) g/dL (n=9)
- FACIT-Fatigue and SF-36 physical and mental component scores at enrollment for patients in the sutimlimab subgroup (**Figure 2**) were indicative of patients on sutimlimab generally experiencing a better QoL than the general CAD population

Figure 1 | Mean hemoglobin and bilirubin levels at diagnosis and enrollment for patients treated with sutimlimab.



SD, standard deviation.

Figure 2 | PRO scores at enrollment in the total CAD population and for patients treated with sutimlimab.



CAD, cold agglutinin disease; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; PRO, patient-reported outcome; SD, standard deviation; SF-36, 36-Item Short Form Health Survey; SF-36 MCS, SF-36 mental component score; SF-36 PCS, SF-36 physical component score.

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Disclosures

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