Autoimmune Hepatitis: Treatment Milestones and Modern Approaches

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Thursday 15 may, 2025

24 jornadas de avances en hepatologia

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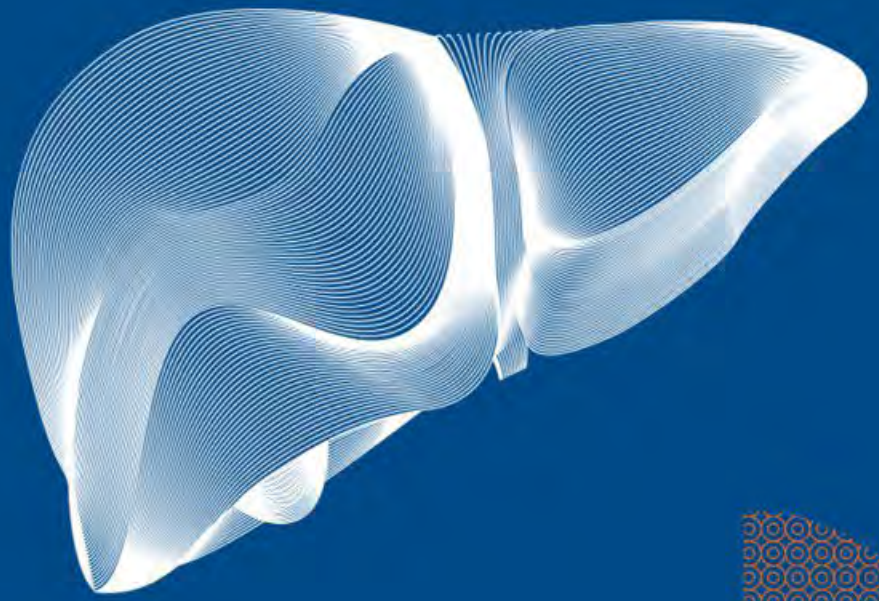


EASL CONGRESS

7-10 May 2025

Amsterdam, the Netherlands

EASL CPG on the management of AIH

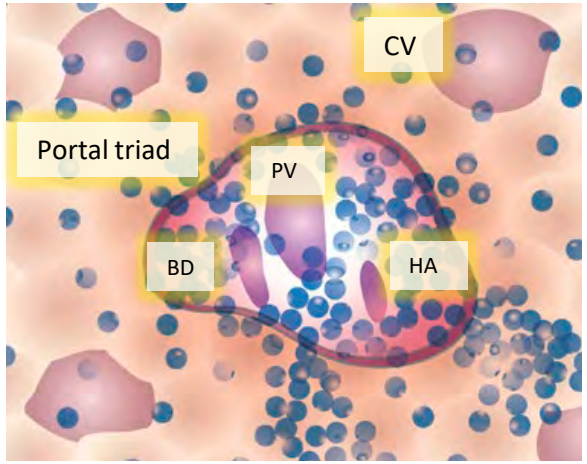
Structure

- Current Management in AIH
- Evidence Based Management in AIH
- Core Outcomes
  - HRQoL
  - Biochemical parameters
  - Histology
- Clinical trial arena in AIH
- CAMARO trial
- Conclusion

Autoimmune Hepatitis

- AIH is a non-resolving chronic liver disease that occurs in both sexes but affects mainly women
- The clinical manifestations of AIH vary from asymptomatic to acute liver failure and they present at any liver fibrosis stage regardless of age, sex, and ethnicity
- Histology
  - Interface hepatitis with plasma cells / lymphocytes
  - Lobular or panacinar necrosis

Portal inflammation / Interface hepatitis



PV portal vein, CV central vein, BD bile duct, HA hepatic artery

Management recommendations from the 2025 guideline

- In adults with AIH, predniso(lo)ne of at least 0.5 mg/kg/day and potentially up to 1 mg/kg/day in more severe and advanced disease in combination with azathioprine (whenever bilirubin is <6 mg/dL and ideally 2 weeks apart from corticosteroids start at initial dose of 50 mg/day to a final dose of 1-2 mg/kg/day) or MMF (1.5-2 g/day) should be the first-line treatments **(LoE 2, Strong recommendation**

- Prednisone is the mainstay, low dose
- Adjunct
  - MMF
  - Azathioprine

EASL CPG AIH 2025

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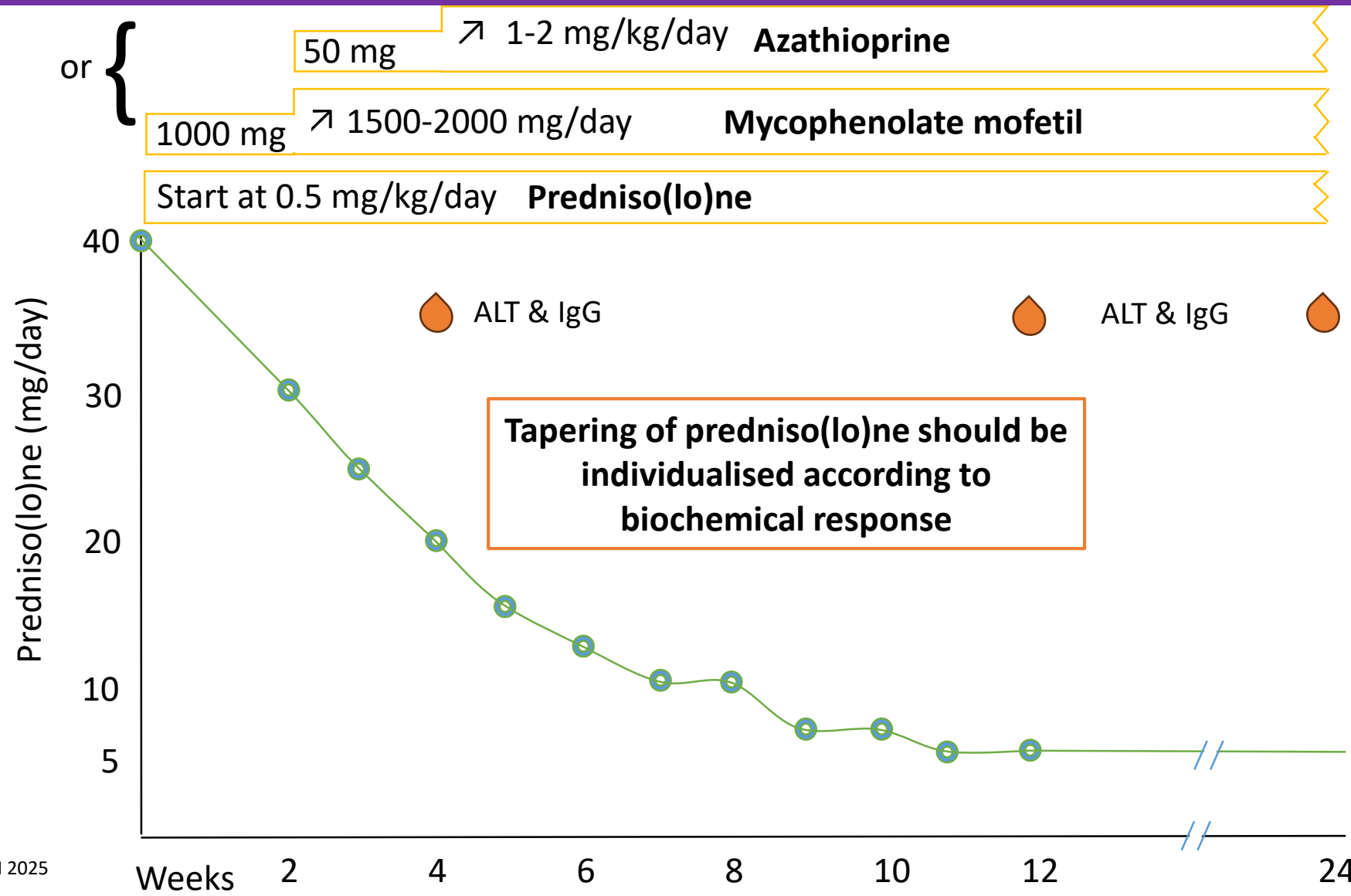
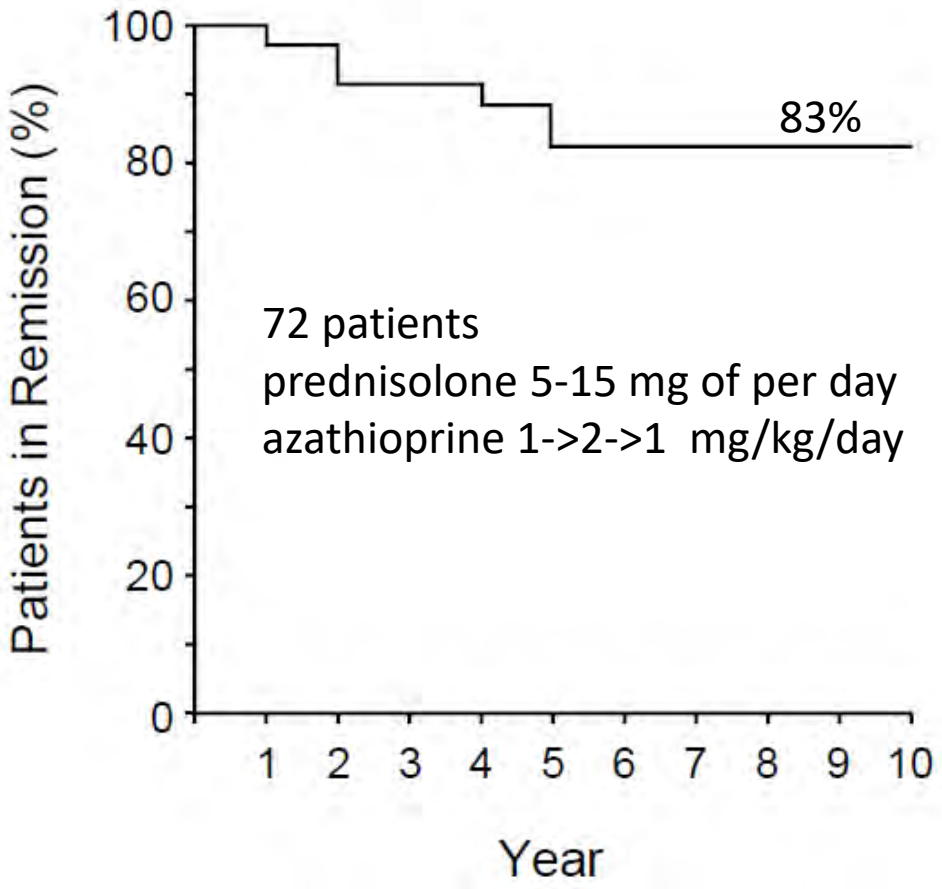
Treatment Schedule according to EASL CPG



Effect of Prednison & Azathioprine



Johnson N Engl J Med 1995; 333:958-963

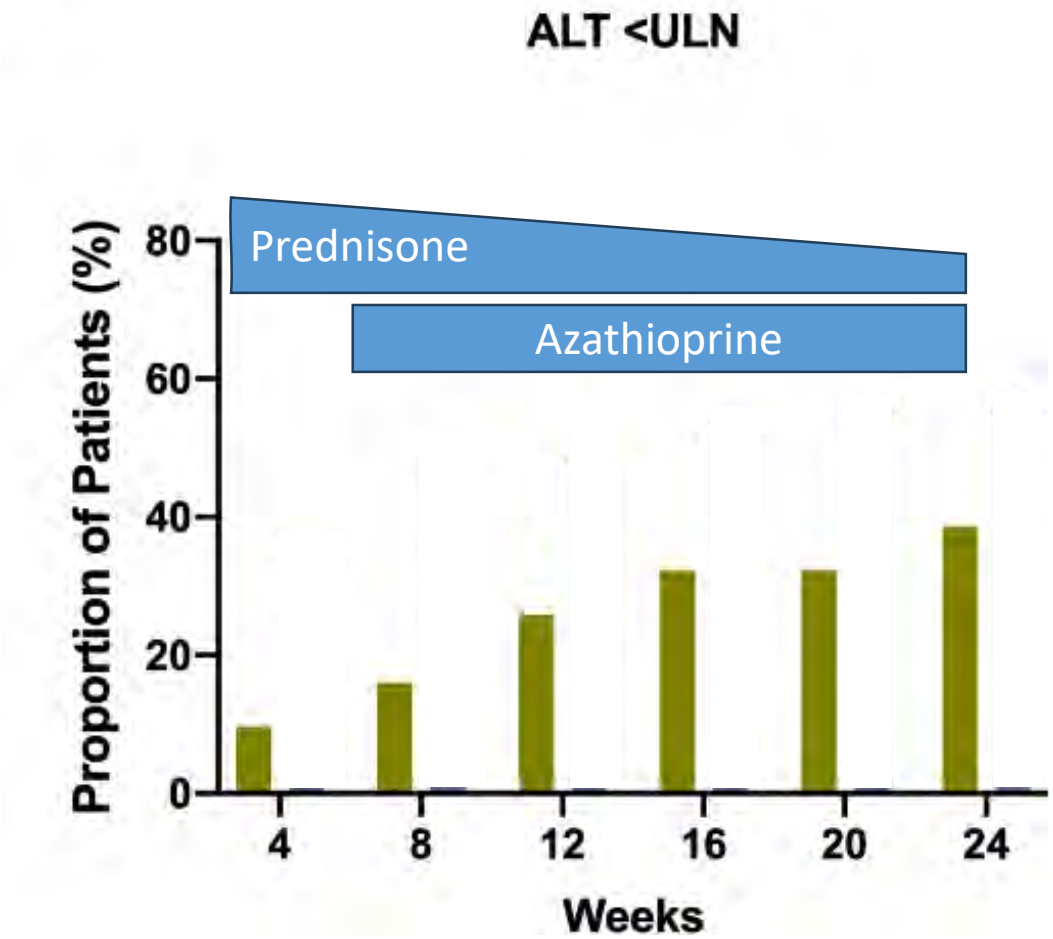
The combination of Prednisone & Azathioprine induces disease remission and prevents mortality in treatment naïve patients with AIH

Remission

- absence of symptoms suggestive of a relapse
- serum globulin & ASAT < ULN

Outcomes of 1st line therapy in AIH

- Standard of care therapy
- Prednisone 40 mg / day
- Azathioprine 50-100 mg /day
- Normalisation of ALT at 6 months in ~40%



Snijders J Hepatology J Hep 2024

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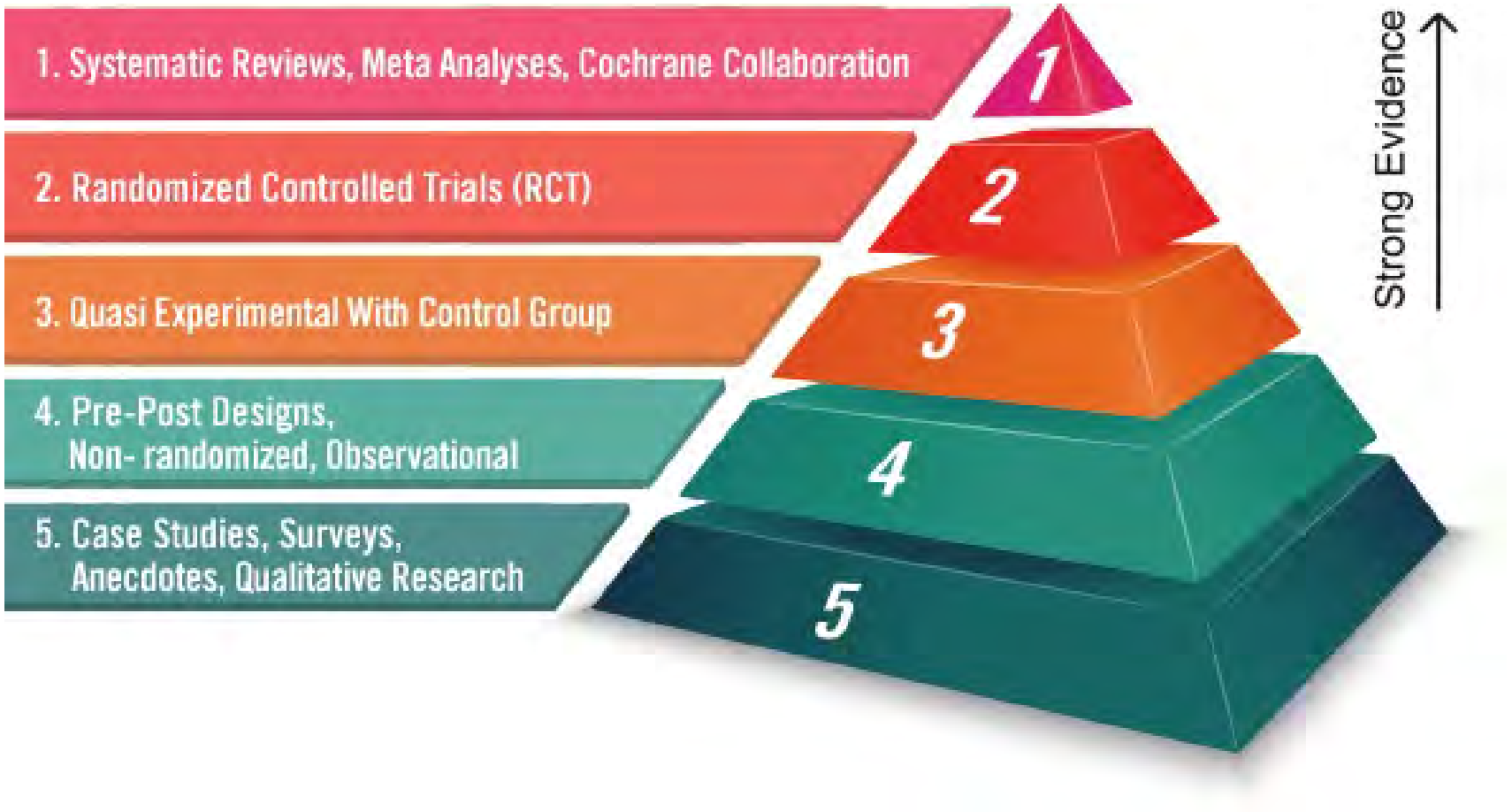
Clinical Trials in AIH



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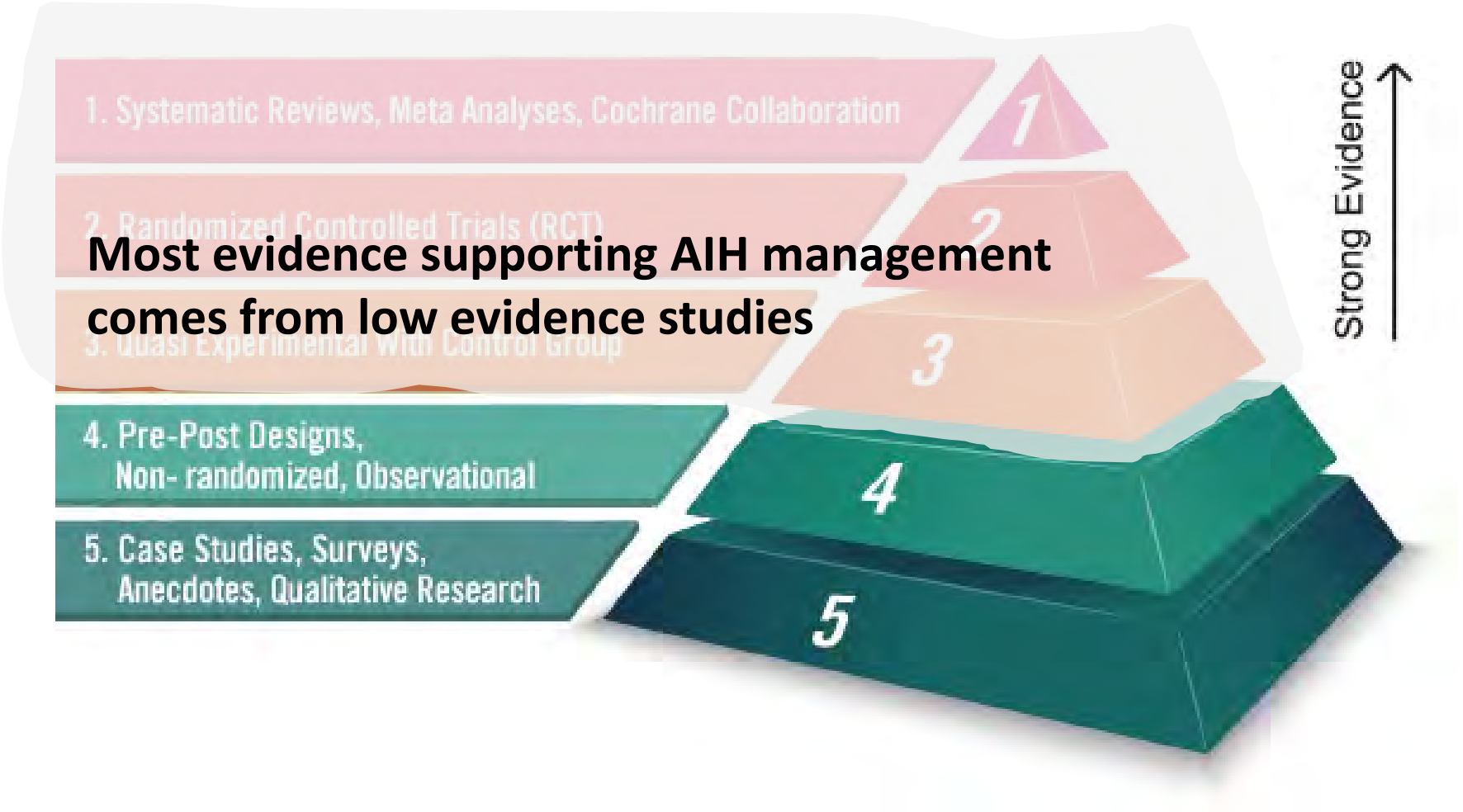
Clinical Trials in AIH



Most evidence supporting AIH management comes from low evidence studies

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RCTs in AIH (2023)

Trial registry	Total trials registered	AIH interventional trials (total/ongoing)
GCTR (GER)	13801	0 (0)
EUCTR (EU)	43117	5 (4)
ISRCTN (UK)	22931	1 (1)
DDRARE (JPN)	33695	7 (4)
Clinicaltrials.gov (USA)	437548	41 (~8)

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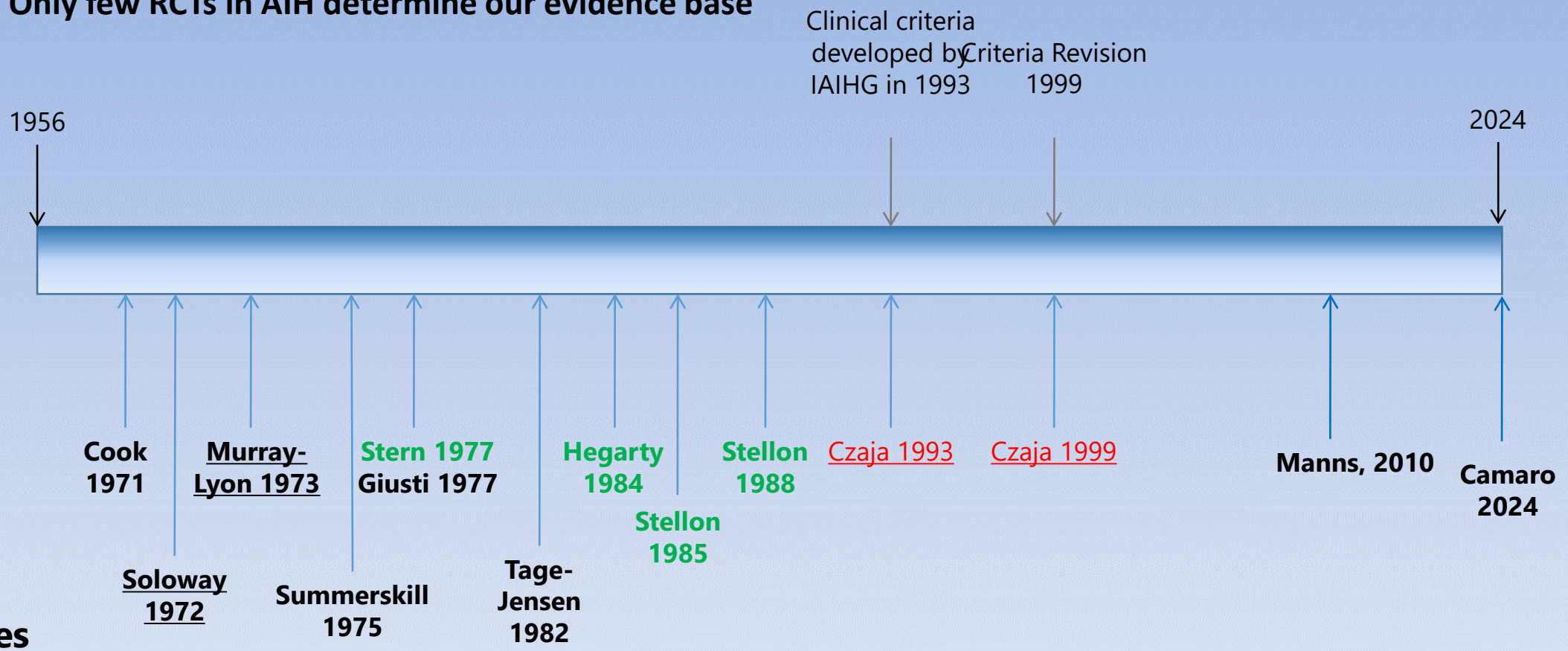
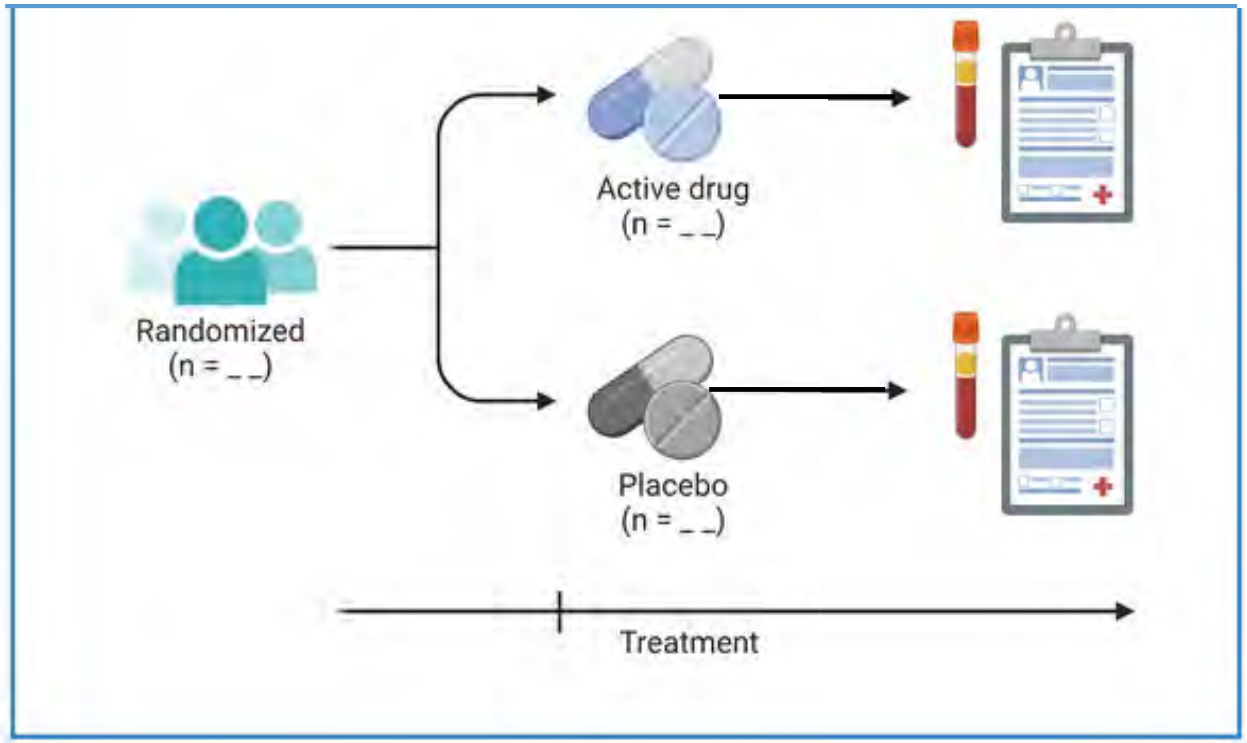
Clinical trials in AIH: 1971-2024 (n=14)

Only few RCTs in AIH determine our evidence base



Naives
Relapsers
Maintenance

Randomised double blind placebo controlled trial
Basic design



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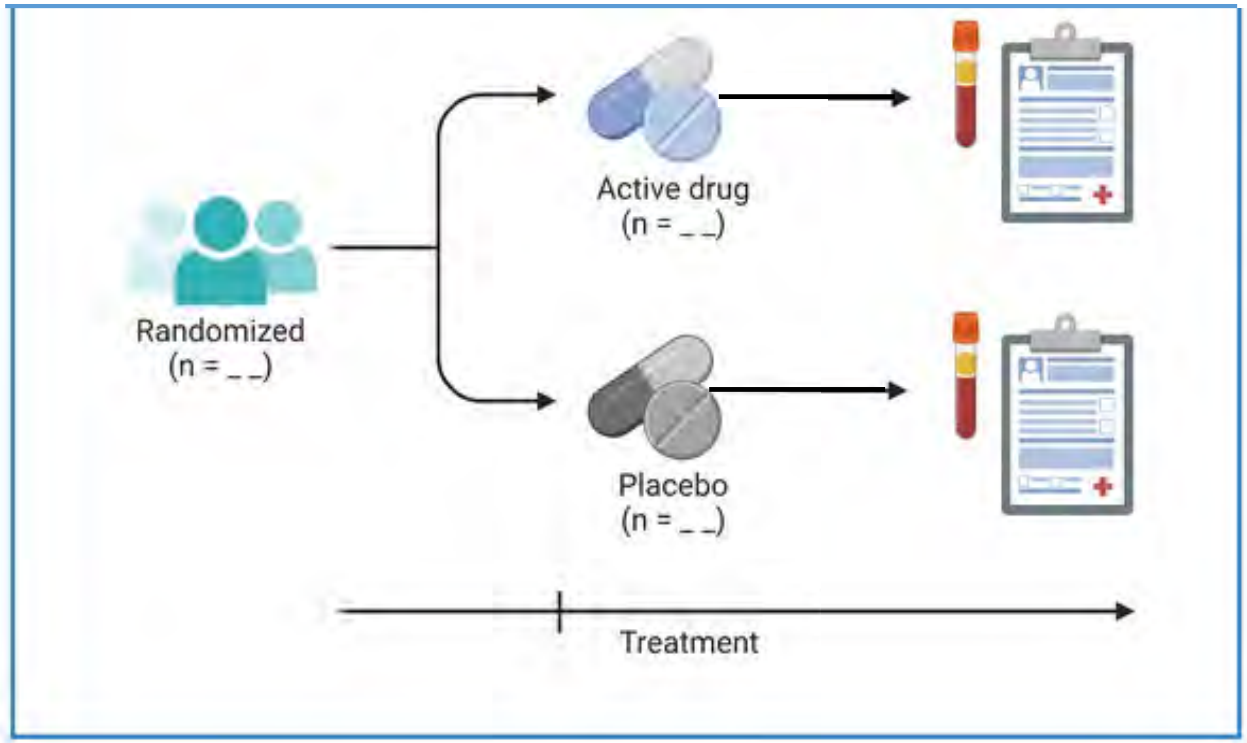
Randomised double blind placebo controlled trial
Basic design

Population Comparator Endpoints



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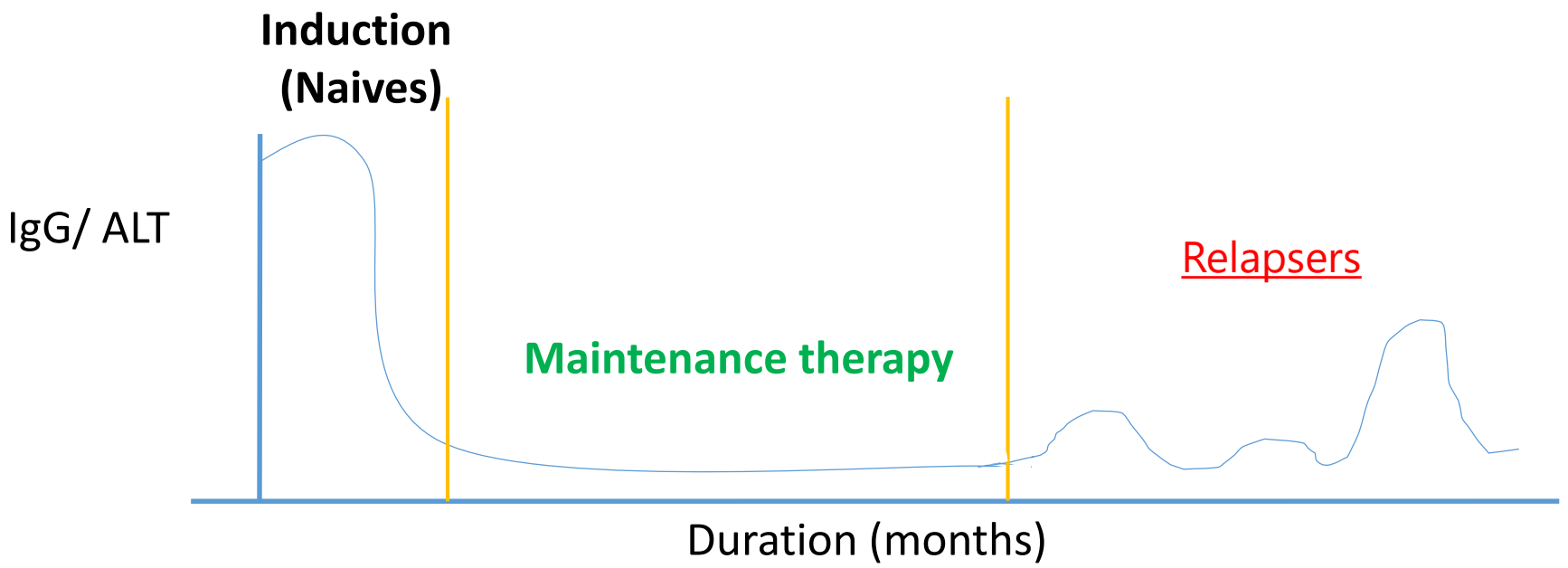
Randomised clinical trials in AIH: 3 different phases



Naives
Relapsers
Maintenance

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Used outcomes in AIH trials (last 3 RCTs)

	Population	Comparison	Endpoint
Czaja	treatment failure, repeated relapse, or incomplete response	ursodeoxycholic acid vs. placebo	ASAT improvement at 6 months
AIH-BUC	Naïve	Prednisone vs. Budesonide	ALAT & ASAT < ULN without predefined steroid-specific side effects*, at 6 months.
CAMARO	Naïve	Azathioprine vs. MMF	ALAT & IgG , < ULN at 6 months

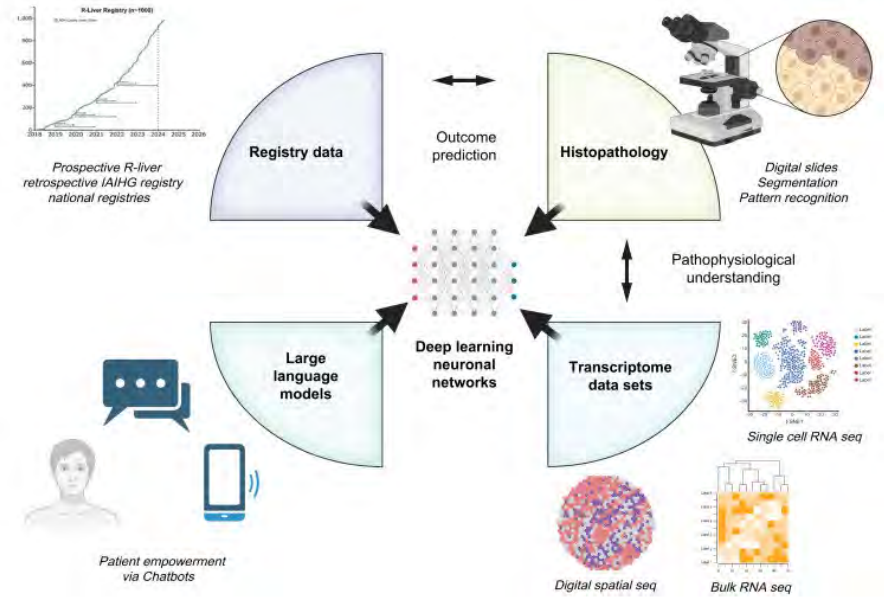
(* moon face, acne, buffalo hump, hirsutism, striae, diabetes, glaucoma, and increased intraocular pressure)

Hepatology. 1999; **30**:1381-1386, Gastroenterology. 2010 Oct;139(4):1198-206, J Hepatol. 2024 Apr;80(4):576-585.

Clinical Trials in AIH

- **Background**
  - 3 RCT's , 1999-2024
  - 3 different primary endpoints
- **Issue**
  - No consensus on outcome measures
  - No consensus on clinical trial designs
- **Possible outcomes**

1. improvement of symptoms
2. biochemical remission of ASAT/ALAT & IgG
3. histological remission mHAI ≤3



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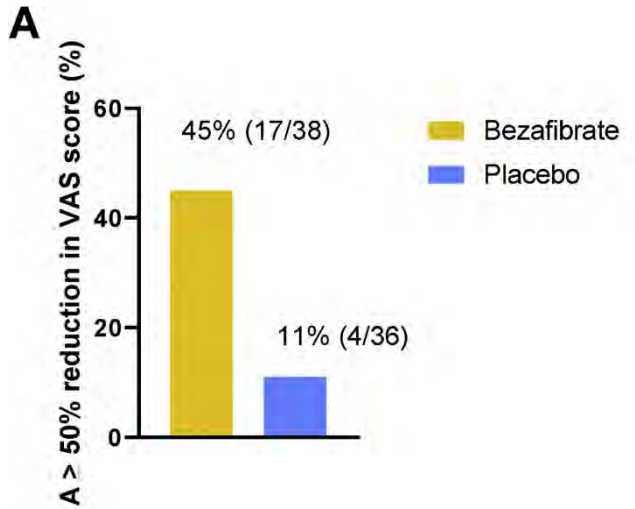
Improvement of Symptoms

HRQoL in clinical trials

HRQoL is recommended as an endpoint in clinical trials

- FITCH study[1] (PBC, PSC, SSC)
  - Primary endpoint: ≥50% reduction of pruritus (VAS)
- CAMARO study[2] (AIH)
  - Secondary endpoints



FDA U.S. FOOD & DRUG ADMINISTRATION

Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments

Draft Guidance

1. De Vries et al. Gastroenterology (2020) 2. Snijders et al. Trials (2022)

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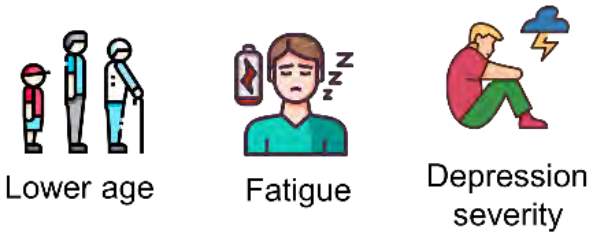
Health Related Quality of Life

PREDICTORS OF HRQOL

Physical HRQOL

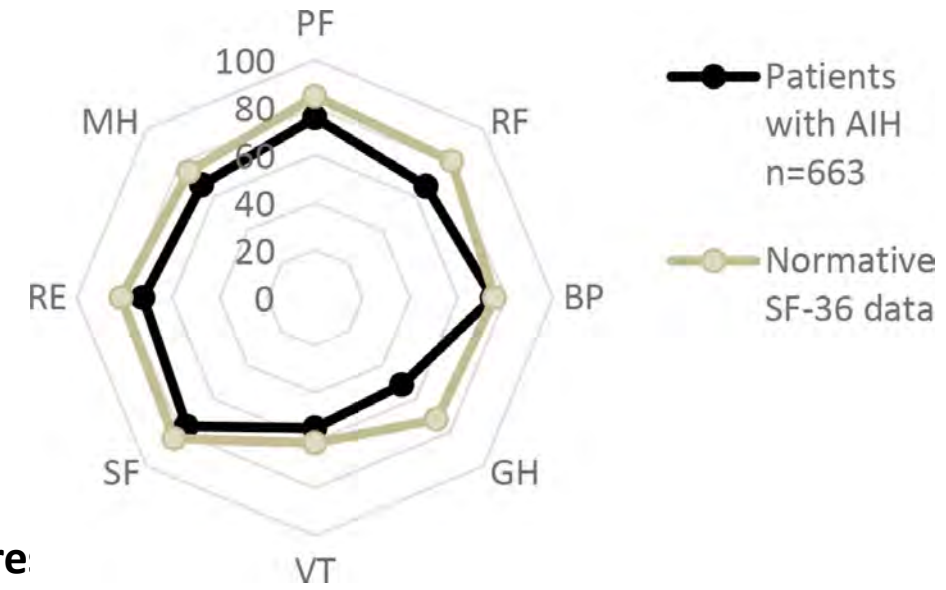
Mental HRQOL



Generic Scales (SF36)

- AIH comes with a lower quality of life
- Patients experience more anxiety and depression

SF-36 Scale



Disease specific questionnaire

- Example: The PBC-40 is a patient-derived, disease specific quality of life measure
- Lacking for AIH

World J Hepatol 2021 Nov 27;13(11):1642-1652

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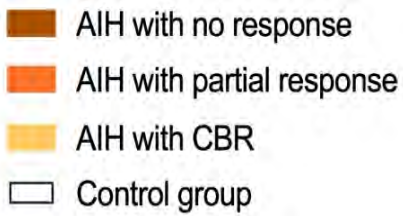
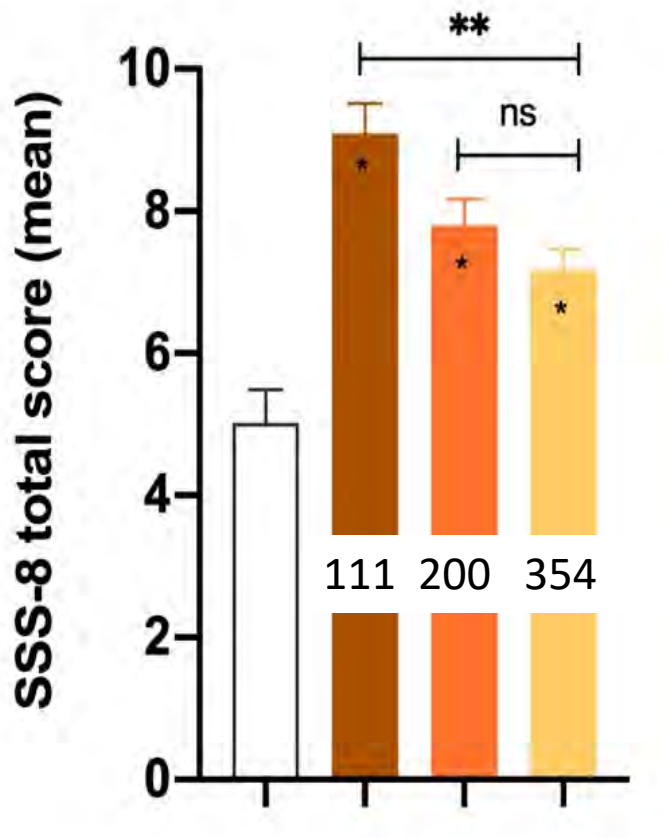
Patients with AIH have higher somatic symptom burden & experience lower quality of life

Somatic Symptom Scale
SSS-8 score
- Low (4-7)
- Medium (8-11)
- High (12-15)





- Reduced HRQoL is linked to physical well-being
- Somatic symptoms, fatigue, and mental health issues contribute to this decline
- The association of CBR with lower somatic symptom burden highlights its significance as an outcome measure.

Snijders et al Hepatology 2025

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Biochemical remission: ASAT/ALAT & IgG

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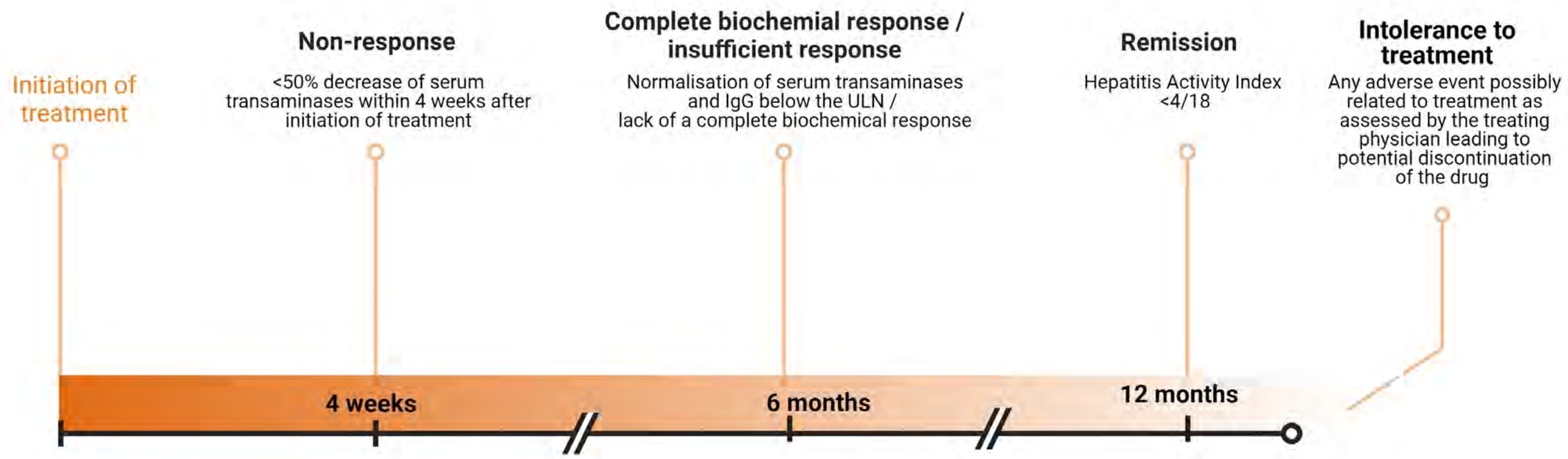
Endpoints



Pape Snijders J Hepatol. 2022 Apr;76(4):841-849

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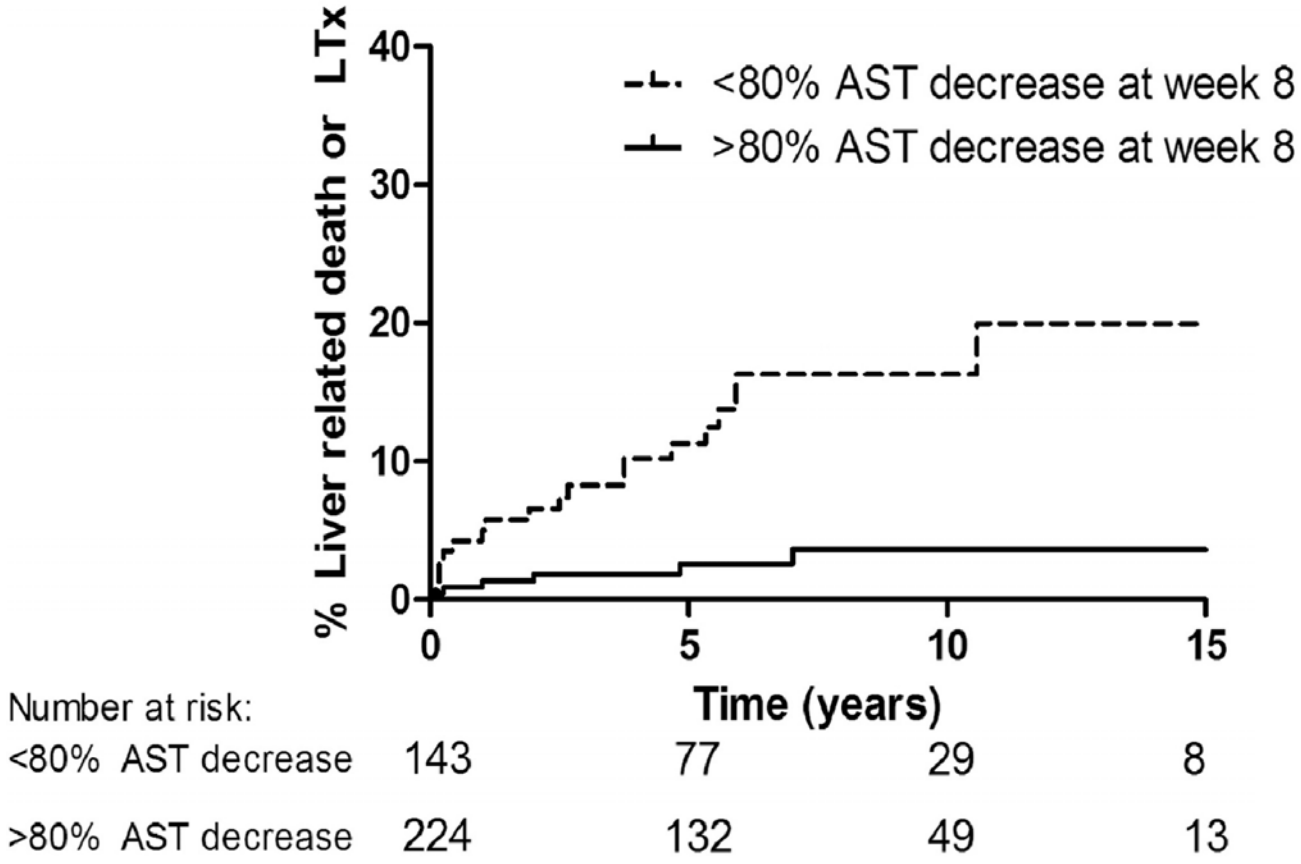
ALAT & IgG response -> Prognosis

8 Weeks

- **Drop of ASAT at 8 weeks predicts**
  - ALAT / ASAT < ULN
  - 26 & 52 weeks
- **Rapid responders**
  - Lower risk of liver-related death or transplantation (HR 0.18; 95% CI 0.05-0.63)



Pape Clinical Gastroenterology and Hepatology 2020 181609-1617.

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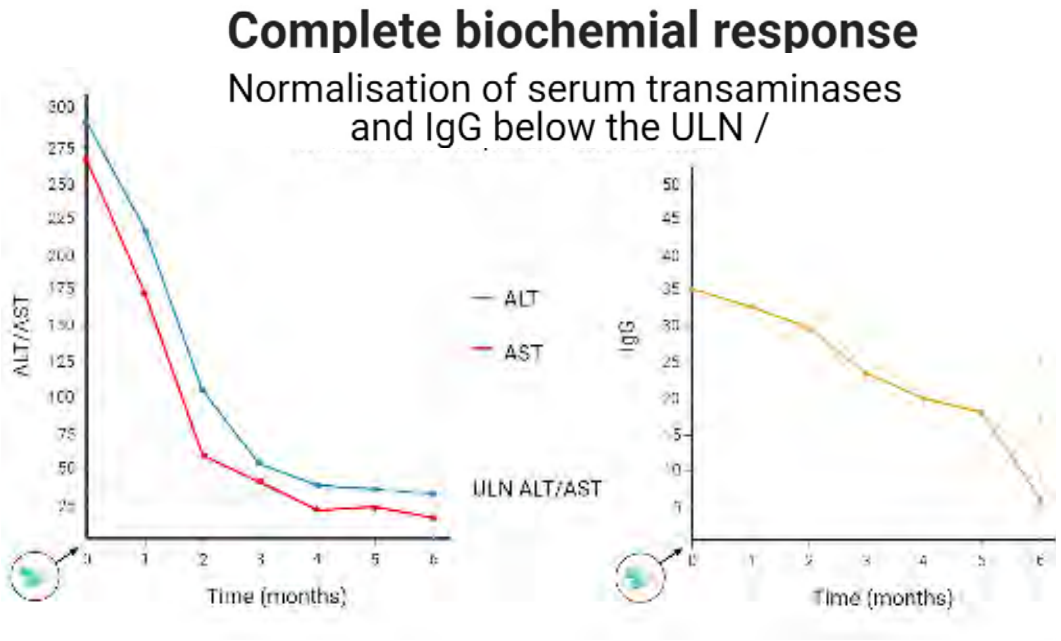
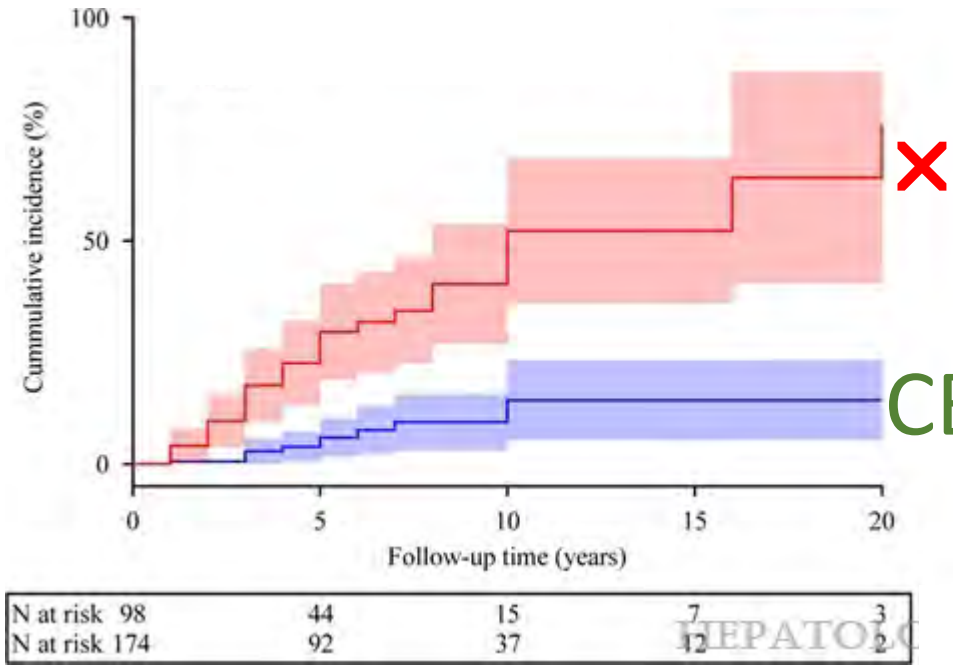
ALAT & IgG response -> Prognosis

6 Months



Cirrhosis development after CBR



N=272 patients

~~Non CBR~~ n=98

CBR n=174

Slooter Hepatology. 2023 Sep 4. doi: 10.1097/HEP.0000000000000589

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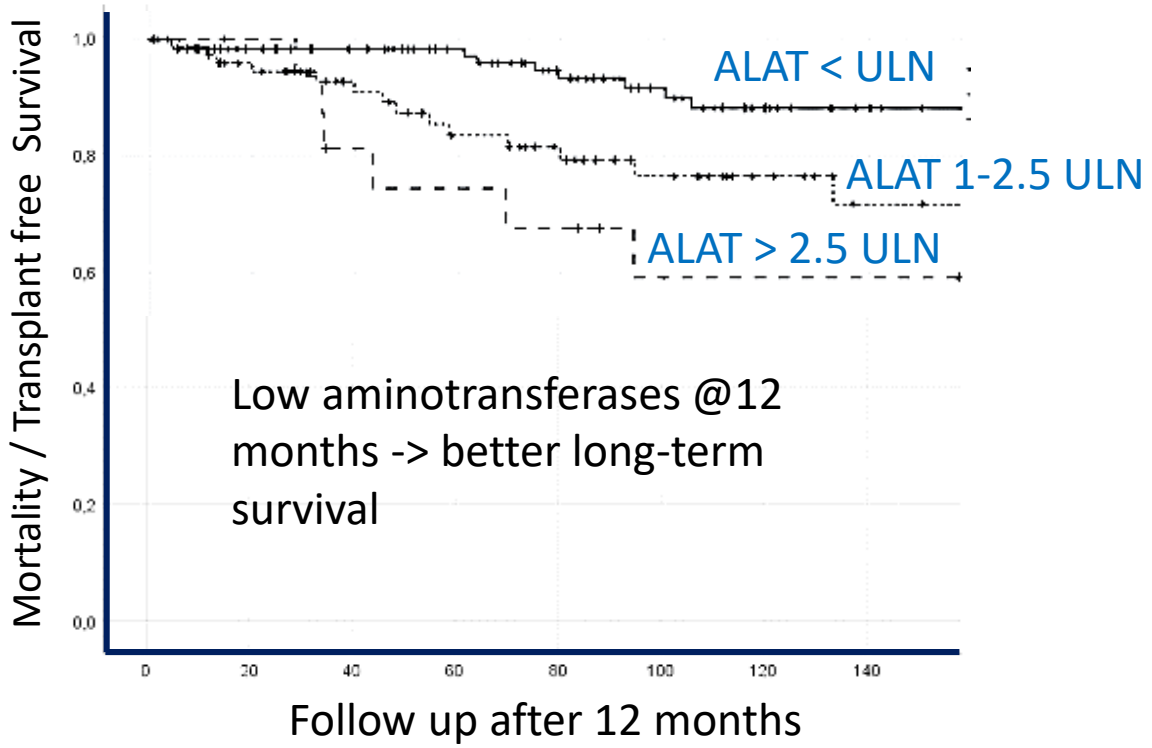
ALAT & IgG response -> Prognosis

12 Months

- AIH patients n=301
- Median follow-up of 99 (7–438) months
- ALAT at 12 months after start of AIH treatment
- **Outcome**
  - mortality & transplant free survival



Normalization of aminotransferases should be the treatment goal for autoimmune hepatitis to improve long-term survival

Biewenga Clinical Gastroenterology and Hepatology 2022;20:1776–1783

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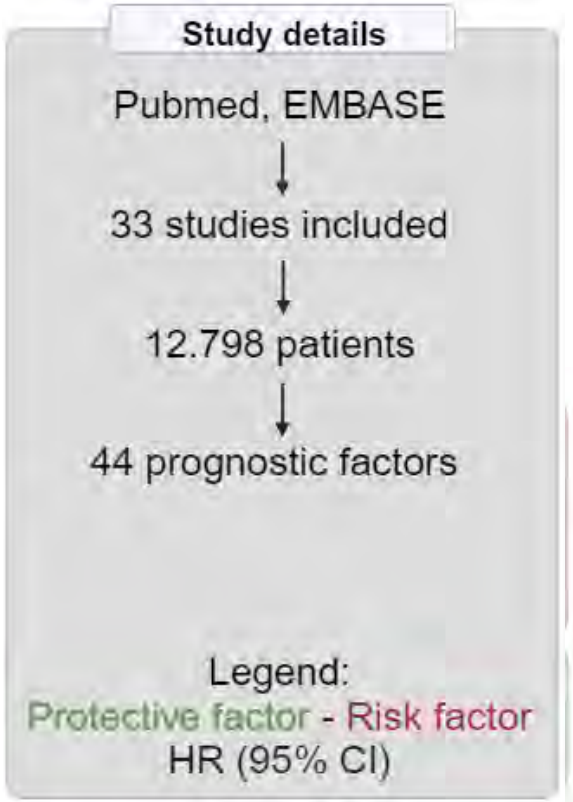
Early prognostic factors for reduced survival in AIH: systematic review and meta-analyses



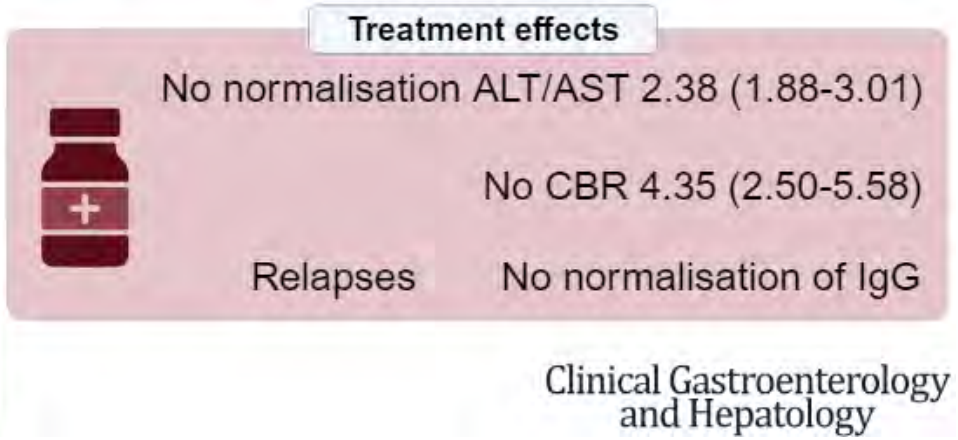
Risk Factors

Unmodifiable

- Demographics, Phenotype

Modifiable

- Treatment effects



Unpublished results

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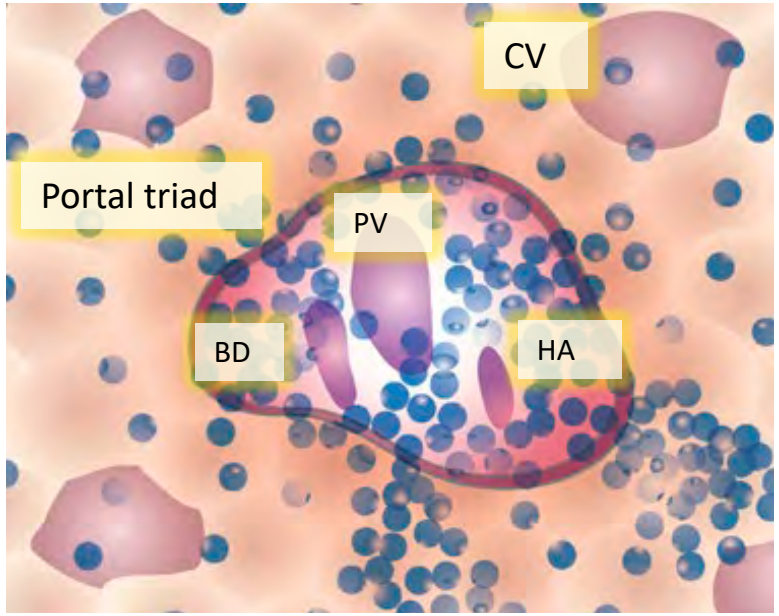
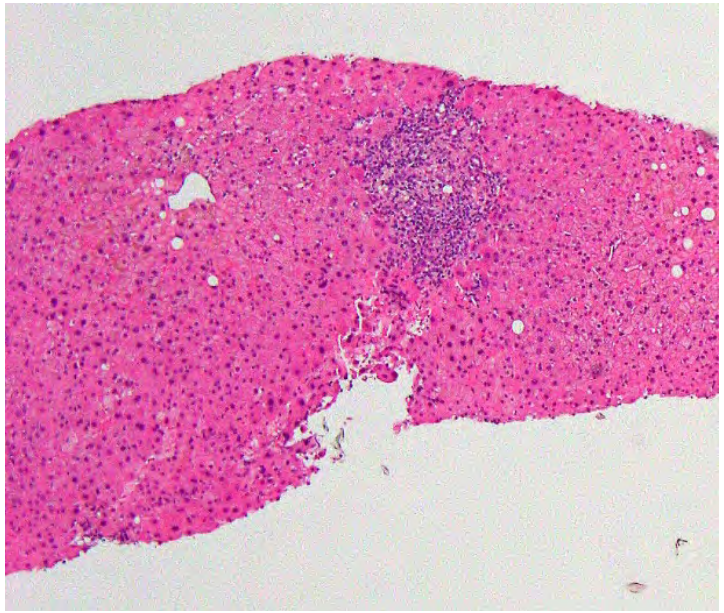
AIH Histology

- Interface hepatitis with plasma cells / lymphocytes
- Lobular or panacinar necrosis

Portal inflammation / Interface hepatitis





PV portal vein, CV central vein, BD bile duct, HA hepatic artery

Histology in AIH: mHAI classification

- Microscopic histological assessment of a liver biopsy is required for establishing the diagnosis of AIH.
- There are no pathognomonic histological features of AIH
- Modified Hepatitis activity score (mHAI) ≥ 4/18)

Hepatitis Activity Score	Score
Periportal or periseptal interface hepatitis	0-4
Confluent necrosis	0-6
Focal (spotty) lytic necrosis, apoptosis & focal inflammation	0-4
Portal inflammation	0-4

CPG AIH J Hep 2015

Liver Int 2022 May;42(5):1058-1069

Limited concordance among pathologists in mHAI assessment

Sample

- 64 AIH liver samples, 10 pathologists

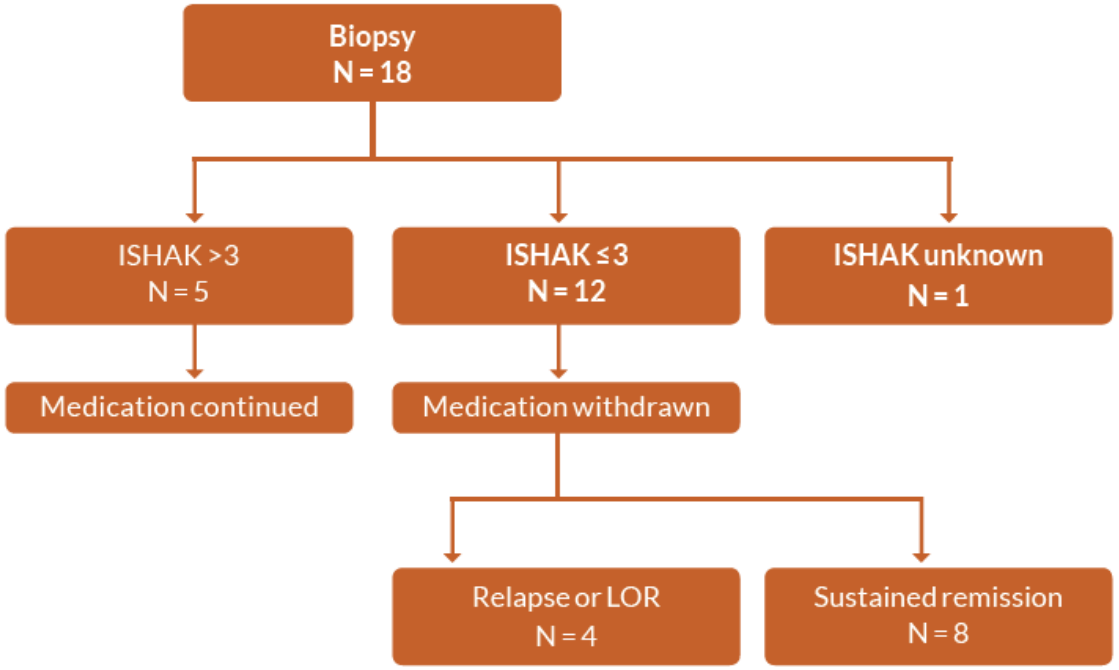
Hepatitis Activity Score	Score	Kappa*
Periportal or periseptal interface hepatitis	0-4	0.29
Confluent necrosis	0-6	-0.31
Focal (spotty) lytic necrosis, apoptosis & focal inflammation	0-4	0.31
Portal inflammation	0-4	0.41
mHAI grade		**0.02**

* Cohen's Kappa: <0 poor, 0-0.20 slight, 0.2-0.4 moderate

Selcuk Med J 2023;39(4): 178-182

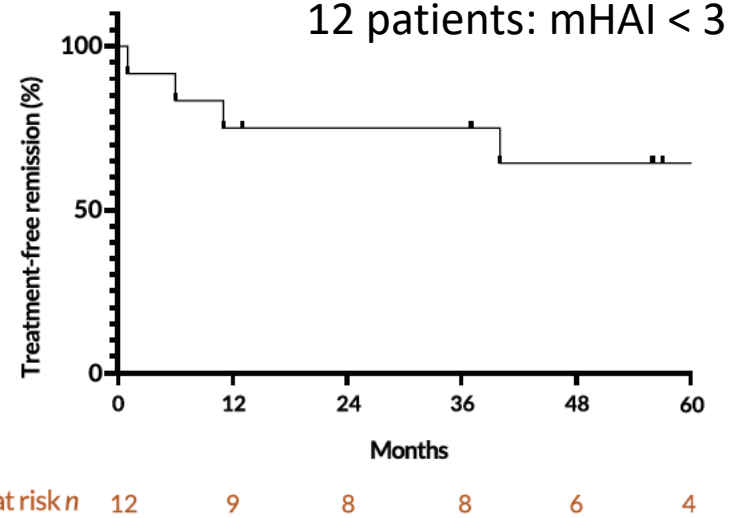
Histology guided stopping

mHAI predicts success of treatment withdrawal in patients with >2 year CBR in 67% of cases



Success rate after histology driven treatment withdrawal

12 patients: mHAI < 3



8/12 remained in treatment-free remission
follow-up 62 months

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Outcome measures

- HRQoL
  - Clearly compromised in AIH
  - No disease specific questionnaire
  - Drug options to affect HRQoL ?
- Biochemical parameters
  - Ease of measurement, Limited interassay variability, repetitive
  - Evidence to support correlation with hard endpoints
- Histology
  - Cumbersome to obtain
  - High interobserver variability
  - Incomplete correlation with hard endpoints

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Clinical Trials in AIH

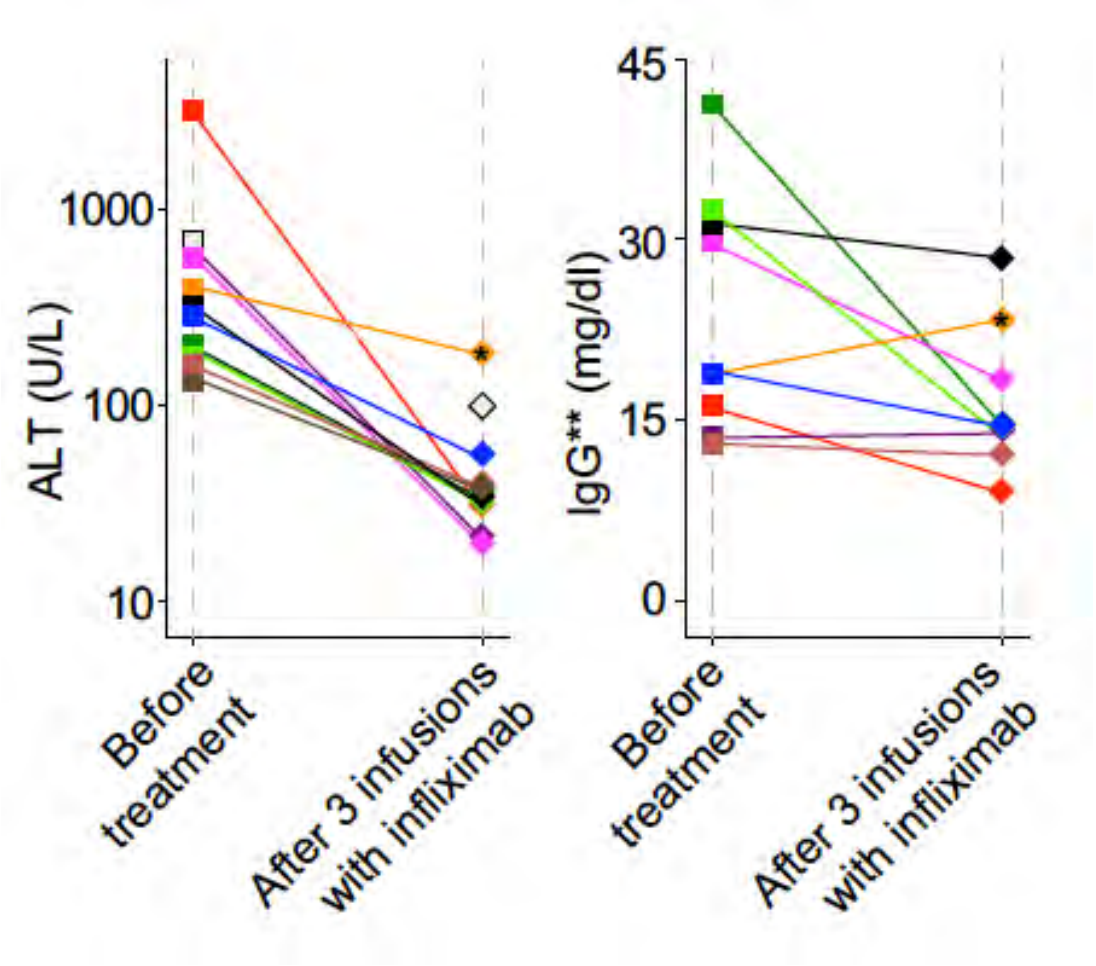
AIH: Current interventional trials

Trial	Sponsor Location	Intervention / Patients	Primary endpoint (simplified)	N	Rdm	Centers	Phase	Status
AIH BUDPRED 1.0	Umea SWE	• Budesonide vs. Prednisone (+ azathioprine)	Normalization of ALT/AST/IgG after 1 year	150	Yes	Multi	IV	Ongoing
AIH-MAB	Hamburg GER	• Infliximab as AIH induction treatment + azathioprine • Acute newly diagnosed AIH	Normalization of ALT/AST/IgG after 6 mo.	12	No	Single	IIA	Completed
MERLIN	Birmingham UK	• Single infusion mesenchymal stromal cells (MSC) • incomplete remission to standard care	Finding highest safe dose (HSD) Determining impact on liver enzymes/IgG/fibrosis	18	No	Multi	I/II	Ongoing

UKE HAMBURG European Reference Networks ERN RARE-LIVER Amsterdam UMC University Medical Centers

Treatment of refractory AIH
effect anti-TNF

- Difficult to treat AIH
- 11 patients (F 7, M 4)
- Cirrhosis n=7
- **Adverse events**
  - Steroids n=7
  - AZA n=6
- **Outcome**
  - Full remission n=8
- **Comedication**
  - PRED 5-20 mg/day



J Hep 2013 vol. 58 j 529–534

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Finished Trial

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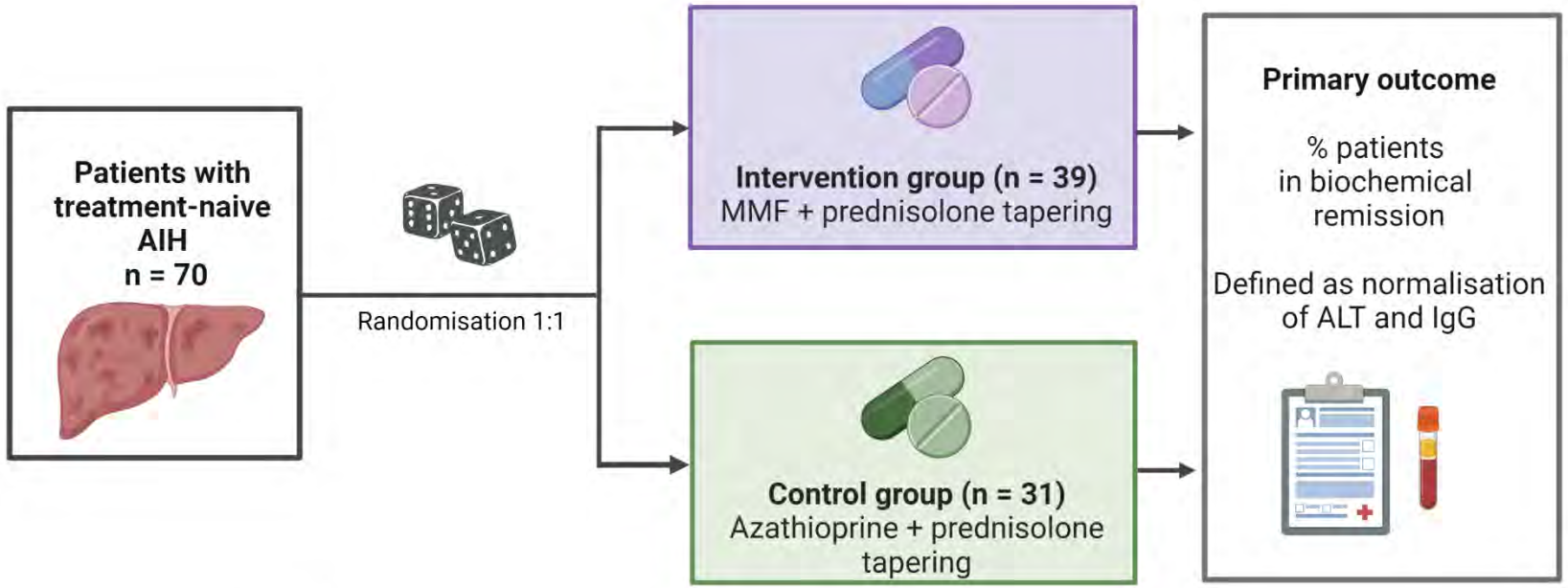
Clinical trial Assessing the efficacy and safety of Mycophenolate mofetil versus Azathioprine for induction of Remission in treatment naive autOimmune hepatitis: CAMARO



1. Hennes EM et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology. 2008;48(1):169-176. doi:10.1002/hep.22322

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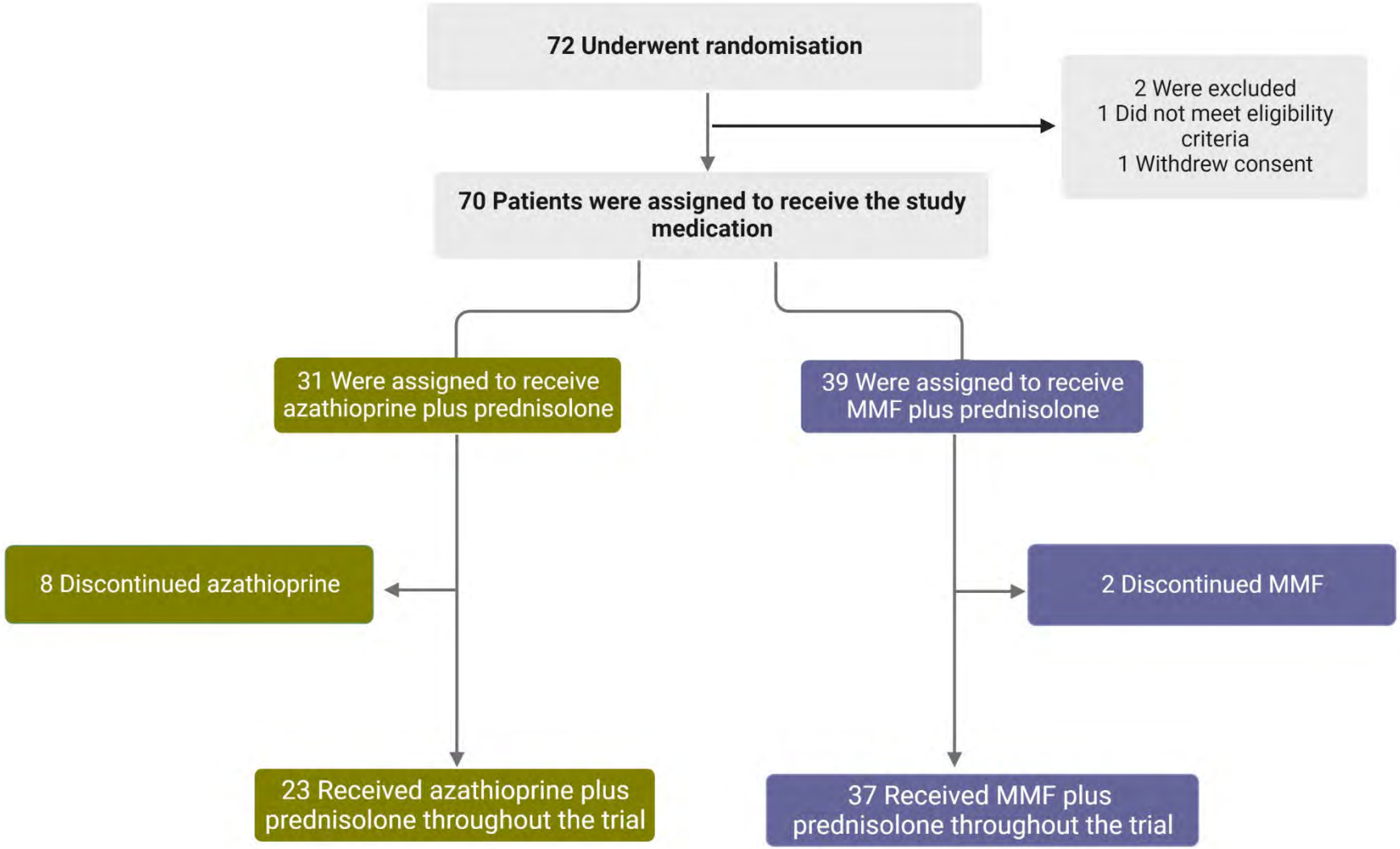
CAMARO Flowchart



Snijders J Hepatol. 2023 Dec 14:S0168-8278(23)05309-6.

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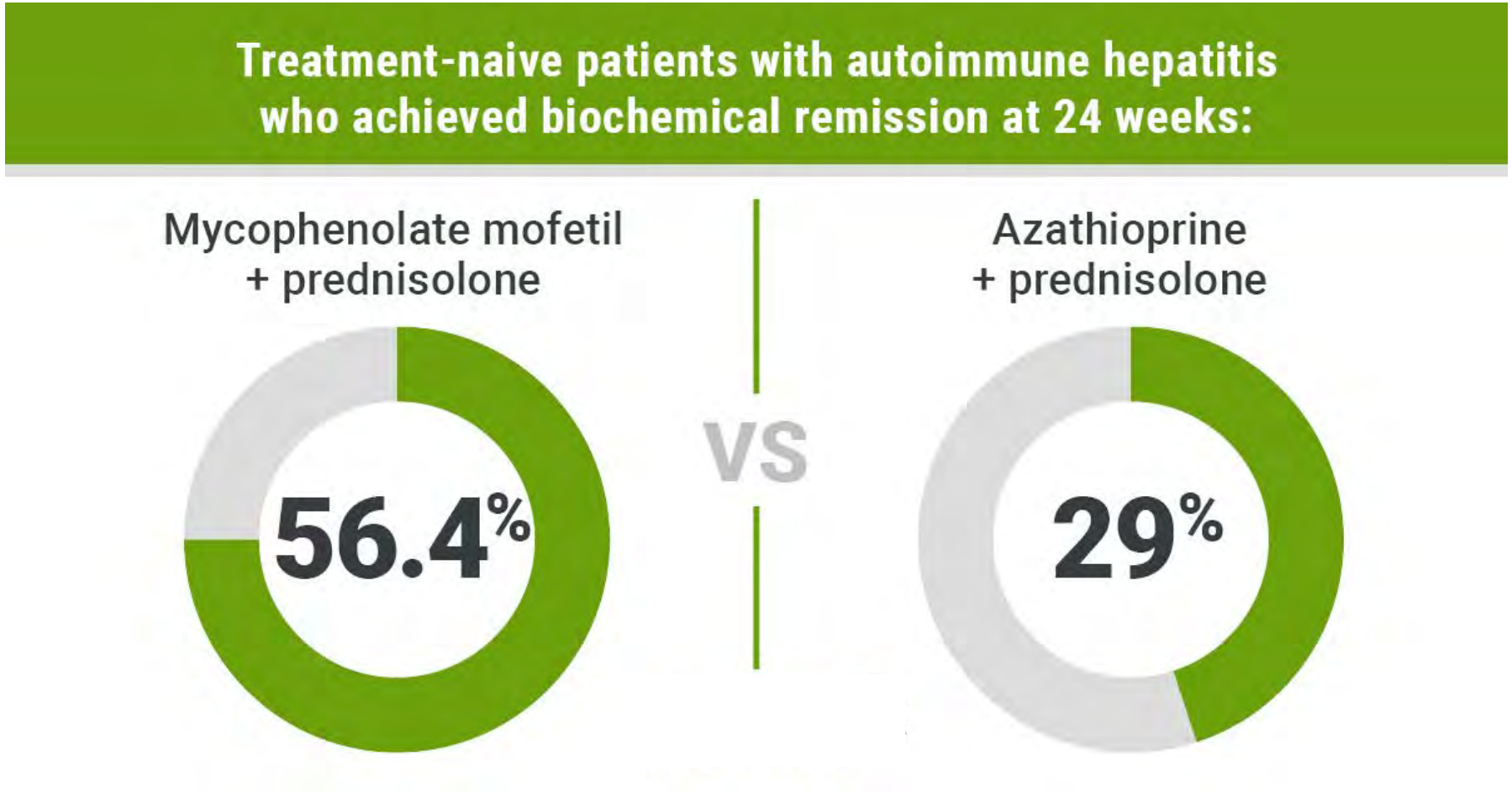
Baseline characteristics

- **Inclusion period**:
- March 2017 - November 2022
- 24 Dutch and Belgian hospitals

	Azathioprine (n = 31)	MMF (n = 39)
Female, (%)	21 (68%)	30 (77%)
Age at diagnosis, years	56±14.4	60±14
Diagnosis simplified criteria	10 (32%)	13 (33%)
Probable, n (%)	21 (68%)	26 (67%)
Definite, n (%)		
Lab values		
ALT (U/L)	541 (175-936)	333 (173-689)
AST (U/L)	332 (130-801)	239 (128-621)
IgG (g/L)	24.6 (17.8-31.7)	23.3 (17.6-31.7)
Cirrhosis at diagnosis	7 (23%)	10 (26%)
BMI (kg/m²)	26 (23-29)	25 (23-28)

Snijders J Hepatol. 2023 Dec 14:S0168-8278(23)05309-6.

Primary efficacy CBR at 6 months



Primary endpoint (CBR)
MMF 56.4%
Azathioprine 29.0%
Independent of prednisone dose

Snijders J Hepatol. 2023 Dec 14:S0168-8278(23)05309-6.

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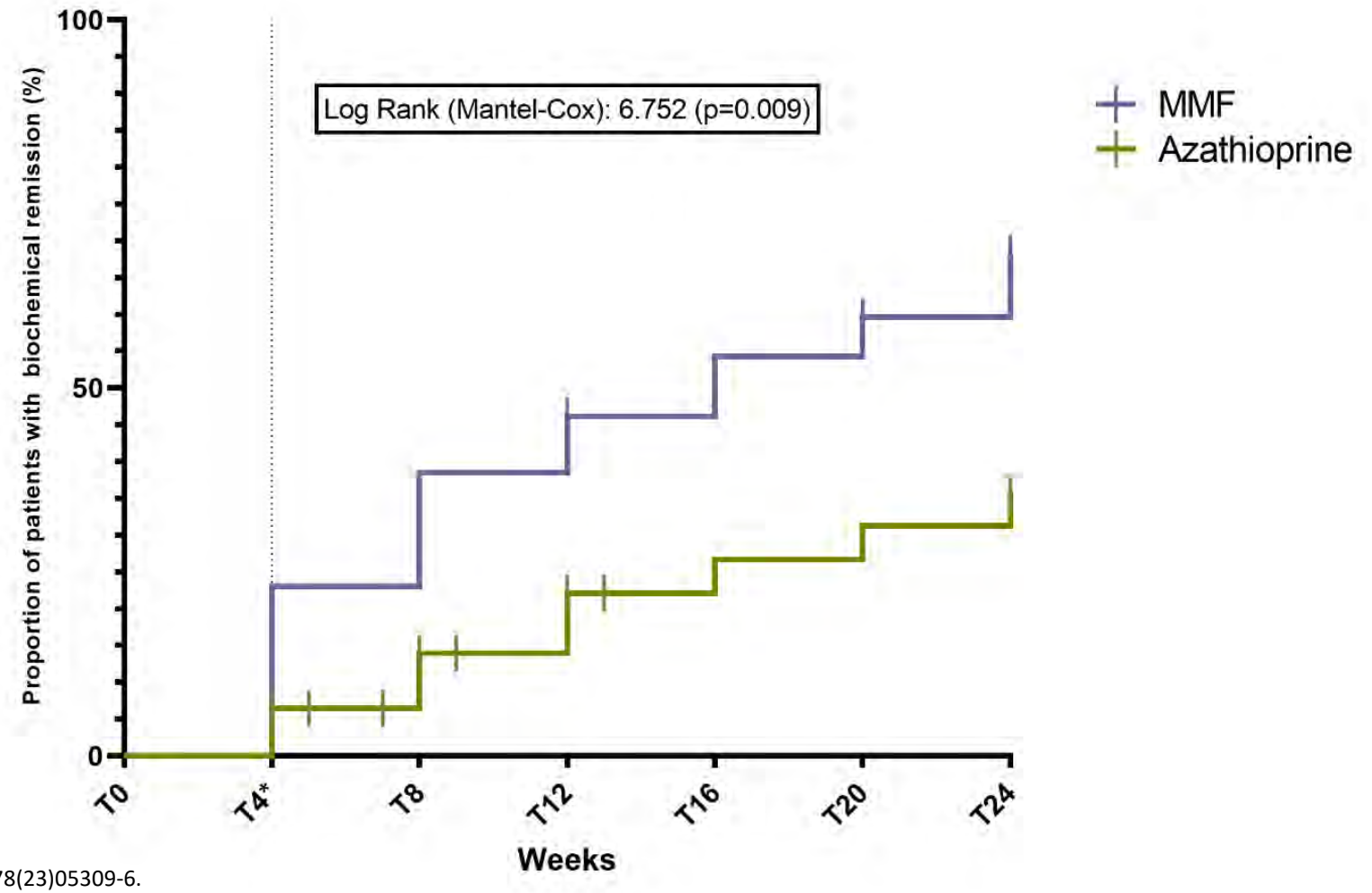
Primary efficacy: time to CBR



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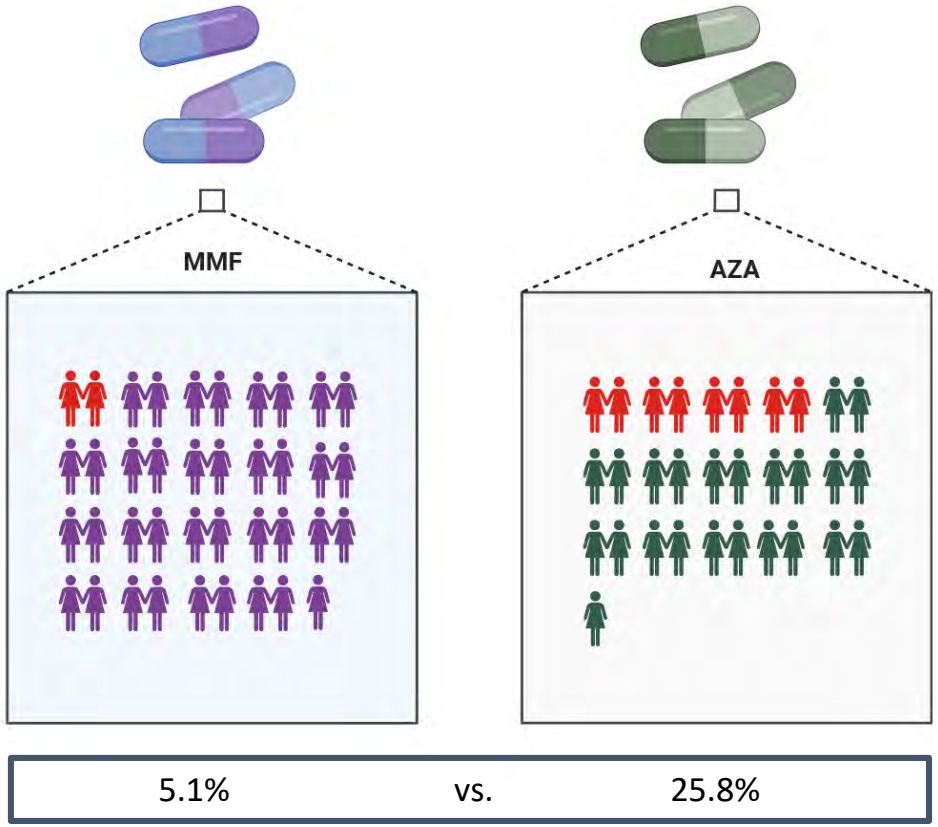
Discontinuation rate



In the azathioprine group, there was a higher discontinuation rate due to (severe) adverse events compared to MMF (p=0.018).

Snijders J Hepatol. 2023 Dec 14:S0168-8278(23)05309-6.

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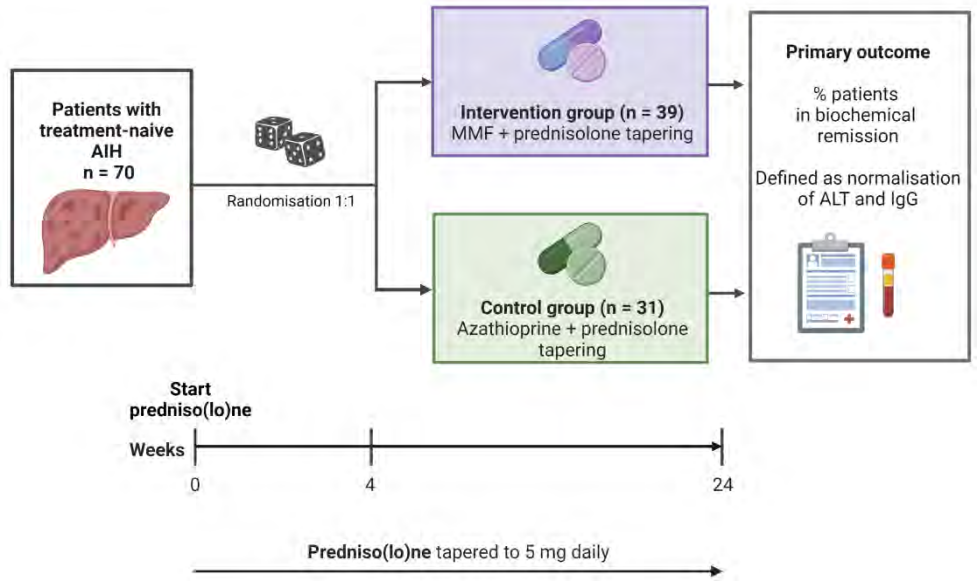
Clinical trial Assessing the efficacy and safety of Mycophenolate mofetil versus Azathioprine for induction of Remission in treatment naive autOimmune hepatitis: CAMARO

MMF is superior to Azathioprine to achieve biochemical remission at 24 weeks

- less AEs in the early treatment of AIH, independent of baseline alanine aminotransferase and IgG levels, or the presence of cirrhosis



1. Hennes EM et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology. 2008;48(1):169-176. doi:10.1002/hep.22322

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AIH: Prematurely discontinued trials

Trial	Sponsor	Target / intervention	Cause of termination
NCT04203875	Duke University, Durham, NC, USA	Abatacept / CTLA4	Lack of participants
NCT04129489	Stero Biotechs	Synthetic Cannabidiol	Lack of participants
NCT04790916	Roche, Switzerland	IL-2/IgG	Assumed lack of efficacy
NCT00608894	Veloxis Pharmaceuticals	Tacrolimus	Lack of participants
NCT03593460	University of Miami, Miami, FL, USA	sPIF	Drop-out of Pharmaceutical Collaborator
NCT05221411	University of Leiden	Tacrolimus	Drop out of PI

Past clinical trials

Effect of RO7049665 on the Time to Relapse Following Steroid Tapering in Participants With Autoimmune Hepatitis (AIH)

Autoimmune Hepatitis (AIH)

- Melredableukin alfa (RO-7049665) is a conjugate of human interleukin-2 and immunoglobulin G.
- Stimulates and expand T regulatory cells but not effector T cells

Regulatory roundup: Roche's ulcerative colitis asset plunges after Phase I terminated

https://www.clinicaltrialsarena.com/features/roche-ulcerative-colitis-regulatory-roundup/

Nov 2021

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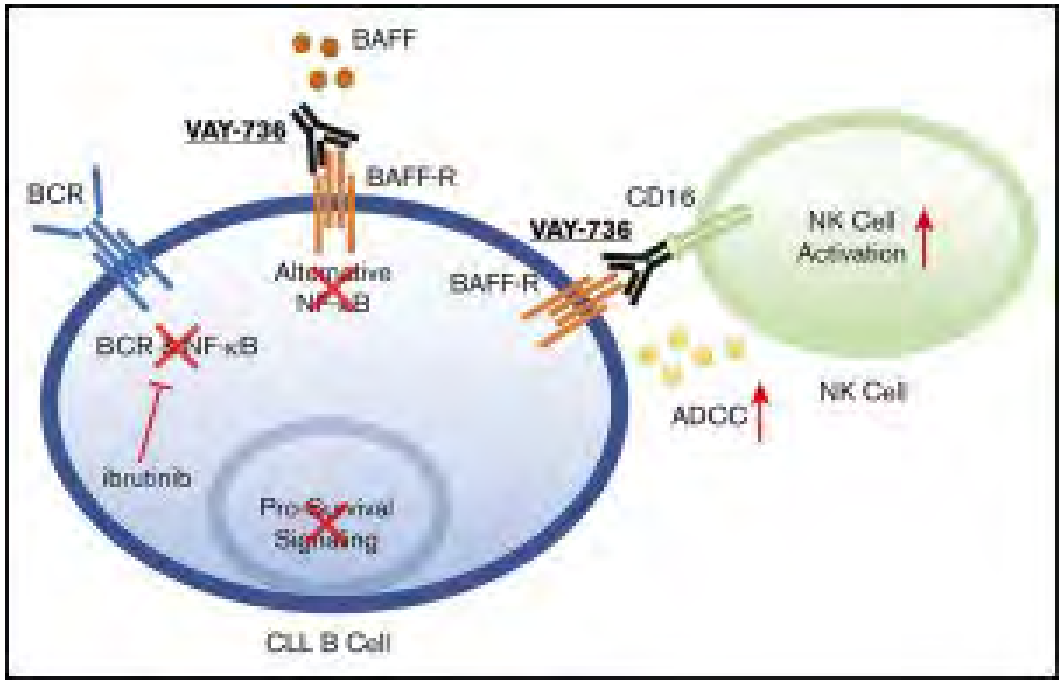
Past Clinical Trials

- Safety and efficacy of ianalumab (VAY736) in autoimmune hepatitis patients with incomplete response to or intolerance of standard therapy
- anti-B-cell activating factor (BAFF) receptor monoclonal antibody, engineered for direct ADCC-mediated B-cell depletion
- 2018 start of enrollment
- Status: ongoing…
- Outcome: not reported
- Ongoing studies in Sjogren syndrome pulmonary fibrosis



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Learning points: how to avoid the trial graveyard

- Trials
  - Large trials allow for subgroups
  - Rigorous design
  - Multicenter

- Structure
  - Nail the hypothesis, believable, unmet need , everyone wants the answer
  - Nail the team, be inclusive, give all credits to others
  - Cheerlead high recruiters
  - Share the (administrative) burden
  - Ask patients for input

AIH: Planned interventional trials

Trial	Sponsor Location	Intervention / Patients	Primary endpoint	N	Rnd	Centers	Phase	Status
JKB-122	Zhubei Taiwan	• JKB-122 (5/15/35mg daily p.o.) + soc vs. • Placebo + soc • 104 weeks • Newly diagnosed AIH	Normalization of ALT/AST/IgG after 6, 12, 24 months	120	Yes	Multi?	II	Not yet recruiting
PORTOLA	San Francisco CA, USA	• Initial 30 mg zetomipzomib, then 60 mg 1x/week + steroids vs. • Placebo + steroids • 24 weeks • Incomplete Remission / flare under first line therapy	Normalization of ALT/AST/IgG after 24 weeks	24	Yes	Multi	IIA	Not yet recruiting
HR19042	Lianyungang China	• HR19042 8/12mg daily p.o. / 4mg 3x daily	Biochemical response after 12 weeks	81	Yes	Multi	II	Not yet recruiting

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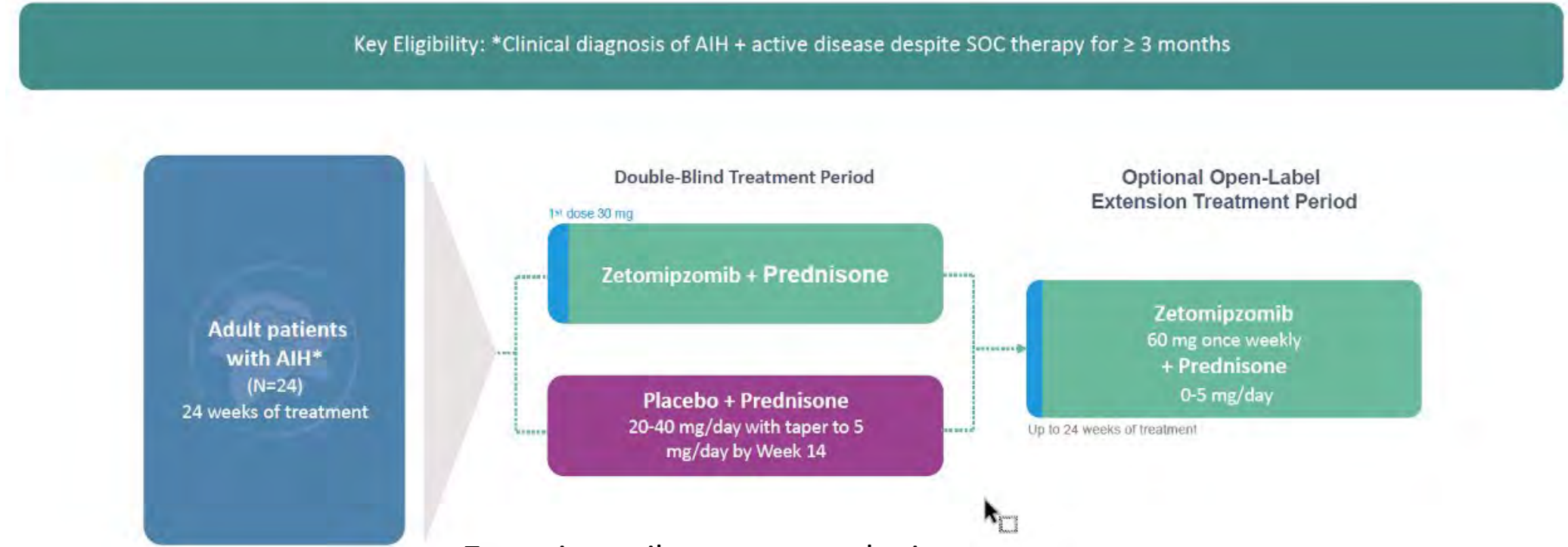
Future Clinical trials

PORTOLA: Phase 2a Placebo-Controlled Trial Evaluating the Safety and Efficacy of Zetomipzomib in Autoimmune Hepatitis



Zetomipzomib suppresses the immunoproteasome

https://liverdiseasenews.com/news/autoimmune-hepatitis-treatment-zetomipzomib-trial-seeks-patients/

Conclusion

- The level evidence in the literature to inform clinical decision making for AIH is mediocre
- Paucity of clinical trials, both from industry and investigator initiated
- Uncertainty about outcome measures -> need to create a core outcome set
  - ALAT / ASAT / IgG ?
  - HRQoL?
  - Liver stiffness measurement?
  - Histology?
- CAMARO demonstrated usefulness of MMF -> EASL CPG recommendation (2025)
- AIH-MAB is on the horizon
- Phase 3 trial design with Zetomipzomib is in the making

Autoimmune Hepatitis: Treatment Milestones and Modern Approaches

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Friday, February 14th Thursday 15 may, 2025

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