Cold Agglutinin Disease

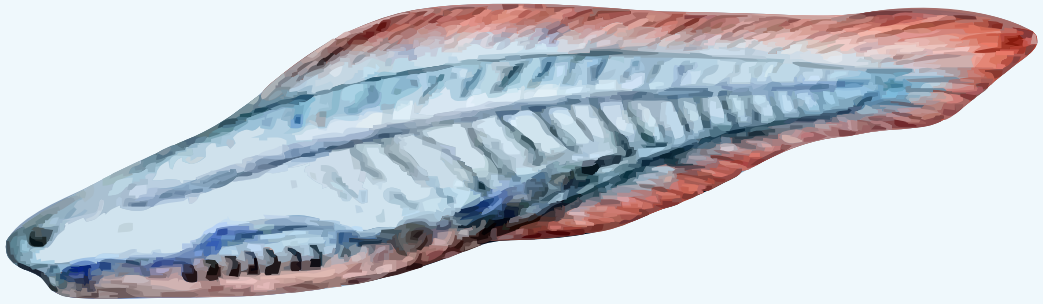
500 Million BCE

When we were fish

IgM evolves.

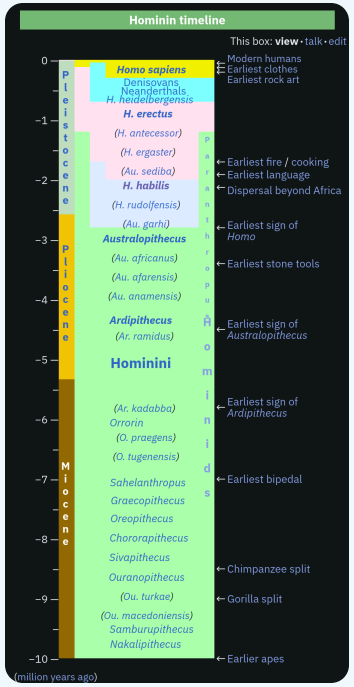
Ancestors of *streptococcus* and *listeria* have proteins closely resembling the I antigen.

Sea water is ~room temperature (20-25C).



3 Million BCE

Then we were us

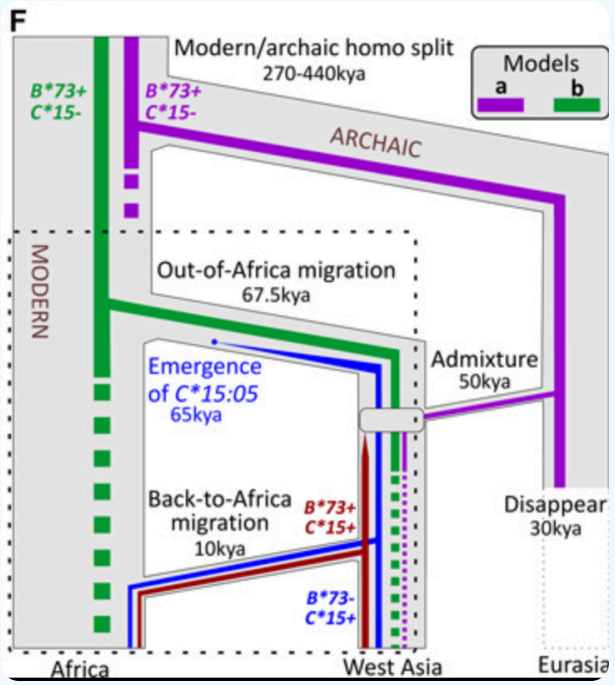


3 Million BCE

Then we were us

We get wild with our immune systems.

But IgM sticks around.



460 BCE

Hippocrates does his thing

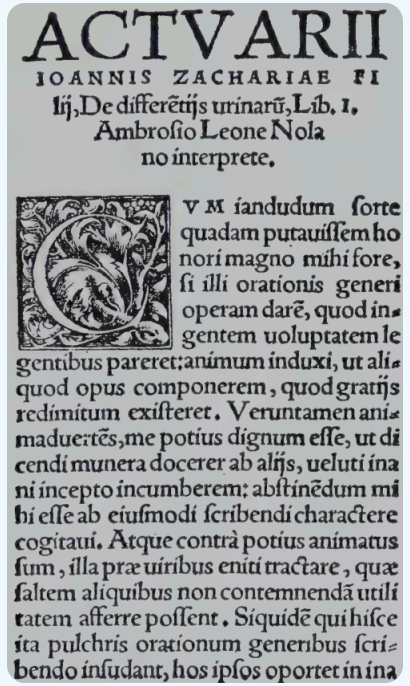
Hippocrates by Anne-Louis Girodet de Roussy-Trioson (1767-1824). Public domain.

1200s

Johannes Actuarius, Constantinople court physician, publishes *De Urinis*, which notes: "Yea indeed an extremely black urine... signifies extreme chilliness."

(syphilis causes paroxysmal cold hemoglobinuria, so used to be much more common)

(but watch out for a resurgence - syphilis cases went up 80%, to 207,000 in 2022)



ACTVARII

IOANNIS ZACHARIAE FI

lij, De differẽtijs urinarũ, Lib. I.

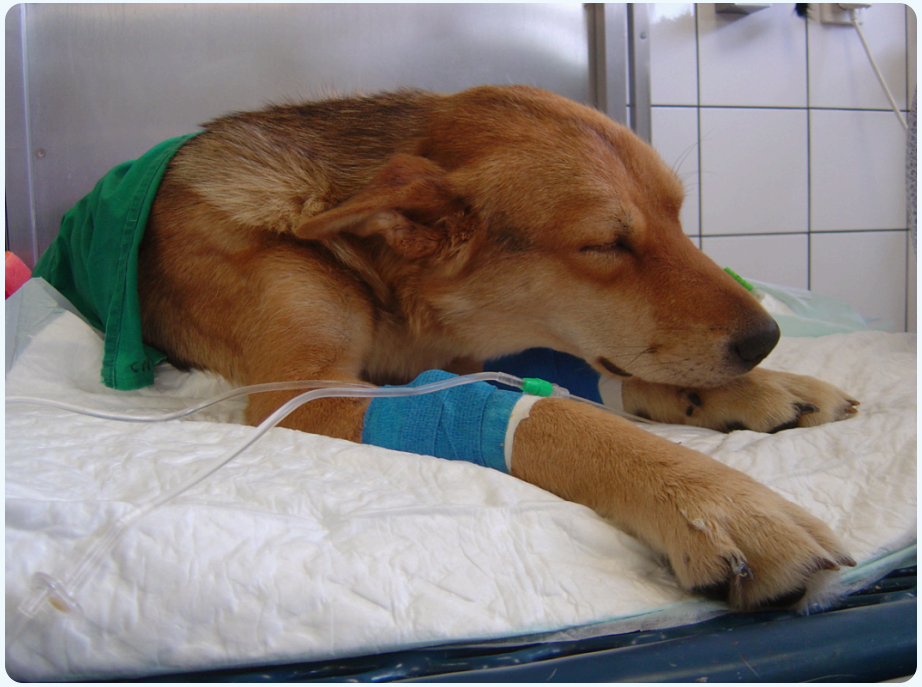
Ambrosio Leone Nola

no interprete.

VM iandudum sorte quadam putauissem ho nori magno mihi fore, si illi orationis generi operam darẽ, quod in gentem uoluptatem le gentibus pareret; animum induxi, ut ali quod opus componerem, quod gratijs redimitum existeret. Veruntamen ani maduertẽs, me potius dignum esse, ut di cendi munera docerer ab alijs, ueluti ina ni incepto incumberem; abstinẽdum mi hi esse ab eiusmodi scribendi charactere cogitaui. Atque contrà potius animatus sum, illa præ uiribus eniti tractare, quæ saltem aliquibus non contemnendã utili tatem afferre possent. Siquidẽ qui hisce ita pulchris orationum generibus scri bendo insudant, hos ipsos oportet in ina

1800s

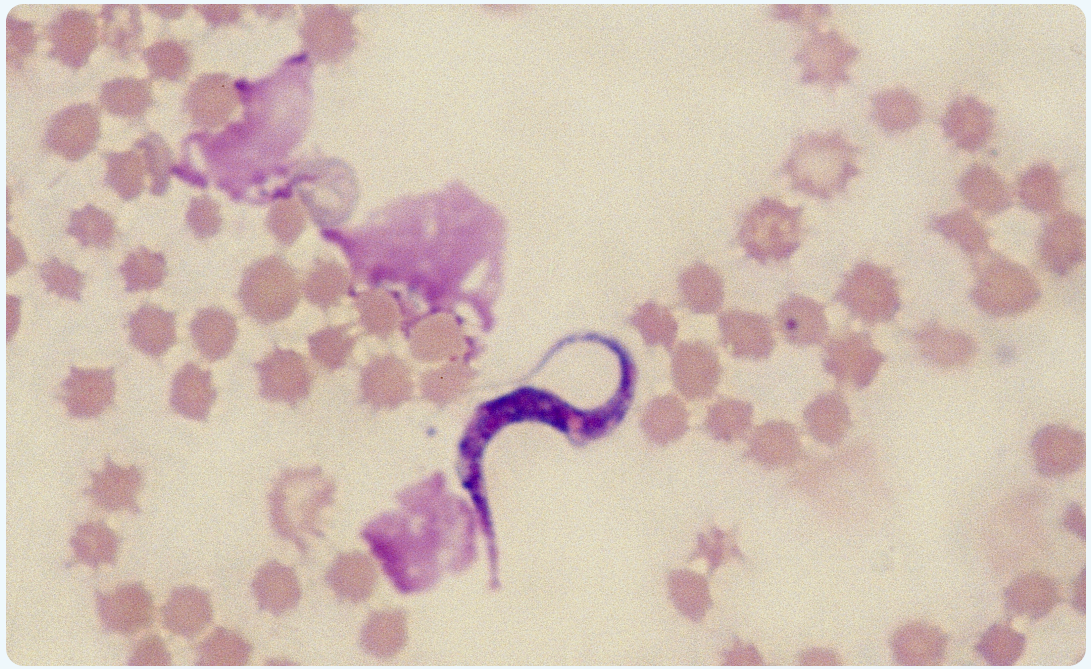
Trypanosomiasis (N'gana, sleeping sickness) is found to cause deep anemias, partially via hemolysis.



1898

Mssrs. Kanthack, Durham, and Blandford describe agglutination in red blood cells of animals infected with trypanosomes.

"Instead of forming rouleaux, the red corpuscles tend to clump into masses and to lose their outlines, especially when the anaemia is pronounced (rabbit, ass, and horse). The serum of such blood, when mixed with normal blood of the same species of animal, causes the red corpuscles to clump together also."



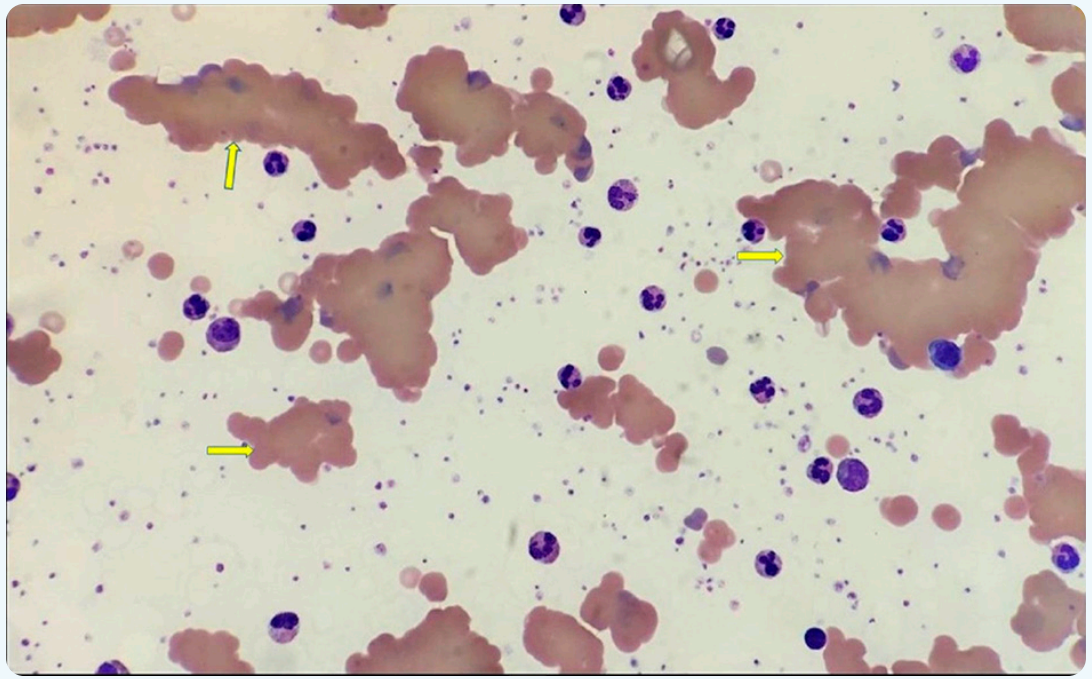
1903

Karl Landsteiner publishes "About Relationships Between the Blood Serum and the Body Cells" (*Über Beziehungen zwischen dem Blutserum und den Körperzellen*), which contains a description of blood agglutination at cold temperatures (thermal amplitude 0-5C).

He's the guy who discovered blood types, under the term "iso-agglutination," and won the Nobel Prize in Medicine for this in 1930.

1918

Clough and Richter publish "A study of an autoagglutinin occurring in a human serum," first definite cases of cold agglutination in humans, describing the relationship between agglutination, hemolysis, and pneumonia.



1937

McCombs and McElroy note that the huge increase in surgical transfusions since Landsteiner's discovery has revealed a number of cases of cold agglutination found in the blood bank (thermal amplitude 0-25 C), confusing technicians nation-wide.

(And occasionally leading to death)

1946

Lubinski and Goldbloom collect and describe 7 cases of cold agglutination with a thermal amplitude of 0-37C, all associated with hemolytic anemia (5 primary cases, 1 sepsis, 1 syphilis).

(CAD incidence: ~2 per million per year)

1957

Christenson et al perform the first isolation of a monoclonal protein, a cold agglutinin. One of the pts also has a cryoglobulin.

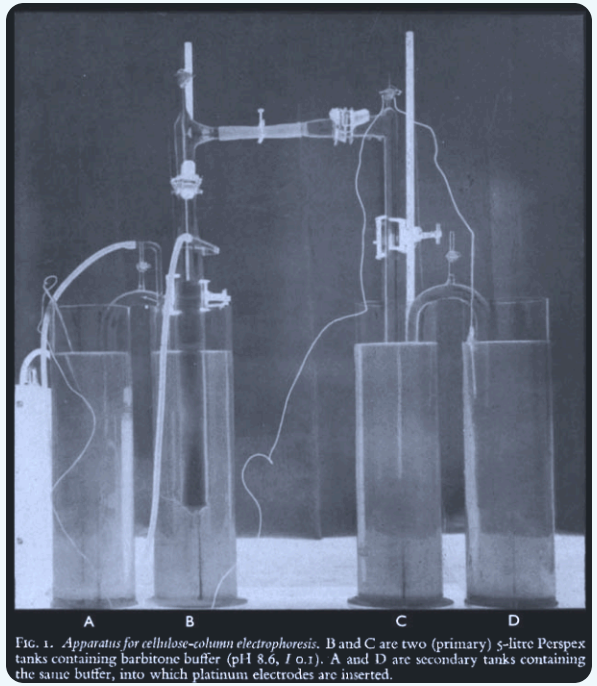


FIG. 1. *Apparatus for cellulose-column electrophoresis.* B and C are two (primary) 5-litre Perspex tanks containing barbitone buffer (pH 8.6, *I* 0.1). A and D are secondary tanks containing the same buffer, into which platinum electrodes are inserted.

Pathophysiology

whence IgM?

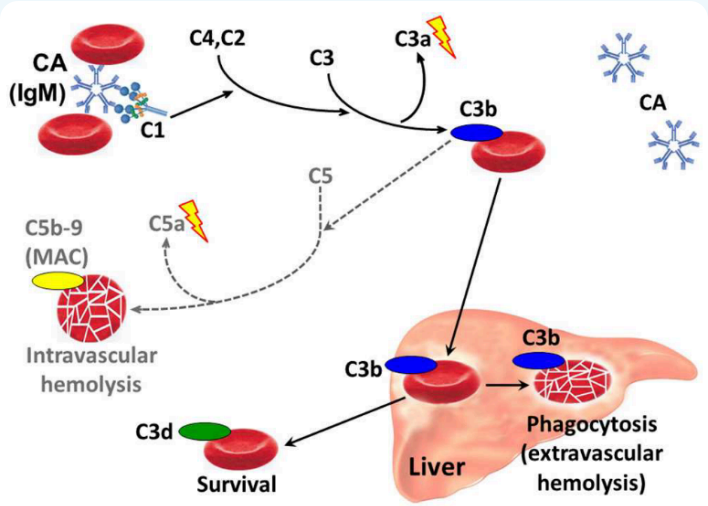


FIGURE 3 | Classical complement pathway-mediated hemolysis in CAD. Only relevant steps and components are shown. Black arrows, major pathways. Gray/dotted arrows, minor pathways. Lightning symbol indicates anaphylotoxin properties. C1, C2, etc., complement proteins; CA, cold agglutinin; Ig, immunoglobulin; MAC, membrane attack complex.

Berentsen, *Frontiers in Immunology*, 2020

1964

Olesen publishes the first paper with a successful drug treatment for CAD, choosing chlorambucil based on the then-recent success of this drug in Waldenstrom macroglobulinemia. Follow-up in 1970 with 4 pts has similar results.

(One pt got cyclophosphamide for 4mo, switched to chlorambucil later on d/t drAE).

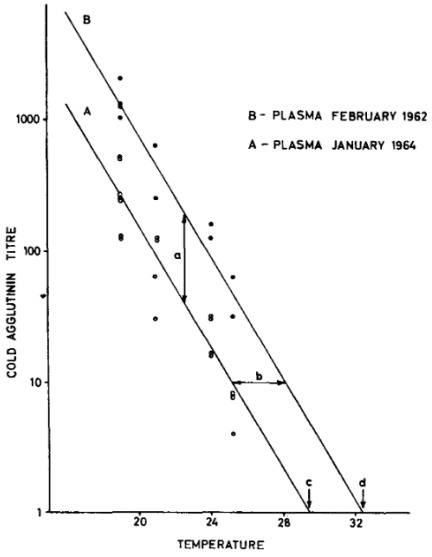


Figure 2. Cold agglutinin titres at different temperatures of plasma from before (B) and after (A) the treatment in a semilogarithmic plot. Vertical arrow (a) indicates decrease in titre to $^1/_4$ to $^1/_8$ of the pretreatment value; horizontal arrow (b) indicates decrease in thermal amplitude (3° C.); arrow c and d indicates temperature at titer 1 (undiluted plasma) under experimental conditions.

1997

Rituximab comes to market.

1998

Lee and Kueck try rituximab (375 x4) in a pt w CAD, and it works.

2001

Berentsen et al report on a small prospective ritux study: 1 CR, 3 PR, 2 no response.

2006, 2013

Berentsen et al retrospective study: ritux-based regimens RR 67-83%.

2017

Berentsen et al, prospective study using BR: 71% RR, 40% CR, 31% PR. 50% RR in the retreatment setting. TTR 2mo. 77% response rate at 5y. Median DOR >88mo.

2018

Rossi et al report on 2L bortezomib (GIMEMA) (single cycle): 32% RR, median DOR 16mo.

2020, 2021

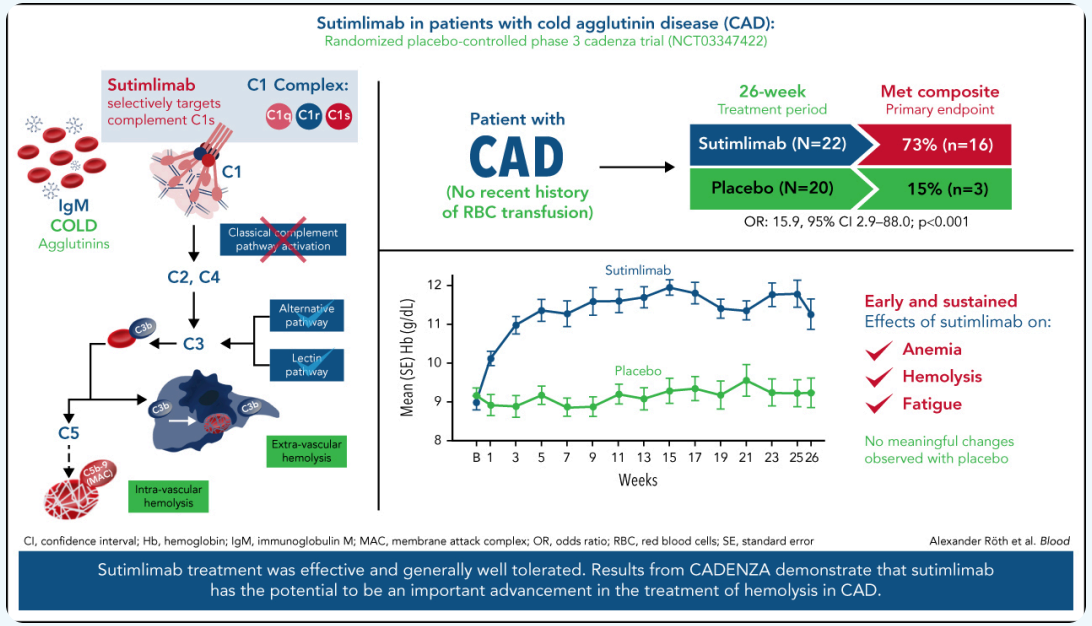
Case reports on CAS d/t pembro (Atiq 2020) and atezo (Acikgoz 2021).

2021

Roth et al report (NEJM) on sutimlimab monotherapy (CARDINAL) (nonrandomized)

2022

Roth et al report (Blood) on sutimlimab monotherapy (CADENZA) (phase III placebo-controlled RCT)



Blood 2022, Roth et al

Supplementary Table 5. Summary of TEAEs experienced by >1 patient in either study group, by preferred term in descending order of incidence in the sutimlimab group (safety analysis set)

TEAEs experienced by >1 patient in either study group[a], n (%)	Sutimlimab (n=22)	Placebo (n=20)
Headache	5 (23)	2 (10)
Hypertension	5 (23)	0
Raynaud's phenomenon	4 (18)	0
Rhinitis	4 (18)	0
Cyanosis (acrocyanosis)	3 (14)	0
Abdominal pain, upper	2 (9)	2 (10)
Anemia	2 (9)	4 (20)

2024

72F, p/w hgb 3.8. A little tired.

Some discoloration of fingers, she says it's worse (and painful) when it's cold.

No notable icterus.

Elevated indirect bili.

LDH elevated. Hapto undetectable.

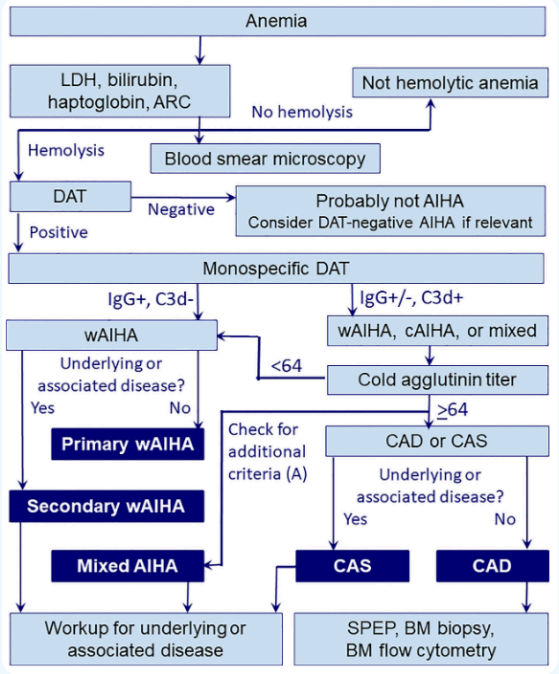
Retic elevated.

+RBC clumping on smear. Other cells normal in morphology and number.

DAT: IgG+ (weak), C3+

Cold agglutinin titre: way >64

Diagnostic algorithm



Berentsen, Fattizzo, Barcellini, *Frontiers in Immunology*, 2023

Differential diagnosis

no B symptoms (may be difficult to separate from infx)

no extramedullary disease (may push you toward MZL)

CD5- (>50% CAD -ve for CD5), CD10- B cells: MZL vs IgM LPL (Waldenstrom)

MYD88 L265P -ve (usu + in LPL)

certain clusters of genomic and cytogenetic changes, e.g. KMT2D variant (69%) complete or partial gain of chromosome 3 (93%)

WHO 2022: CAD is now a distinct lymphoid neoplasm (CAD-associated LPD) (hopefully, more

Tx options overview

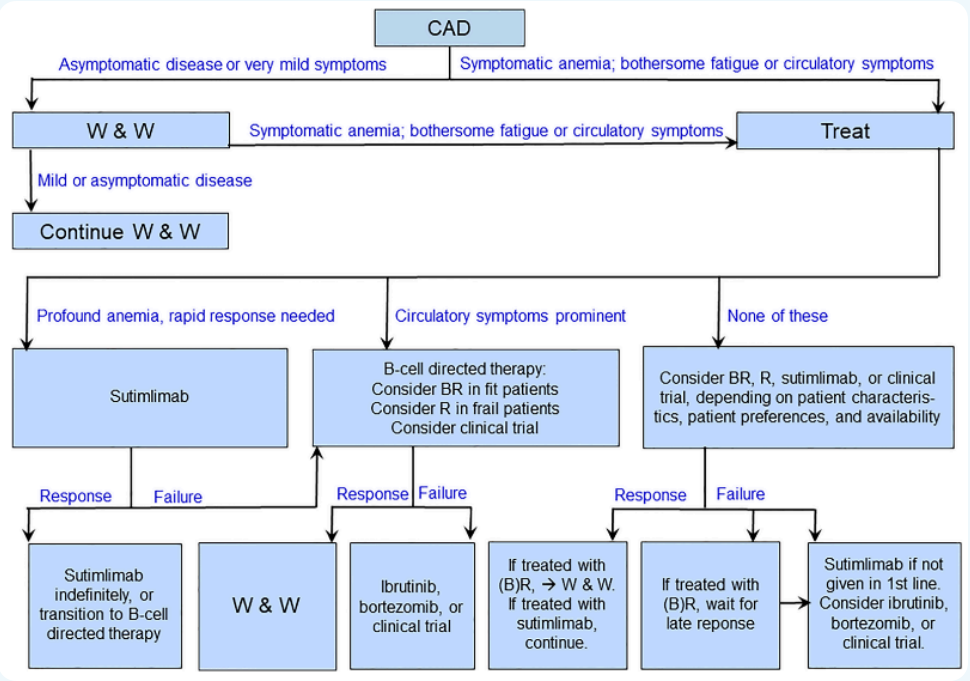
TABLE 3 Published studies of therapy in CAD.

Target	Treatment	Study (Reference)	Study design	ORR[1] (%)	CR[2] rate (%)	Median response duration (months)	Toxicity
B-cell directed theapies	Rituximab monotherapy	Berentsen et al., 2004 (78) Schöllkopf et al., 2006 (79)	Prospective, non-randomized	45-55	<5	6.5-11	Low
	Rituximab plus fludarabine	Berentsen et al., 2010 (80)	Prospective, non-randomized	76	21	>66	Significant
	Rituximab plus bendamustine	Berentsen et al., 2017 (81) Berentsen at al. 2020 (61)	Prospective, non-randomized	78	53	>88	Moderate, manageable
	Bortezomib monotherapy	Rossi et al., 2018 (82)	Prospective, non-randomized	32	16	>16	Low
	Ibrutinib monotherapy	Jalink et al., 2021 (83)	Retrospective	100	NR[1]	ND[1]	Low
Complement-directed therapies	Sutimlimab	Röth et al. (CARDINAL study) 2021 (70)	Prospective, non-randomized	>73[3]	NR[1]	>24	Low
		Röth et al. (CADENZA study) 2021 (77)	Prospective, randomized				
	Pegcetacoplan	Grossi et al., 2018	Part of prospective phase 2 study	ND/ high[3]	NR[1]	ND[1]	Low

[1]ORR, overall response rate; ND, not determined; NR, not relevant.
[2]CR, complete response. Criteria for CR included eradication of detectable bone marrow lymphoproliferative disorder.
[3]ORR was not an endpoint of this study. Estimated ORR is based on data from the original publication.

Berentsen, Fattizzo, Barcellini, *Frontiers in Immunology*, 2023

Tx sequencing overview



Berentsen, Fattizzo, Barcellini, *Frontiers in Immunology*, 2023

And the kitchen sink

2010: p/w hemolytic anemia, eventually found to have cold agglutinin disease

2010 - 2015: rituximab, multiple cycles

2016: rituximab + fludarabine

2018: rituximab + bortezomib

2019: rituximab + bendamustine

2022: sutimlimab recommended

2024: sutimlimab given. Kind of works sometimes for a while. Flares in late 2024/early 2025.

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