Koude AIHA 2022

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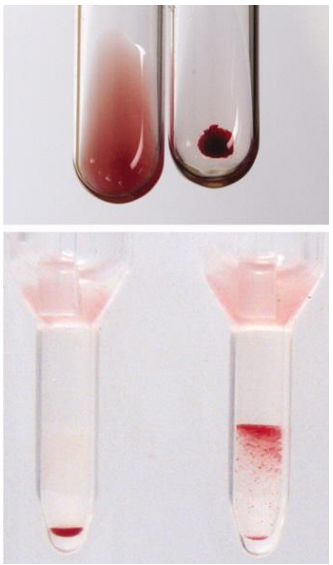
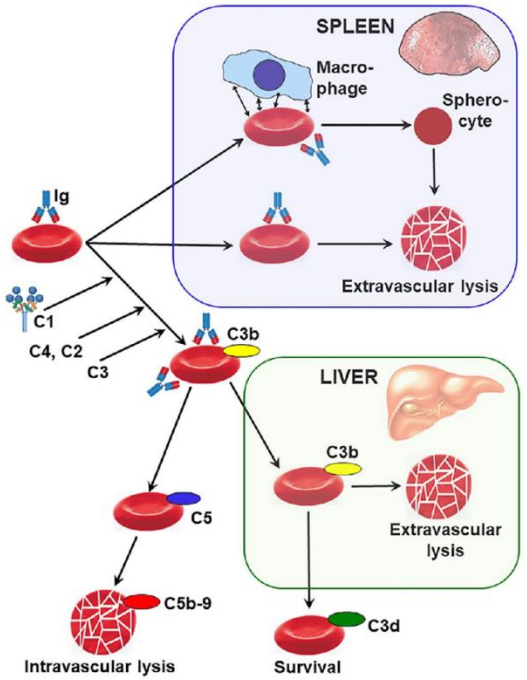
AIHA expertise center

Auto immune hemolytic anemia

- Hemolytic anemia caused by the destruction of RBCs through autoantibodies directed against antigens on their surface





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AIHA Epidemiology

- The exact incidence is unknown
- Adults: ~2/100.000/year
- Children: ~ 0.81/100,000
- The Netherlands ~ 300-400 new AIHA per year????

- ~70% warm AIHA
- **~25% cold AIHA ~100 new cold AIHA per year -> chronic condition**
- Remaining: mixed or DAT negative.

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Epidemiology: climate dependent!

Prevalence and incidence

	Population, 10^6	Prevalence, cases/10^6 inhabitants	Incidence, cases/10^6 inhabitants/y	Outdoor temperature, °C, yearly-average
Norway	5.32	20.5	1.9	6.0*
Lombardy, Italy	7.0†	5.0	0.48	13.1

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Berentsen et al, Blood 2020

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Classification: Cold AIHA

- Cold AIHA (cAIHA; ~25%)
  - a monospecific DAT strongly positive for C3d (and negative or weakly positive with IgG) and a cold agglutinin (CA) titer of 64 or greater at 4°C.
  - **Primary Cold Agglutinin Disease (CAD):**
    - B-cell clonal lymphoproliferative disorder detectable in blood or marrow but no clinical or radiological evidence of malignancy
  - **Cold Agglutinin Syndrome (CAS)**
    - Secondary to associated condition, for example infection (mycoplasma), autoimmune disorder, overt evidence of a B-cell lymphoma (clinical or radiological), or other malignancy.

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Cold AIHA (Cold Agglutinin Disease)

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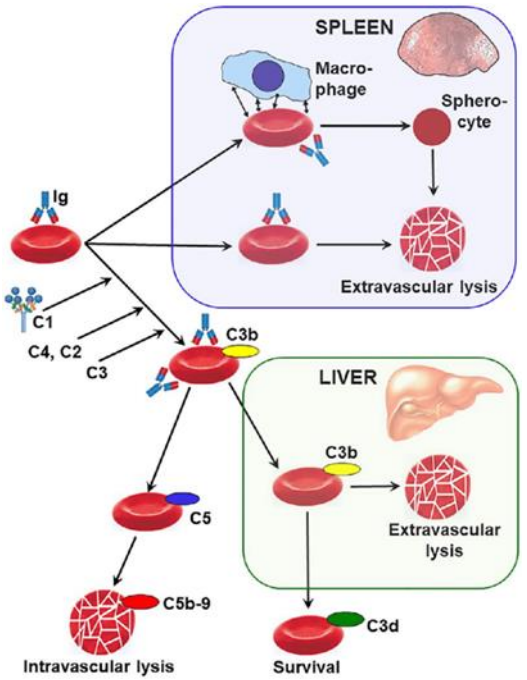
Pathophysiology cold AIHA

- Binding of CA to the RBC results in agglutination and induces complement-dependent hemolysis by activation of the classical pathway.
- Hemolysis mainly extravascular, mediated by opsonization with complement protein C3b and subsequent phagocytosis
- Terminal complement activation with intravascular hemolysis also occurs



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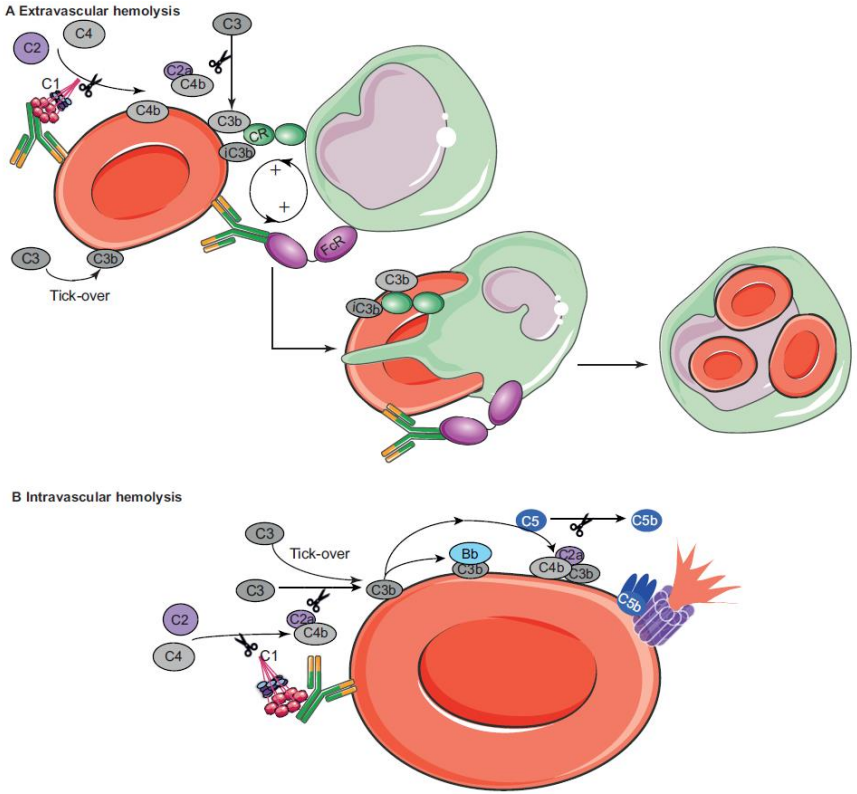
Complement Pathway in cAIHA



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Jalink, de Boer et al, 2021

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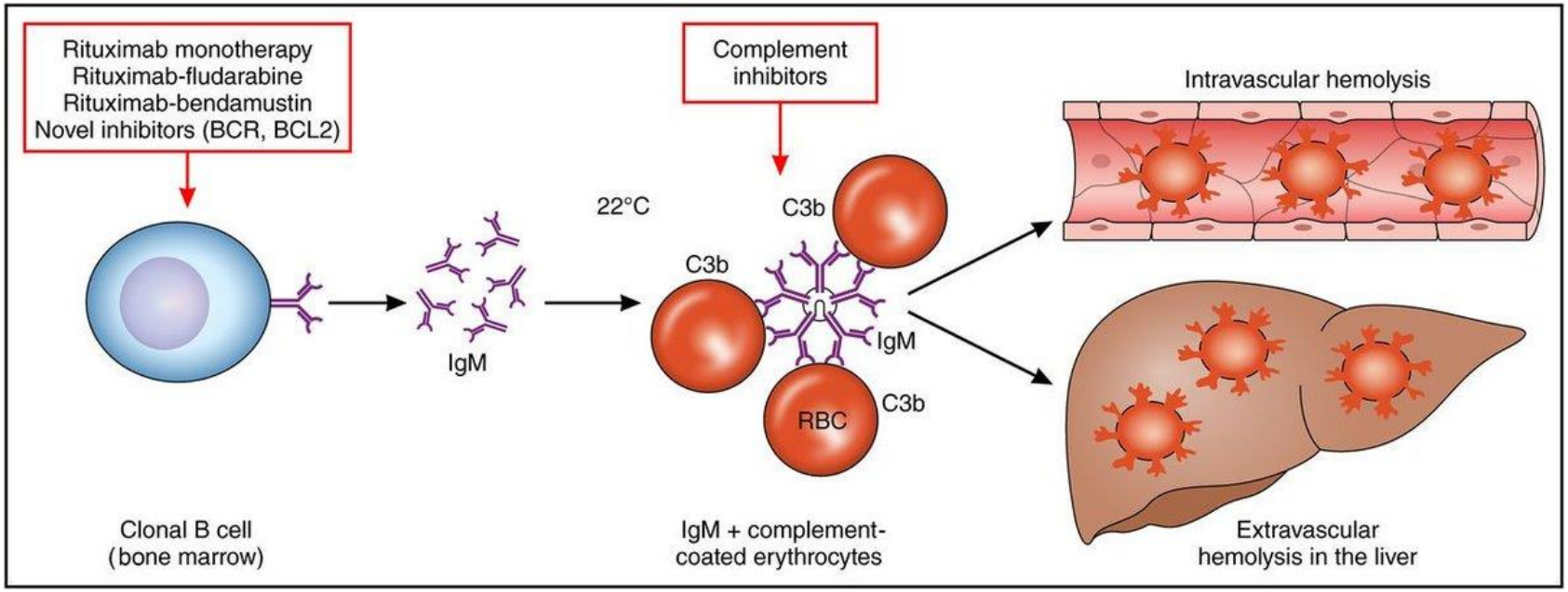
Causes of Cold AIHA

- Primary Cold Agglutinin Disease
  - Chronic hemolysis, relevant CA titer (most often defined as >64) at 4 Celsius,
  - IgM autoantibodies against I-antigen
  - Complement DAT (+/- IgM, can have low IgG)
  - **90% IgM kappa paraproteinemia +/- low grade NHL only in BM**
  - No overt malignancy or extramedullary disease

Pathophysiology Cold Agglutinin Disease



Berentsen Blood 2021

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Causes of cold AIHA

- Secondary CAS
  - B-cell malignancies (WM, CLL)
  - Infection (EBV, Mycoplasma, COVID)
  - Auto-immune diseases
  - Primary immunodeficiency (Hyper IgM Syndrome)

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Work up: cold AIHA

- Immunoglobulins including SPEP/immunofixation
- Bonemarrow/PB examination + flow cytometry
- Testing for mycoplasma/EBV
- (CT scan)

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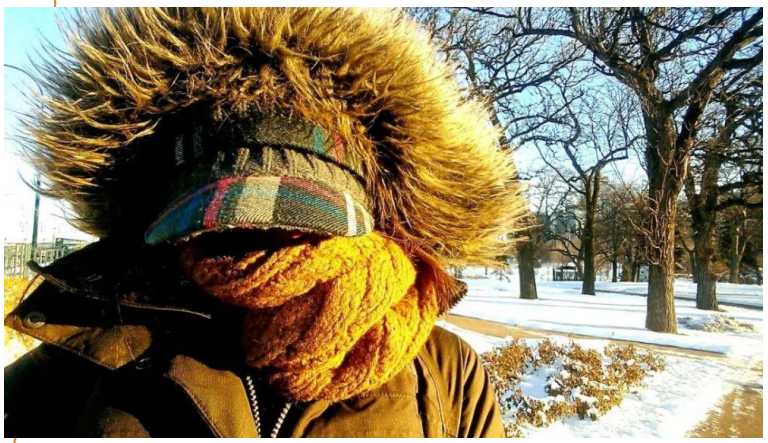
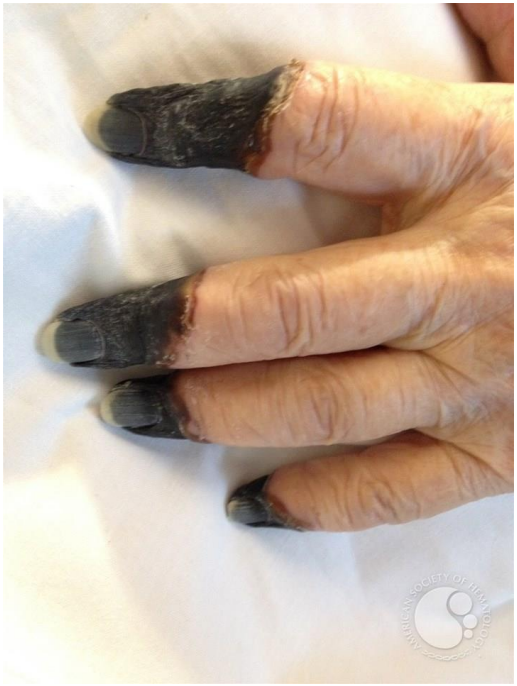
Cold AIHA: symptoms

- Anemia
- Fatigue
- Can have intravascular hemolysis
- Acrocyanosis
- Keep warm





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Cold AIHA symptoms

- 90% hemolytic anemia wv 70% no/grade 1 circulatory symptoms
- 20% grade 2-3 circulatory symptoms
- 10% circulatory symptoms with compensated AIHA

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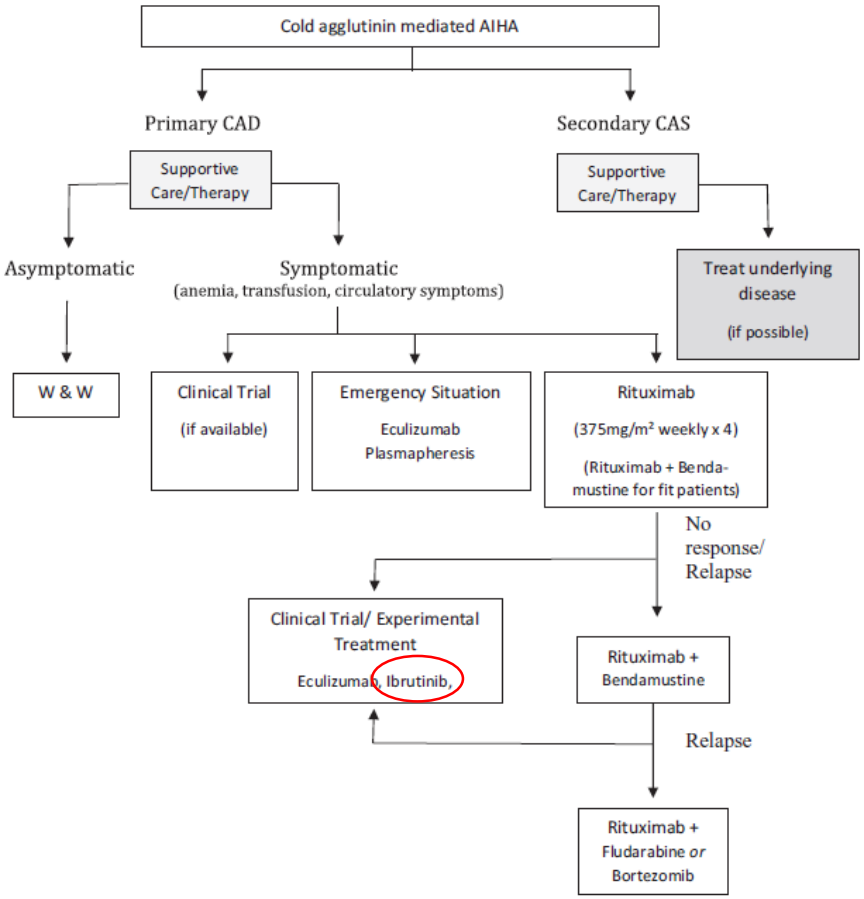
Treatment cold AIHA



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Treatment – cAIHA – secondary CAS

- Observation or treat underlying condition

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Treatment cAIHA
primary Cold Agglutinin Disease

- “keep warm”
- Observation
- Transfusions always warm!
- Consider thrombosis prophylaxis in severe excacerbation or clinical admission

- Ineffective treatments:
  - Steroids
  - Unspecific immunosuppression
  - Splenectomy

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Treatment – primary CAD – Rituximab monotherapy

- **Rituximab monotherapy**
  - ORR (mostly PR) ~50%
  - Median response duration ~ 9 months
  - No data on maintenance

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Treatment primary CAD

- ***Rituximab + fludarabine***
  - *ORR ~76 %, 21% CR*
  - *Median response duration ~ 77 months!!*
  - *41% grade 3-4 neutropenia, frequent infections*
  - *Concern for secondary malignancies*
- ***Bortezomib monotherapy***
  - *6/19 patients responded, 4/6 at least 6 months*
  - *Only 4 single doses (d1,4,8,11)*
- **Rituximab + bendamustine (4 cycles)**
  - ORR ~78 %, 53% CR (long term follow up_
  - Median response duration > 88 months!!
  - 30% grade 3-4 neutropenia, 11% infections
  - Less concern for secondary malignancies

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Treatment primary CAD – complement inhibition

- Case report C1-esterase inhibitor in sever cAIHA

- Ecaluzimab (C5 inhibitor)
  - N=13
  - Modest effect on Hb (+ 0.8 g/dL)
  - Will not block c3b mediated phagocytosis in the liver

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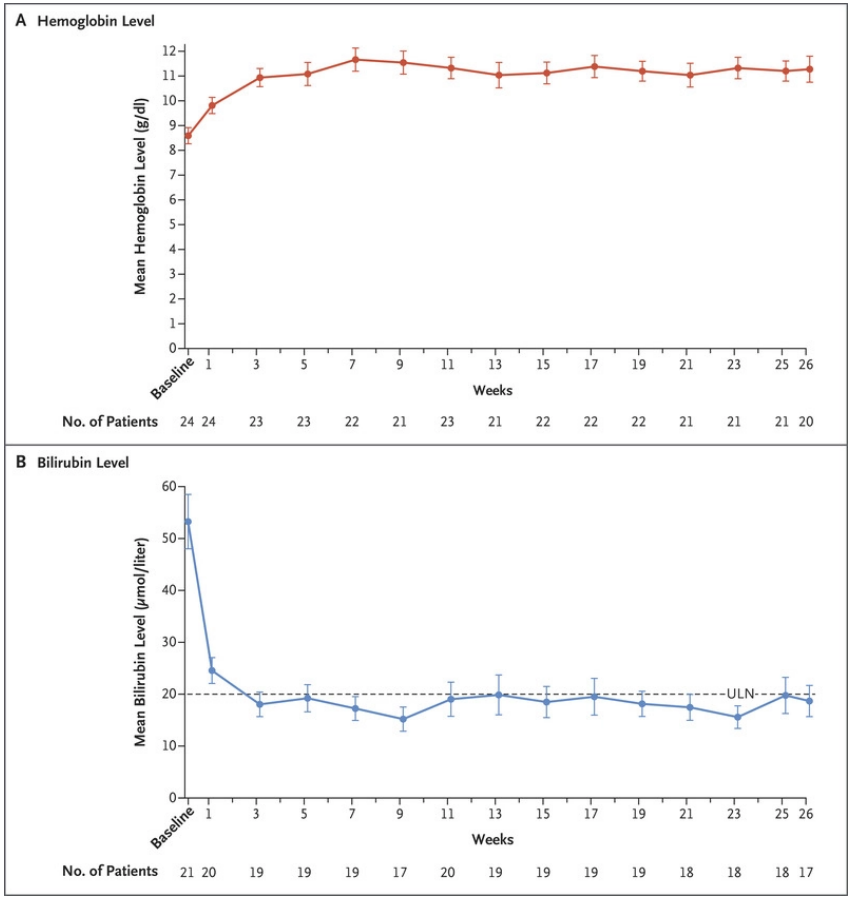
Treatment primary CAD – complement inhibition

- Sutimlimab (C1s inhibitor) – Cardinal study
  - N=24, all transfusion dependent
  - 71% became transfusion independent
  - Mean Hb rise 2,6 g/dL
  - Safety:
    - 2 (8%) infusion reactions
    - Infections (2 (8%) serious infections, not considered related)
    - No meningococcal infections
  - ! Complement inhibition not expected to have effect on acrocyanosis !



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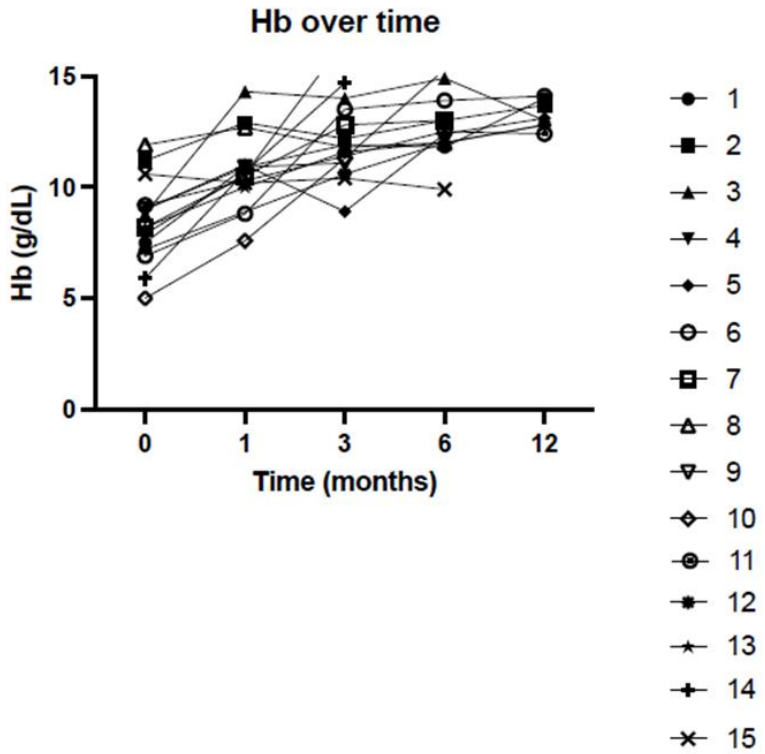
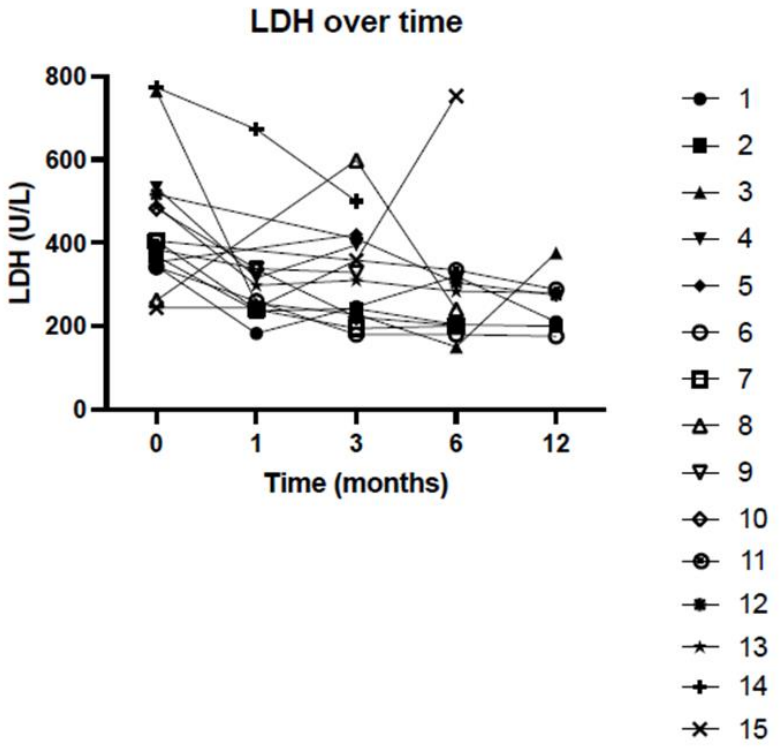
Other novel complement inhibitors in CAD

- Pegcetacoplan (C3 inhibitor) - ongoing trial
- ANX005 (C1q inhibitor): in vitro data
- BIVV020 (active C1s inhibitor): trial completed

Novel treatments – CAD: Ibrutinib (BTK inhibitor)





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New: HOVON CaZa study (Q4 2022)

- Zanubrutinib in primary Cold Agglutinin Disease
- 2nd generation BTK-1
- 4 countries (The Netherlands, UK, Norway, Denmark)
- Outcome: hemolytic anemia AND acrocyanosis

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Fulminant cold AIHA (Hb < 4 mmol/L, unstable):

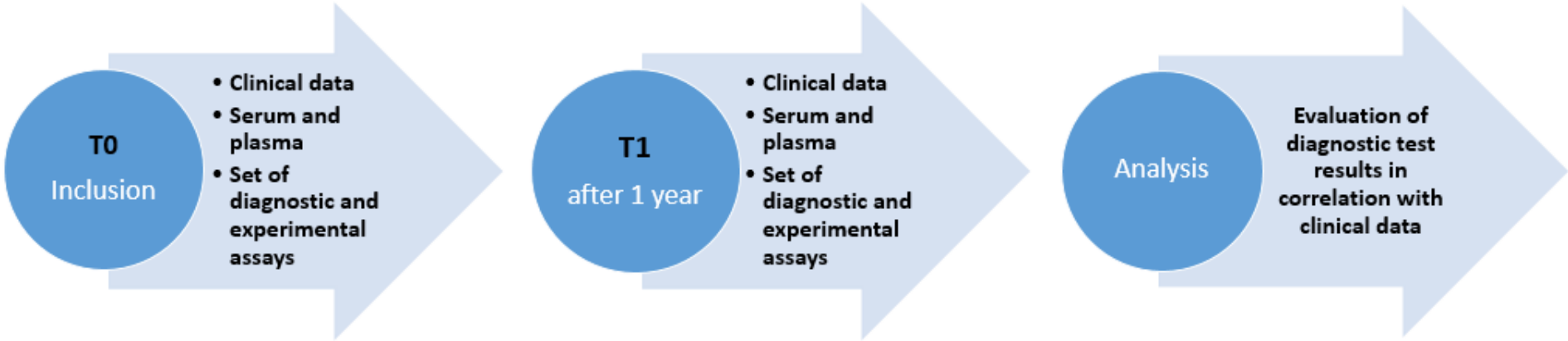
- Start treatment at underlying cause (ie rituximab etc)
- EPO suppletion
- Warm transfusion – contact bloodbank
- Warm plasmapheresis (albumine, not plasma which holds complement) ?
- (Temporary) complement-inhibitor?
- Thromboprofylaxis !

DRAIHA study

Data Registry of AutoImmune Hemolytic Anemia, to improve diagnostic testing for the development of personalized treatment protocols in AIHA patients.

Marit Jalink
Masja de Haas, Claudia Folman en Josephine Vos

Tijdlijn DRAIHA studie



	Gestart	Inclusies
• Radboud UMC	Juli 2019	15
• Amsterdam UMC, AMC	Jan 2020	34
• Leiden UMC	Okt 2020	6
• OLVG	Jan 2020	4
• Isala	Jun 2020	1
• St Antonius Ziekenhuis	Mei 2020	3
• Haga Ziekenhuis	Juli 2021	1
• Sanquin (donors)	Aug 2021	15
• Amsterdam UMC, Vumc	Feb 2022	0
	Totaal	**79**

	Gepland:
• UMC Groningen	Feb 2022
• Jeroen Bosch Ziekenhuis	Feb 2022
• Maastricht UMC	April 2022?
• MST	Mei 2022?
• Erasmus MC	niet gepland
• UMC Utrecht	niet gepland

DRAIHA studie

Focus op cAIHA:

Wat is de correlatie tussen titer, thermale amplitude en ziekte ernst?

- Is hoogte van antistoftiter voorspellend voor ernst van de ziekte?
- Is het bepalen van thermale amplitude alleen voldoende om ernst van ziekte te voorspellen?
- Wat is de meerwaarde van warm afnemen en warm scheiden in vergelijking met resorberen bij aankomst in laboratorium (opnieuw verwarmen en scheiden van bloedsample).

Focus in wAIHA:

Bij welke mate van complement positiviteit in DAT zijn er (IgM) autoantistoffen die complement activeren in wAIHA?

- Evalueren nut en noodzaak van complementactivatie test door erytrocytenautoantistoffen

Questions