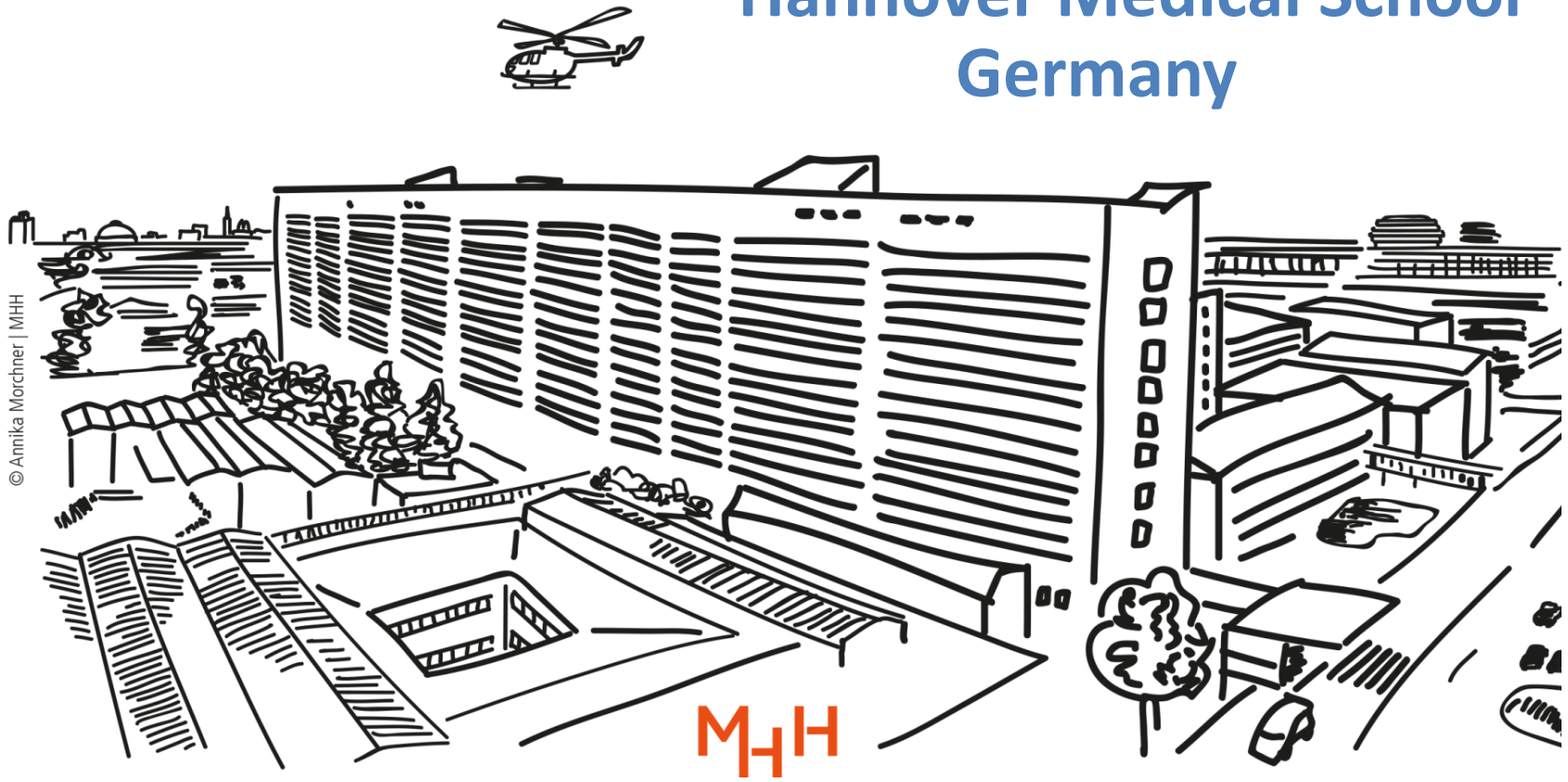
What is New in Autoimmune Liver Disease

Michael Manns
Hannover Medical School
Germany



Deutsche Leberstiftung
German Liver Foundation

European Reference Network
for rare or low prevalence complex diseases
Network Hepatological Diseases (ERN RARE-LIVER)
Member Medizinische Hochschule Hannover — Deutschland

Paris Hepatology Conference, Paris, 18 March 2024

Conflict of interest

Falk Pharma, Freiburg, Germany

Novartis, Basel , Switzerland

Roche, Basel, Switzerland

Intercept Pharmaceuticals

Acknowledgements

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- Bastian Engel, Hannover
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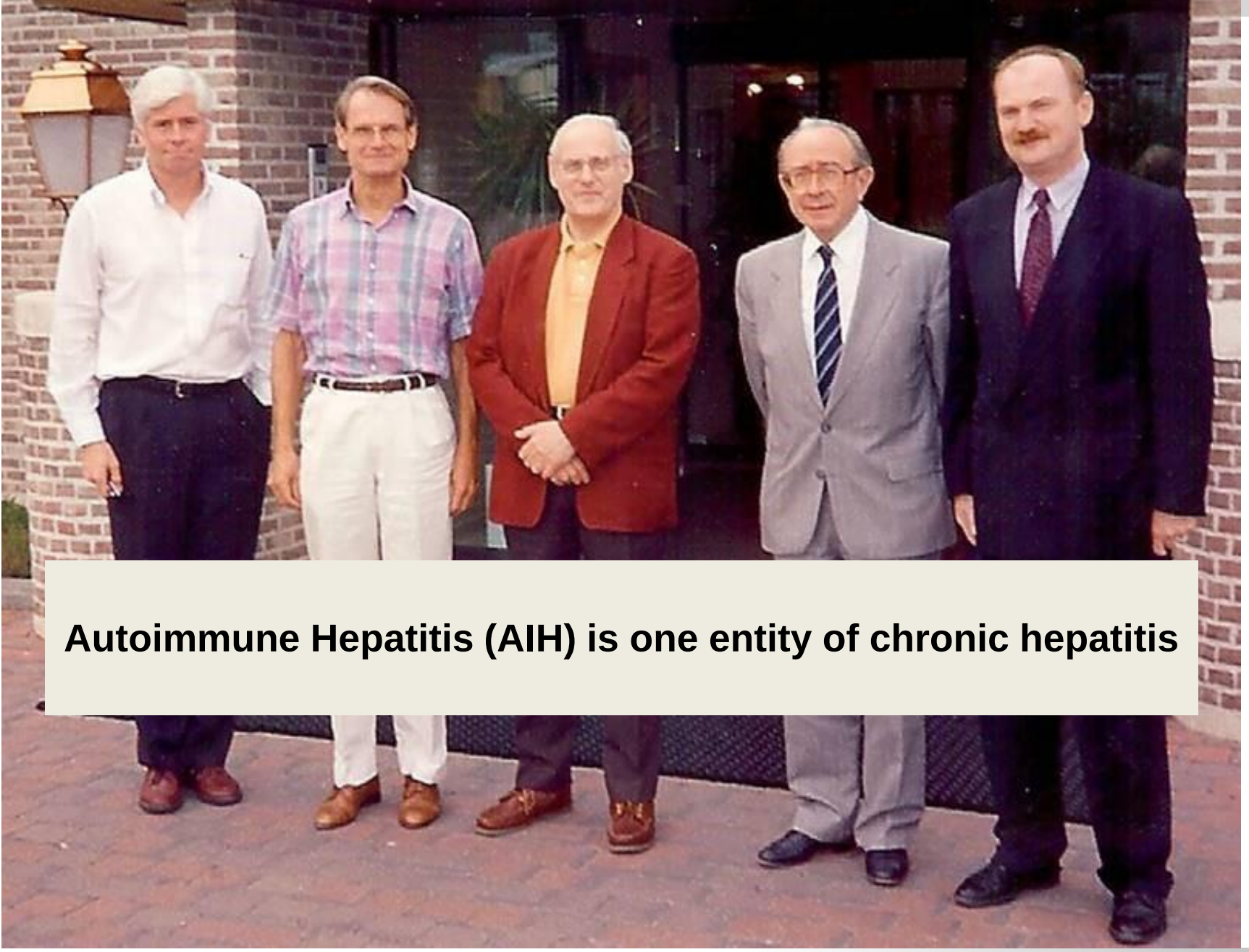
- The AASLD 2020 AIH Practice Guidance and Guidelines writing committee



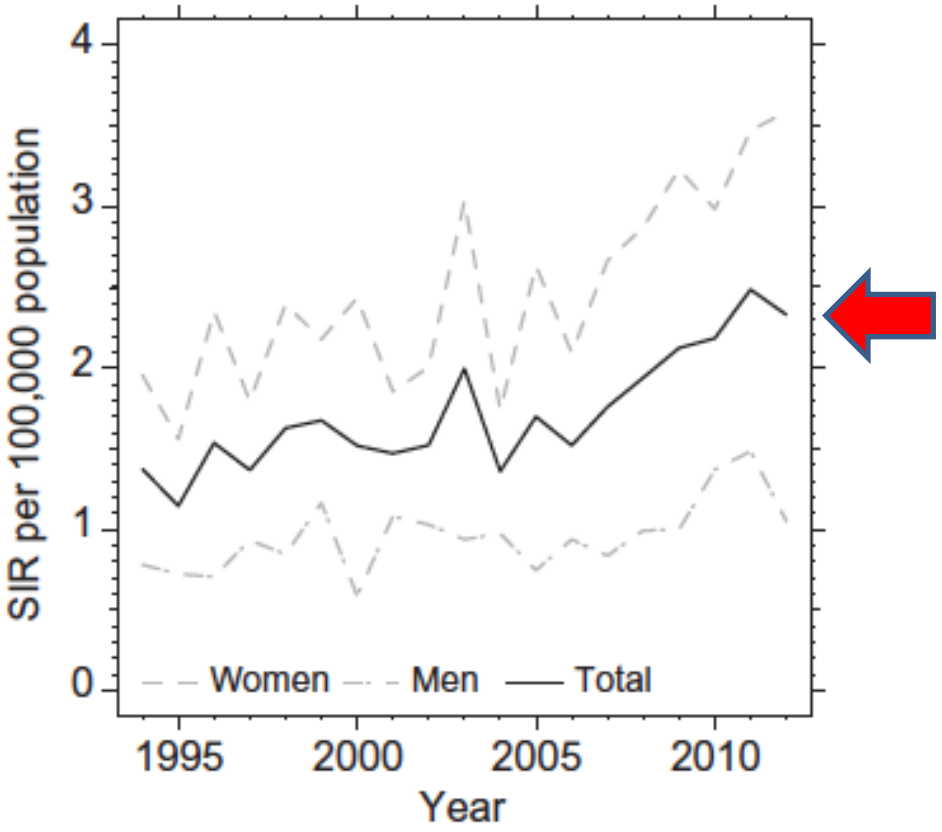
Autoimmune Hepatitis (AIH) is one entity of chronic hepatitis

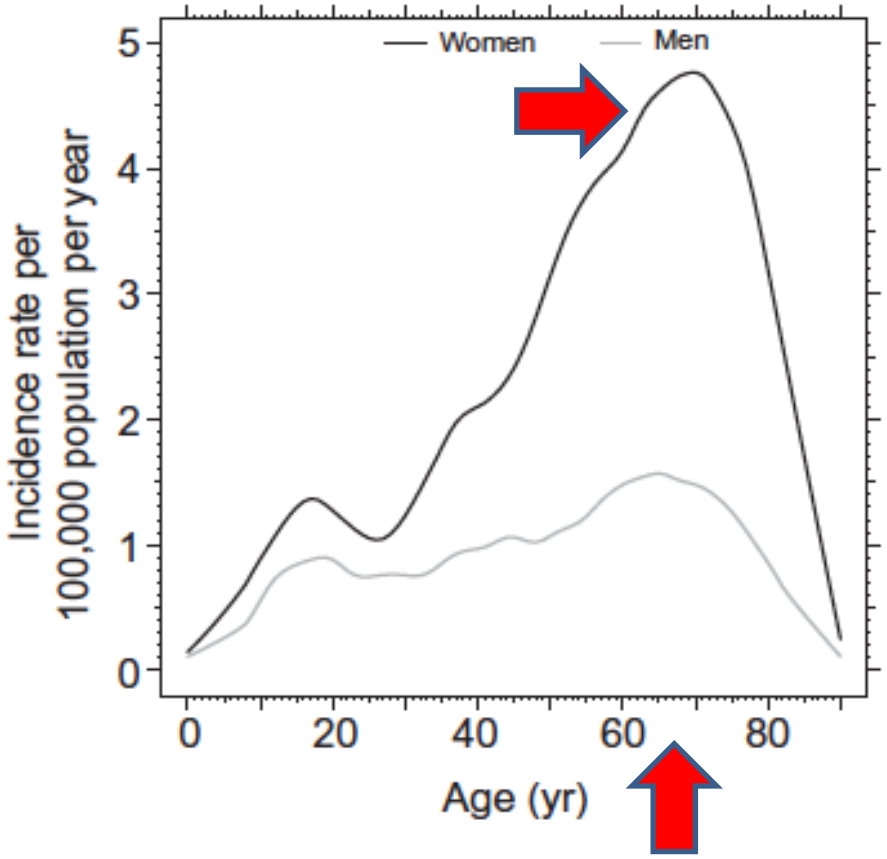
Classification of Chronic Hepatitis: Diagnosis, Grading and Staging

Desmet, Gerber, Hoofnagle, Manns, Scheuer, HEPATOLOGY 19: 1513-20, 1994

Epidemiology of AIH

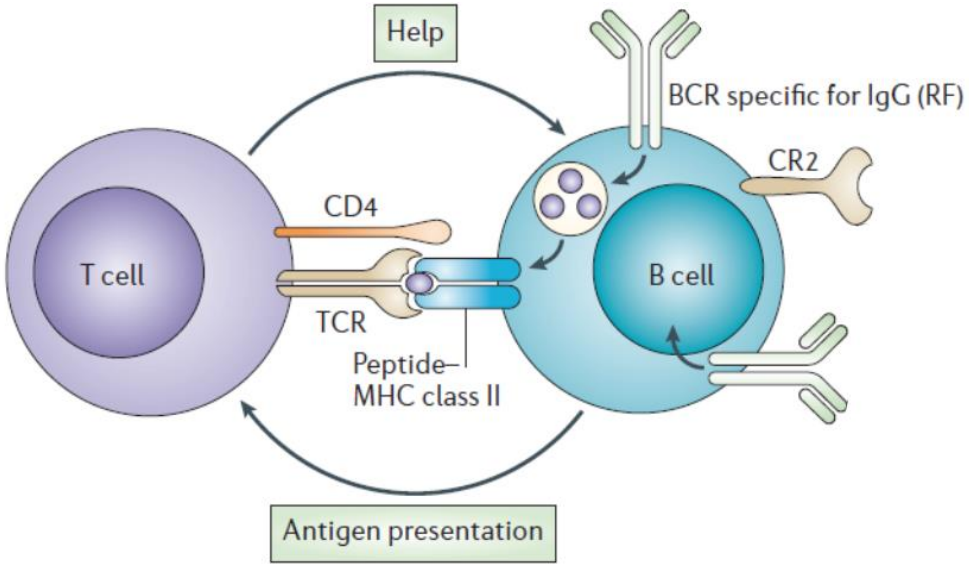
- Near 50% increase in incidence over the last few decades
- Occurs at all ages and within all ethnic groups around the world.

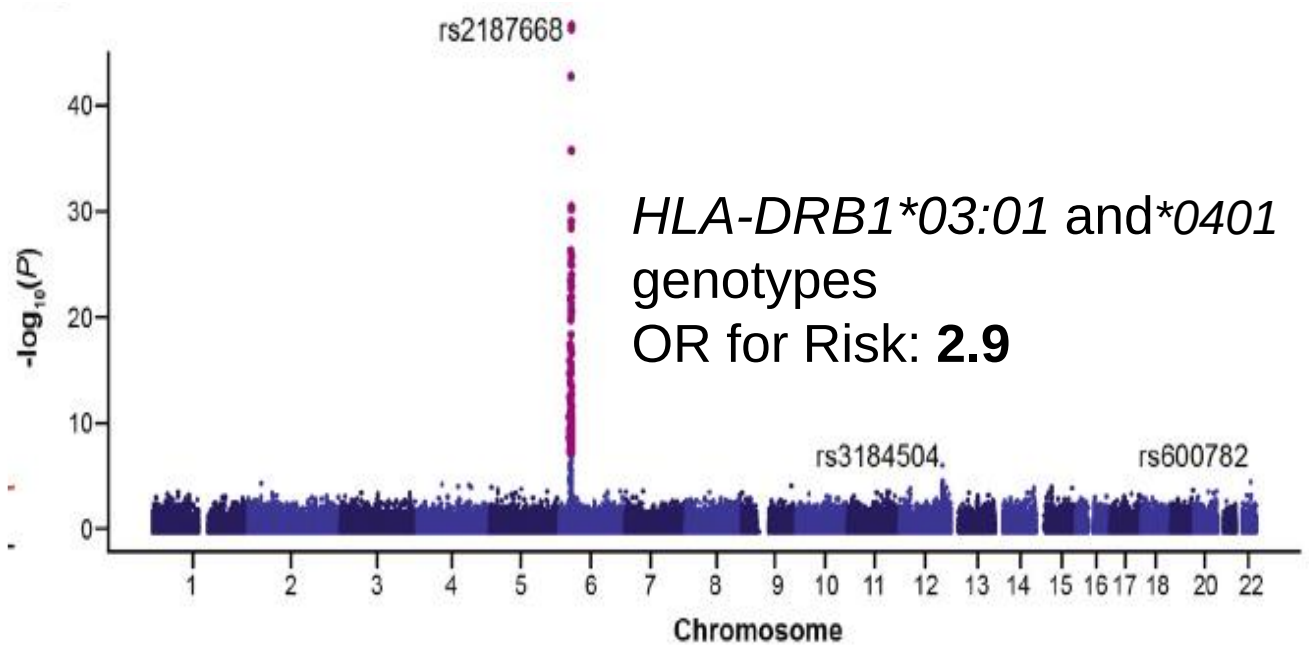




Grønbæk, et al. J Hepatol. 2014;60:612-7.

Genetic Background in AIH





*HLA-DRB1*03:01* and**0401* genotypes
OR for Risk: **2.9**

Modified from Edwards JC, Cambridge. Nat Rev Immunol 2006: 6:394-403
de Boer, et al. Gastroenterology. 2014;147:443-52

Autoimmune Hepatitis Update

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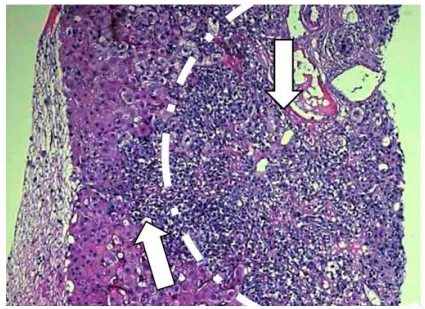
Diagnosis

Autoimmune Hepatitis - AIH

Hepatitis

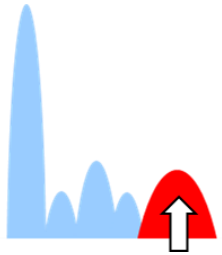
expandierte Portalfelder mit lymphoplasmazellulärem Infiltrat



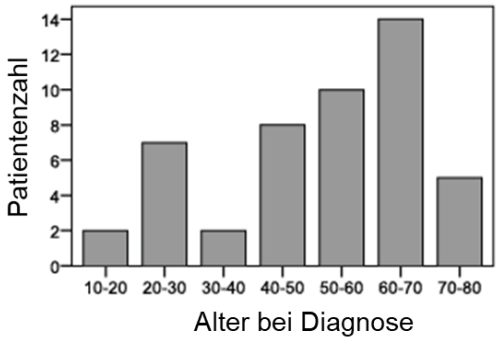
Interface-Hepatitis

zur Verfügung gestellt von Dr. J. Schlue

polyclonal Hypergamma-globulinemia

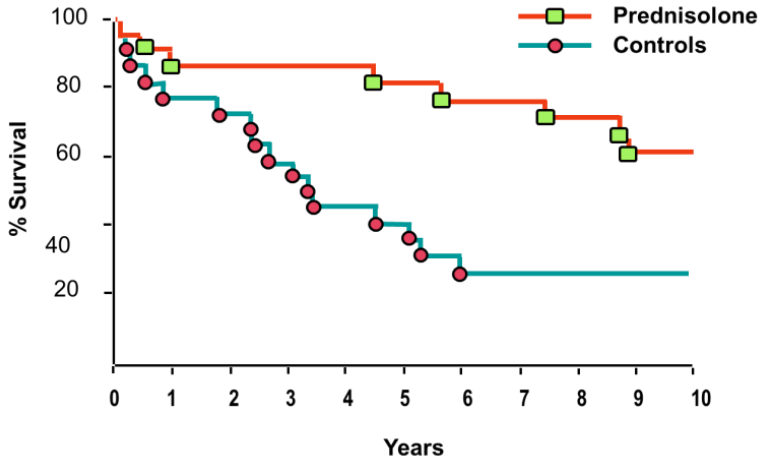


In all age groups!!!

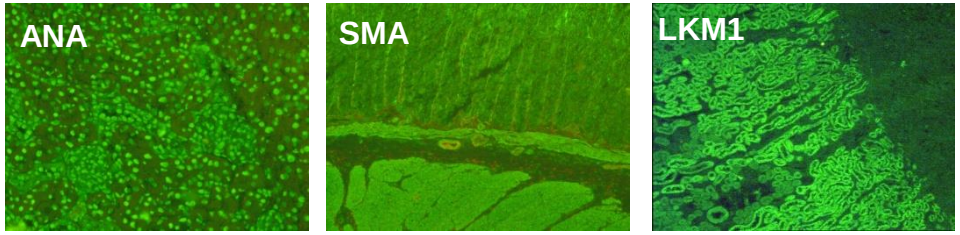


Modifiziert nach Taubert et al.
J Hepatol. 2014;61(5):1106-14

Fatal natural disease course



Autoantibodies

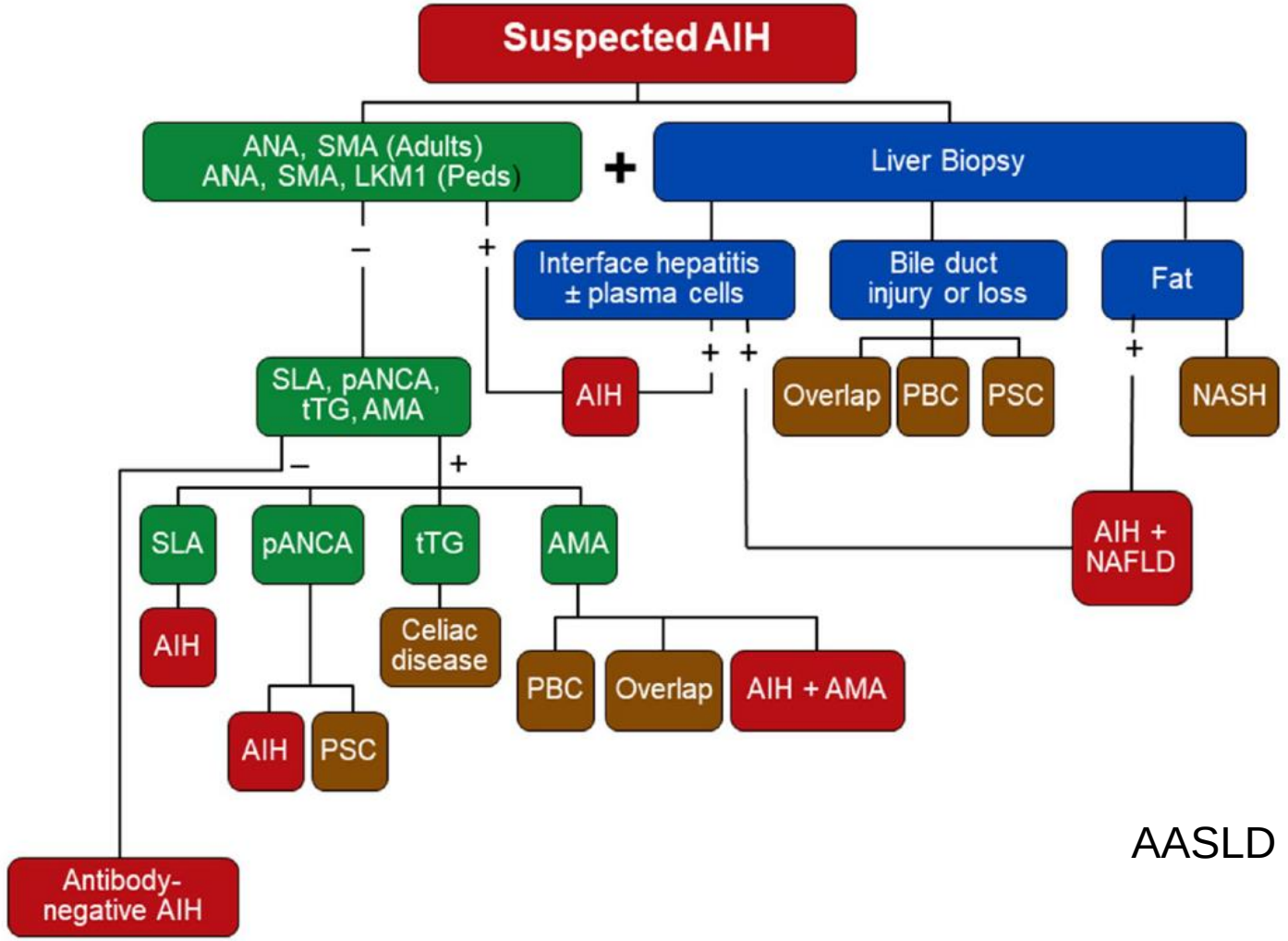


♀ ♂

3-4:1

Manns et al. Hepatology. 2010 Jun;51(6):2193-213
Kirk et al., Gut. 1980 Jan;21(1):78-83
Taubert et al. J Hepatol. 2014;61(5):1106-14

Diagnostic Algorhythm for Autoimmune Liver Diseases: Autoantibodies and Liver Biopsy



AASLD Guidelines 2020

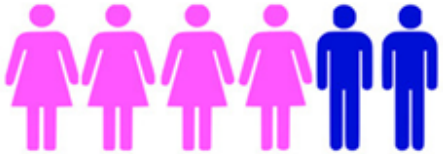
Mack,…., Manns,…. et al. Hepatology, VOL . 72, NO. 2, 2020: 671-722 (AASLD Guideline)

Outcome of patients with autoimmune hepatitis (AIH) and non-alcoholic fatty liver disease (NAFLD)

MASLD !

NAFLD presence or even components of MetS in patients with AIH may affect prognosis

640 AIH patients (474 females)

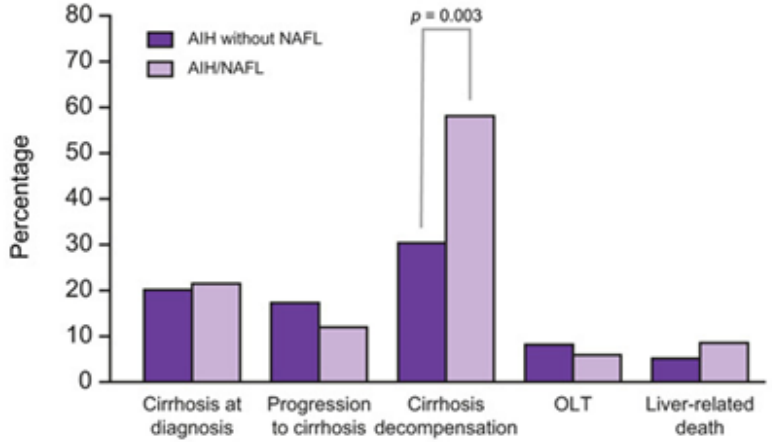


Presence of NAFLD/NASH in liver biopsy

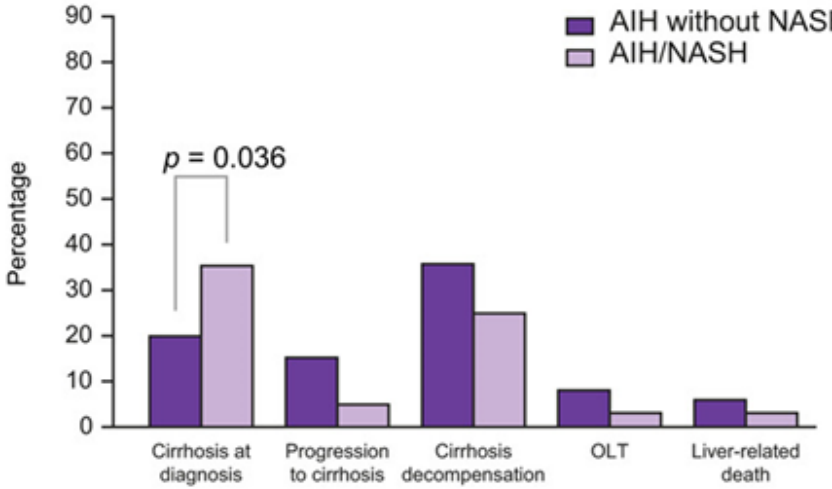
146 (22.8%) AIH/NAFLD

115 (18%) AIH/NAFL

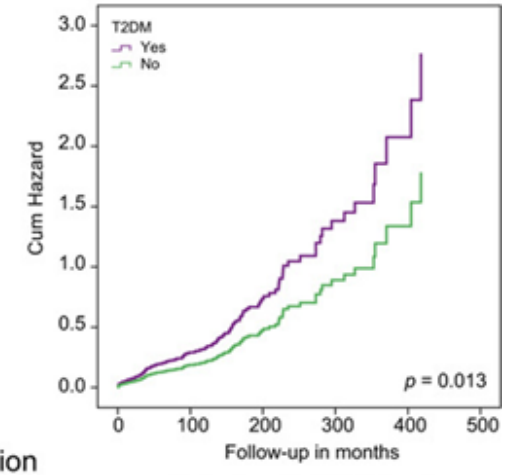
31 (4.8%) AIH/NASH



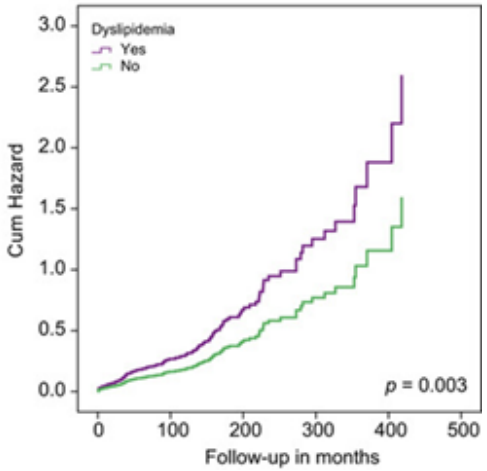
Patients with AIH/NAFL cirrhosis had higher frequency of decompensation



Patients with AIH/NASH had more frequently cirrhosis at diagnosis



Patients with T2DM and dyslipidemia had increased hazard of disease progression



Zachou et al. JHEP Rep. 2023 Apr 22;5(8):100778.
doi: 10.1016/j.jhepr.2023.100778

Autoimmune hepatitis

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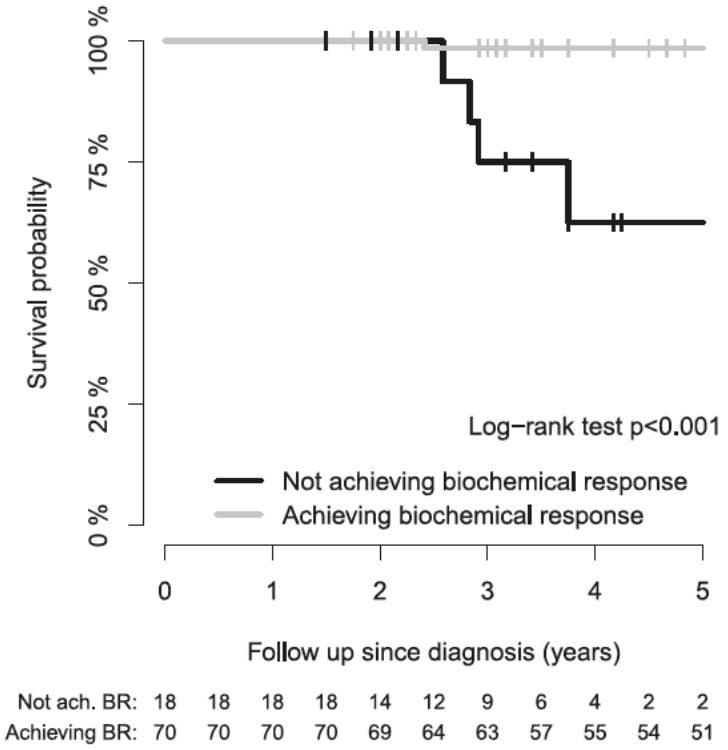
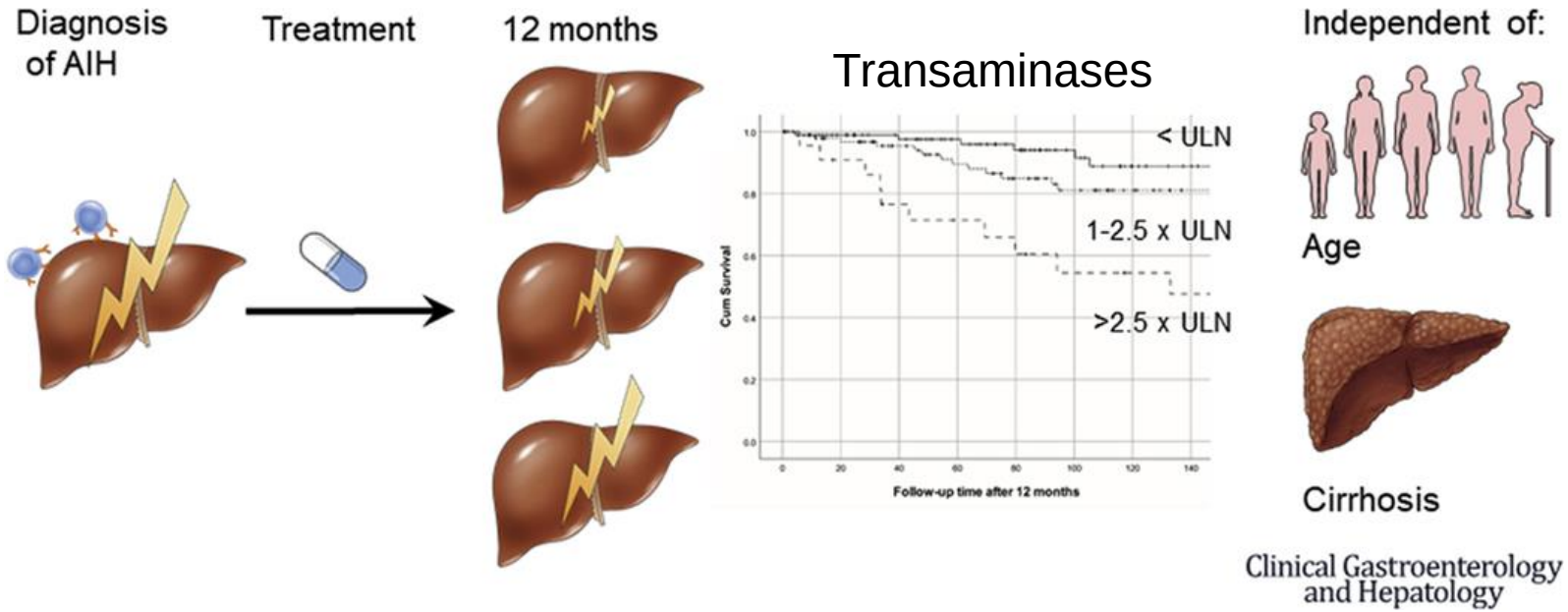
Treatment goals

AIH – role of biochemical remission



A. Gerussi, N. Halliday and F. Saffioti et al., Digestive and Liver Disease, 2020.

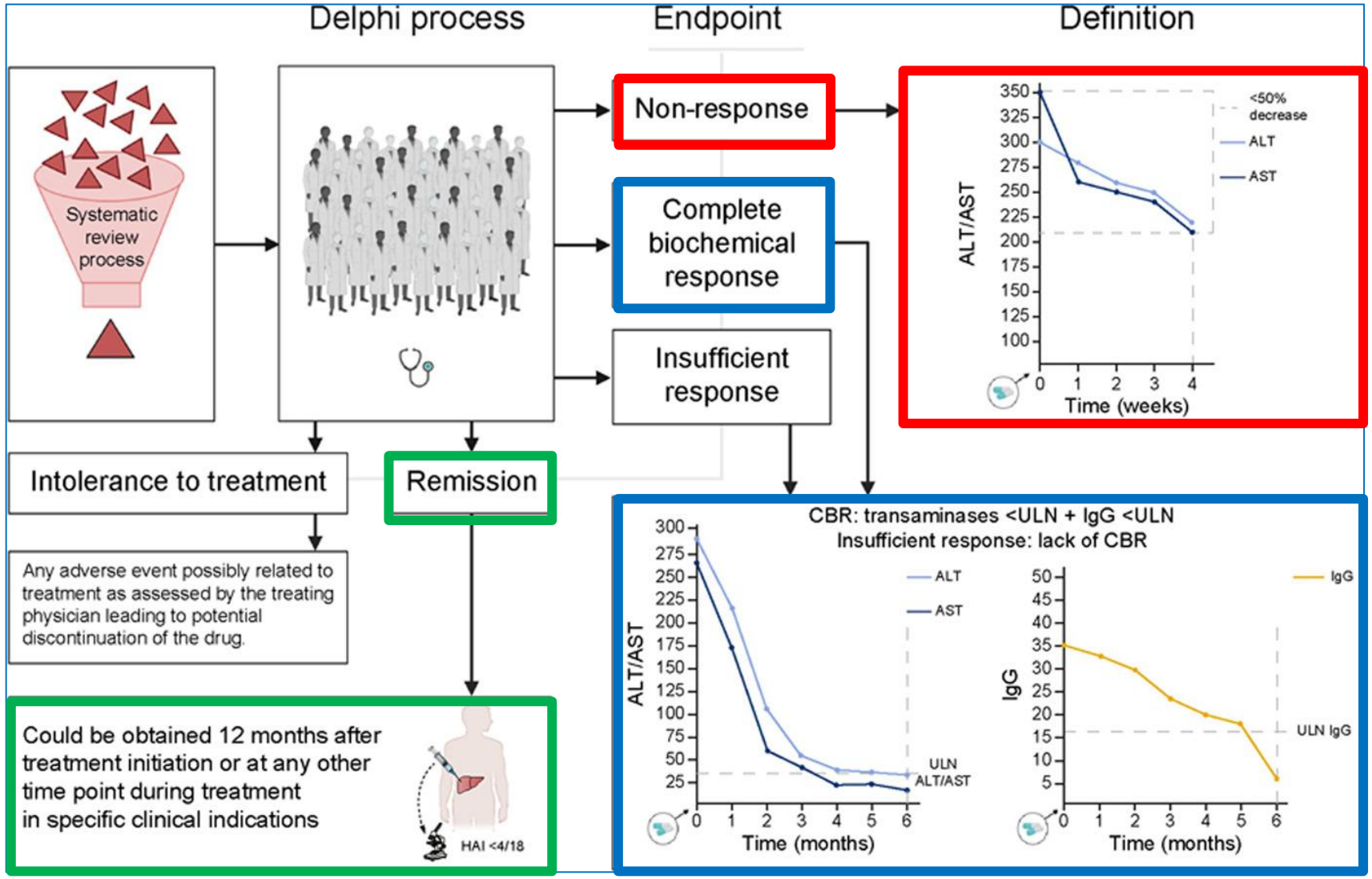


BIewenga et al. Clinical Gastroenterology and Hepatology, 2021.

Goal: Normalization of ALT, AST, IgG*

*since 2010 AASLD AIH Guidelines (Manns et al, Hepatolgoy, 2010)

Definition of treatment endpoints



Pape, Snijders et al. J Hepatol. Volume 76, Issue 4, April 2022, Pages 841-849
Systematic review based on 17 studies leading to IAIHG recommendations

Lack of complete biochemical response (normal ALT/AST and IgG) at 6 months is associated with liver-related adverse outcome in autoimmune hepatitis

Study design

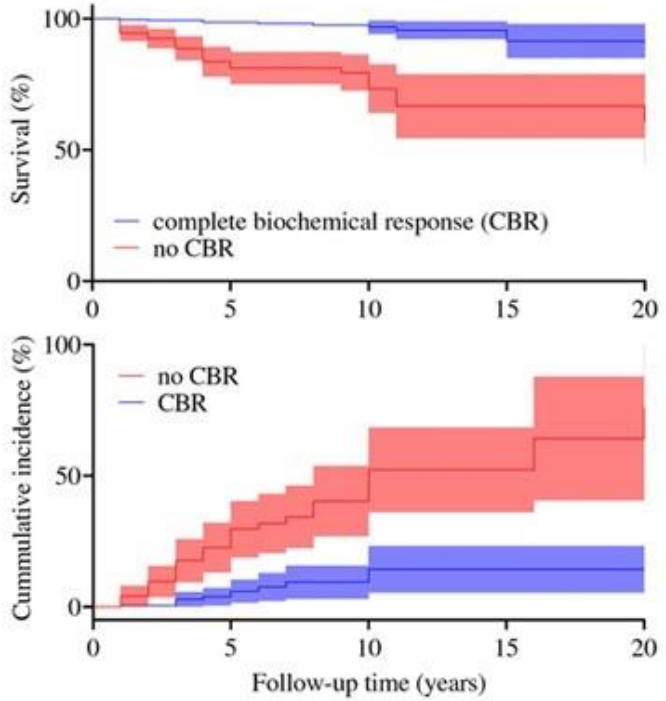
IAIHG-Retrospective Registry cohort study

2559 AIH patients
38 centers
7 countries

Quality control

Clinical characteristics, treatment response and follow-up

Survival analysis



Key findings

The IAIHG-RR registry is a suitable platform for patient selection in future studies

Lack of complete biochemical response to treatment, non-white ethnicity, cirrhosis and PSC-AIH are associated with liver-related death and liver transplantation

Lack of complete biochemical response to treatment is associated with cirrhosis development

Slooter et al. Hepatology. 2024;79:538–550
DOI: 10.1097/HEP.0000000000000589

HEPATOLOGY

AIH – role of biochemical remission in children

117 children with autoimmune hepatitis
type 1= 65 type 2 = 52
immunosuppressive therapy
Median follow up 20 years in survivors

Normalization of transaminase and prothrombin ratio in **93%** and **84%** of children
Sustained remission after treatment withdrawal **in 24%**
(median follow-up 7 years)
Treatment-free remission in **11** of **24** children
(follow-up 4-22 years)

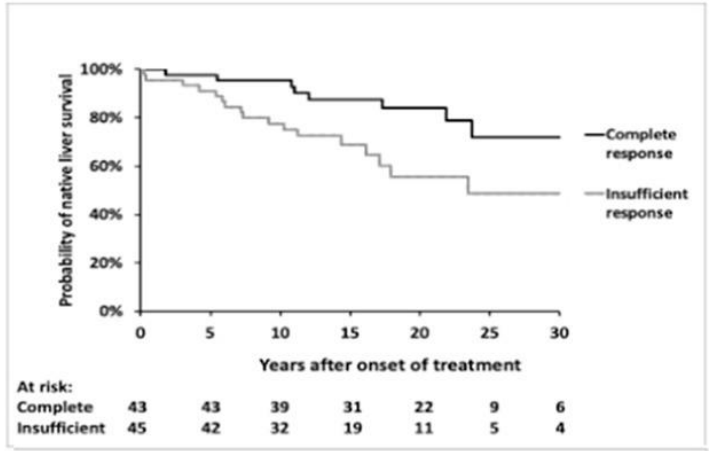
Liver transplant= 23

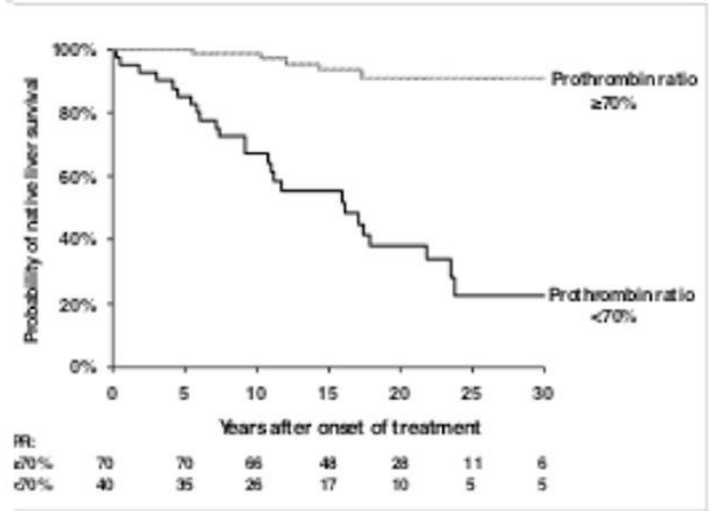
Deaths = 17

No differences in outcomes between types 1 and 2 hepatitis

Withdrawal of treatment is possible without liver histology

Persistent abnormal prothrombin predicts the need for liver transplantation





Maggiore et al. J Hepatol 2023: https://doi.org/10.1016/j.jhep.2023.01.013.

Autoimmune hepatitis

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Therapy

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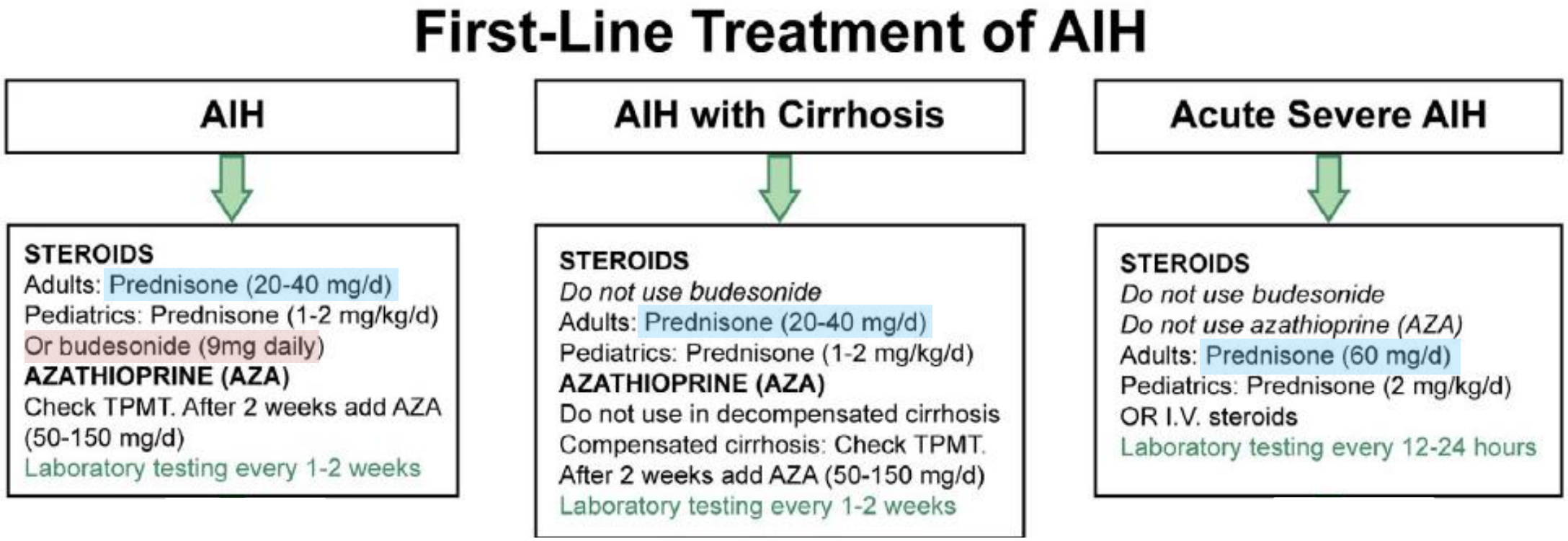
First line therapy

Induction therapy of AIH



Mack,…,Manns, … et al. Hepatology, VOL . 72, NO. 2, 2020: 671-722 (AASLD Guideline)

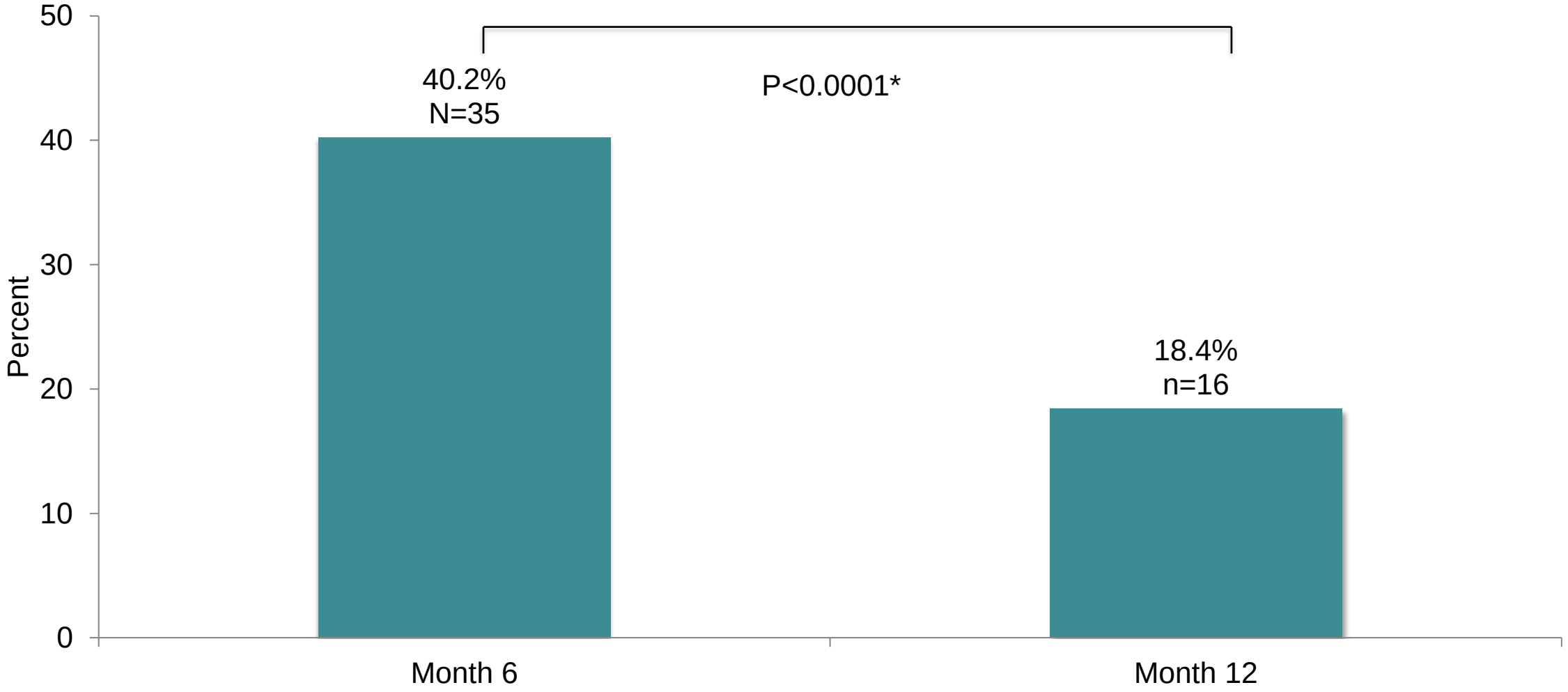
acute severe AIH
(jaundice, INR 1.5-2,
no HE, first manifestaton)

Frequency and Nature of Side Effects (Adults)

Prednisone-Related Side Effects		Azathioprine-Related Side Effects	
Type	Frequency	Type	Frequency
<u>Cosmetic (usually mild)</u> Facial rounding, Weight gain, Dorsal hump striae, Hirsutism, Alopecia <u>Somatic (usually mild)</u> Emotional Instability, Glucose intolerance, Cataract	80% (after 2 years)	Hematologic (mild) Cytopenia	46% (especially with cirrhosis)
<u>Somatic (severe)</u> Osteopenia, Vertebral compression, Diabetes (brittle), Psychosis, Hypertension (labile)	13% (Treatment ending)	Hematologic (severe) Leukopenia Thrombocytopenia	6% (Treatment ending)
<u>Inflammatory/Neoplastic</u> Pancreatitis, Opportunistic infection, Malignancy	Rare	Somatic (mild) Nausea, Emesis, Rash, Fever, Arthralgias	5%
		Neoplastic	3% (after 10 years)
		Hematologic /enteric Bone marrow failure, villous atrophy, Malabsorption	Rare
		Teratogenic	Rare (theoretical)

AASLD Clinical Practice Guidelines: Manns MP, et al. *Hepatology.* 2010 Jun;51(6):2193-213.

Decrease Of Steroid Specific Side Effects In Patients Switched From Prednisone To Budesonide (n=87)

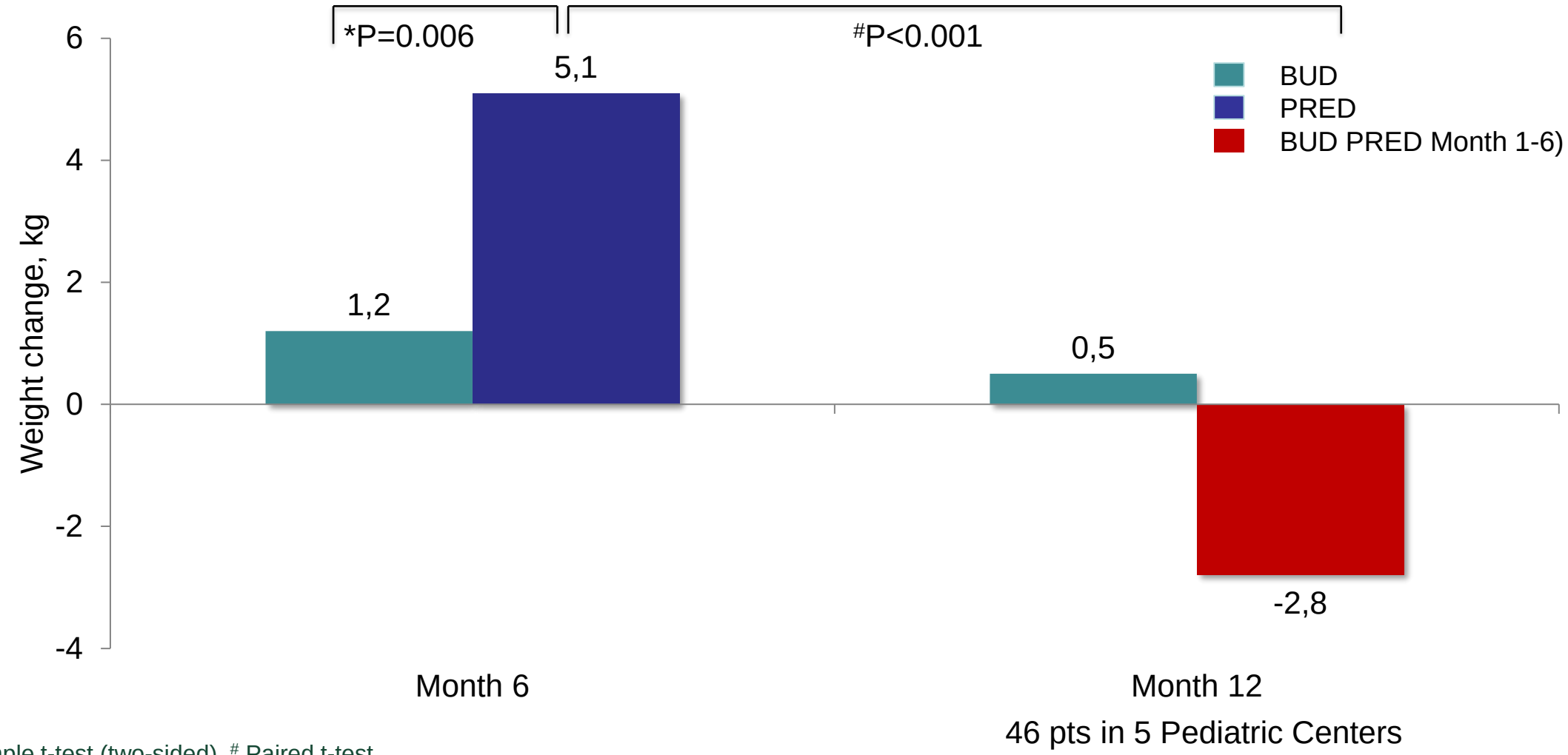


*McNemar's test for paired proportions

Manns MP, et al. Gastroenterology 2010;139:1198-1206

European AIH-BUC Pediatric Subanalysis

Mean weight change at Months 6 and 12

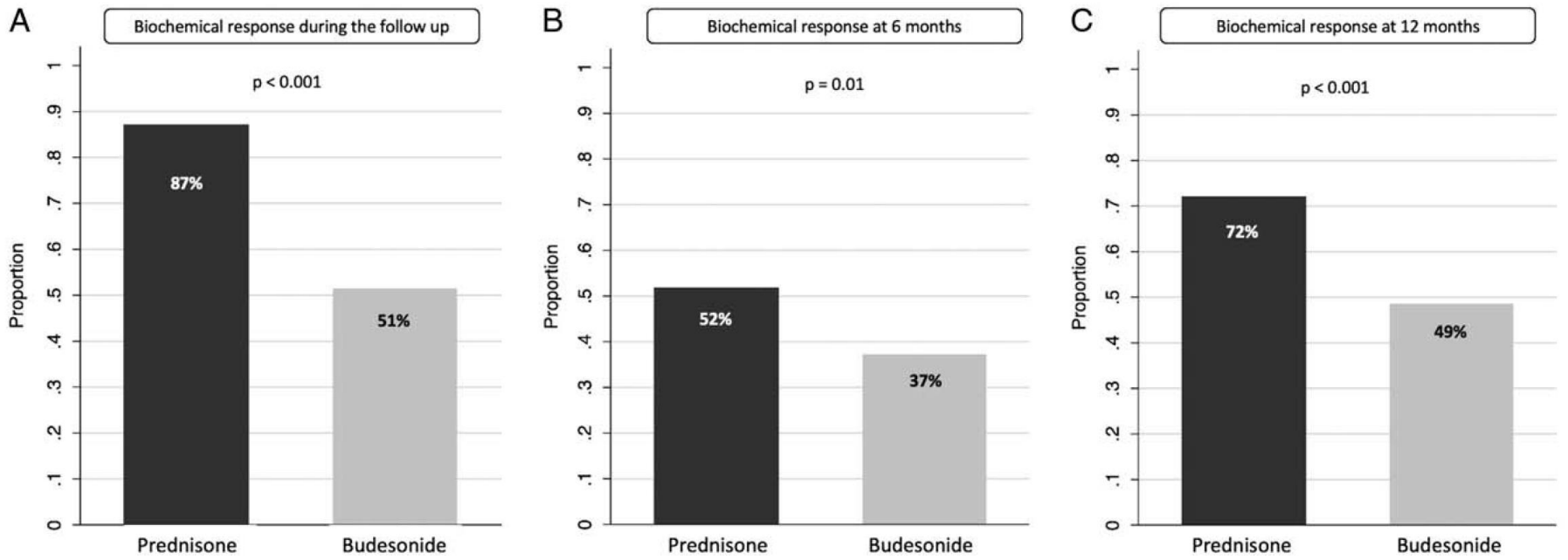


*Two sample t-test (two-sided). # Paired t-test

Woynarowski,….., Manns *J. Pediatrics* 2013

Budesonide in a Spanish real world cohort

- Retrospective multicenter study
- 105 Budesonide
- 276 Prednisone

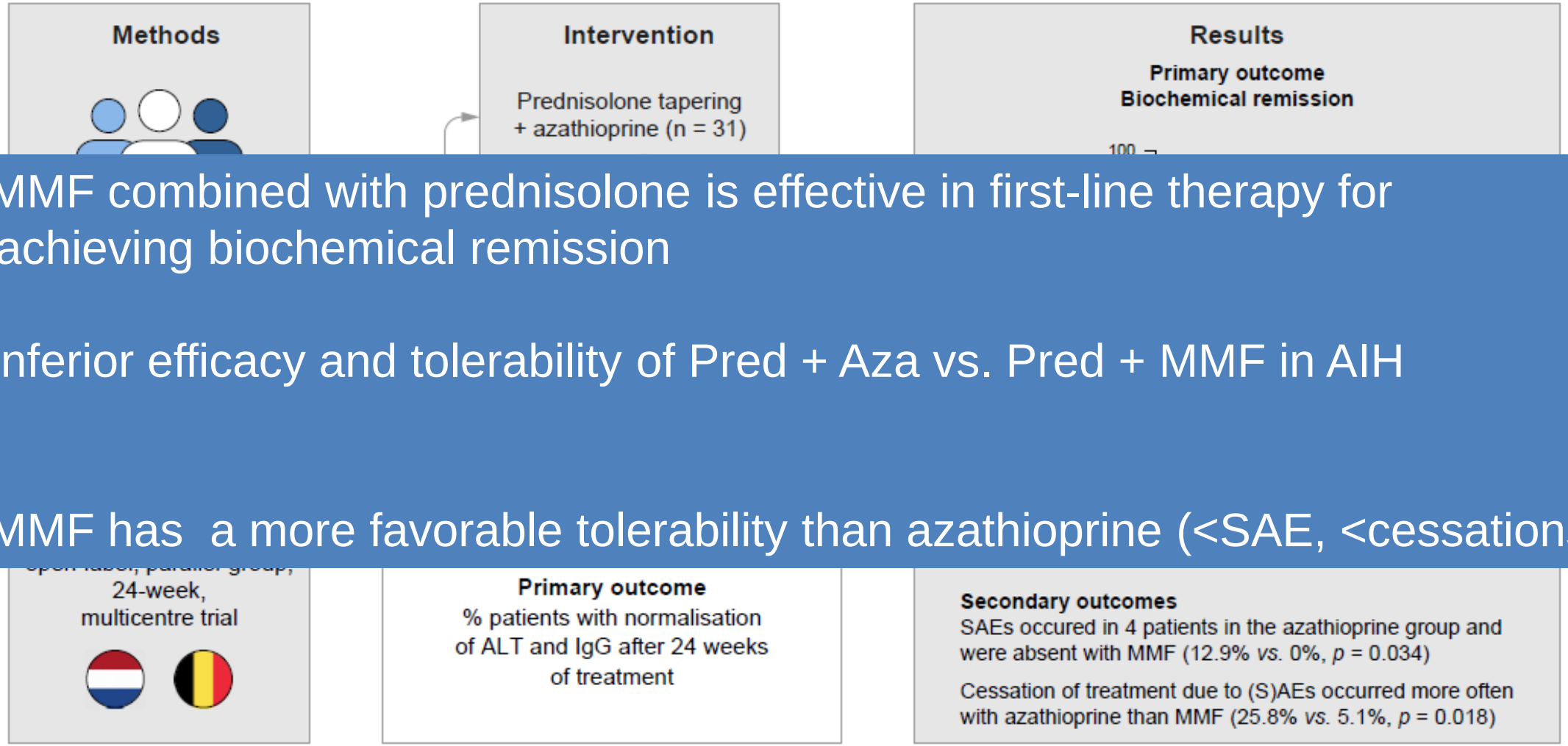


Rate of steroid intake	n.a.	79%	68%	66%	41%
		p=0.057		P<0.001	

- transaminases <2 × upper limit of normal: similar BR in both treatment groups
- Prednisone with higher adverse events (24.2% vs. 15.9%, p = 0.047).

Díaz-González et al. Hepatology 2023: DOI: 10.1097/HEP.0000000000000018

Mycophenolate as superior first line therapy ?



- MMF combined with prednisolone is effective in first-line therapy for achieving biochemical remission
- Inferior efficacy and tolerability of Pred + Aza vs. Pred + MMF in AIH
- MMF has a more favorable tolerability than azathioprine (<SAE, <cessations)

Snijders et al.
JHEP 2023: https://doi.org/10.1016/j.jhep.2023.11.032

Autoimmune Hepatitis

Second Line Therapy

First Meta-Analyses for AIH 2017-2019

Study		Study cohort	Patients	Drugs	Treatment response	Adverse events (AE)	Conclusion
Yu et al. 2019	Meta-Analysis of 7 studies	MMF as first line therapy	583	MMF+prednisone Standard of care (SOC)	ALT/AST normalization: 55-89% vs 33-87% ($p < 0.05$) IgG normalization: 62-89% ($p < 0.01$) non-response 6-33% ($p < 0.01$) AST/ALT/IgG normalization: 33-87% non-response 15-67% ($p < 0.01$)		MMF+Pred superior to SOC
De Lemos-Bonotto et al. 2018	Meta-Analysis of 15 studies	Second line therapy agents	283	MMF+prednisone Tacrolimus+prednisone Ciclosporin+prednisone	improvement of aminotransferases 79% histological remission 89% improvement of aminotransferases 94% improvement of aminotransferases 91%	liver transplantation 11% mortality 7 %	Tac+Pred best for improvement of aminotranferases
Santiago et al. 2019	Meta-Analysis of 12 studies	MMF as second line therapy	397	MMF 0.5-4.0 g/d	pooled response rate 58% (82% intolerance to SOC; 32% in nonresponders)	pooled AE rate 14% pooled discontinuation rate due to side effects 8%	switch to MMF was effective (better for intolerance than for non response)
Zizzo et al. 2017	Meta-Analysis of 15 studies	Second line therapy agents in children	76	MMF Ciclosporin Tacrolimus	normalization of ALT/AST at 6 months: 36% normalization of ALT/AST at 6 months: 83% normalization of ALT/AST at 6 months: 50%	pooled estimates for AE: 45% pooled estimates for AE: 78% pooled estimates for AE: 42%	CsA most effective but most AEs

None of the second line therapies for AIH treatment failure are approved yet !

873-877.
eb;30(2):212-216.
):830-839.
(1):6-15.

AIH Guideline Recommendations : 2nd Line Therapy

In children or adults with AIH who have treatment failure, incomplete response, or drug intolerance to first-line agents, ***the AASLD suggests the use of MMF or TAC to achieve and maintain biochemical remission*** *(conditional recommendation, low certainty).*

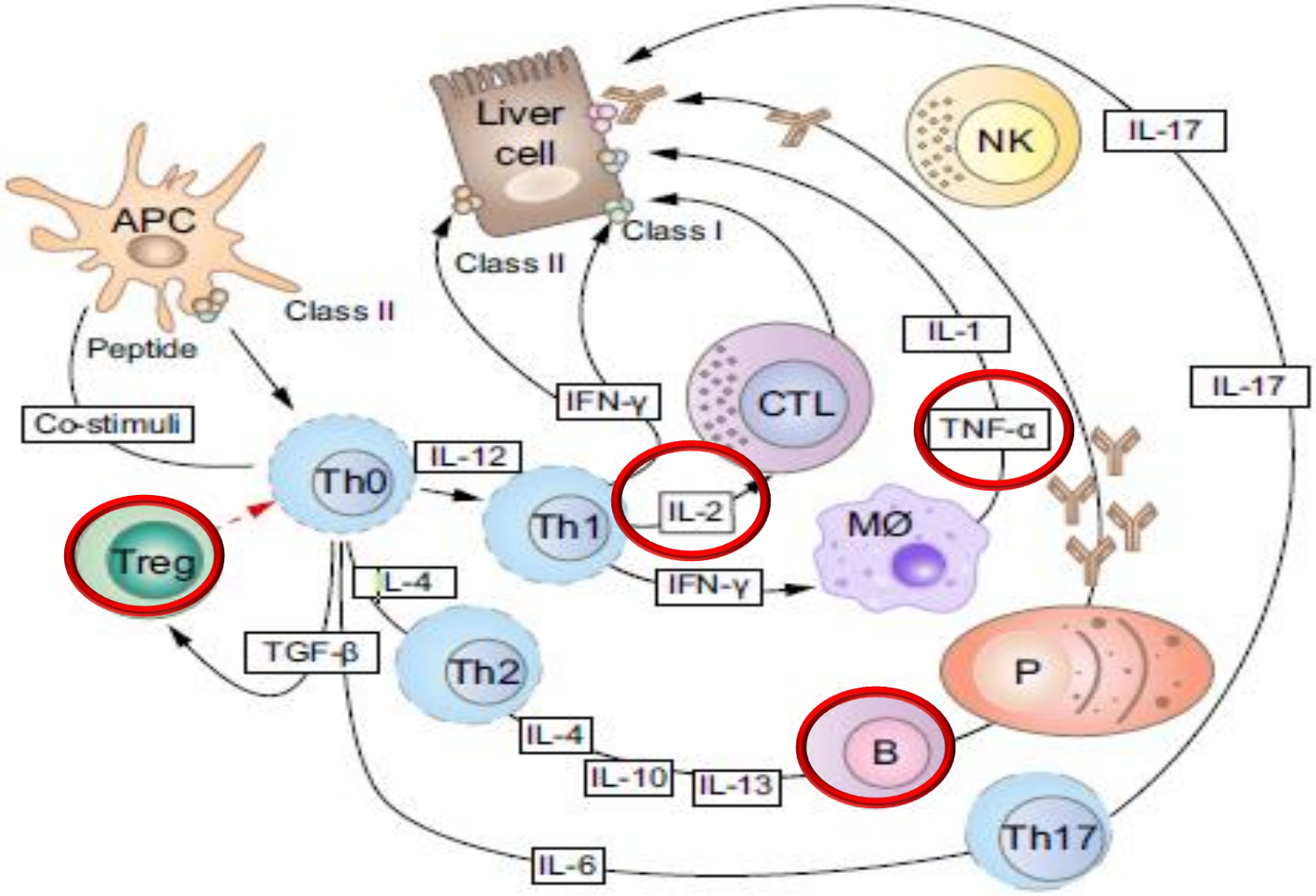
*Based on a superior ease of use and side-effect profile****, the AASLD suggests a trial of MMF over TAC as the initial second-line agent in patients with AIH*** *(conditional recommendation, very low certainty).*

Mack,…., Manns,…. et al. Hepatology 72, 2020: 671-722 (AASLD Guidelines)

Autoimmune Hepatitis

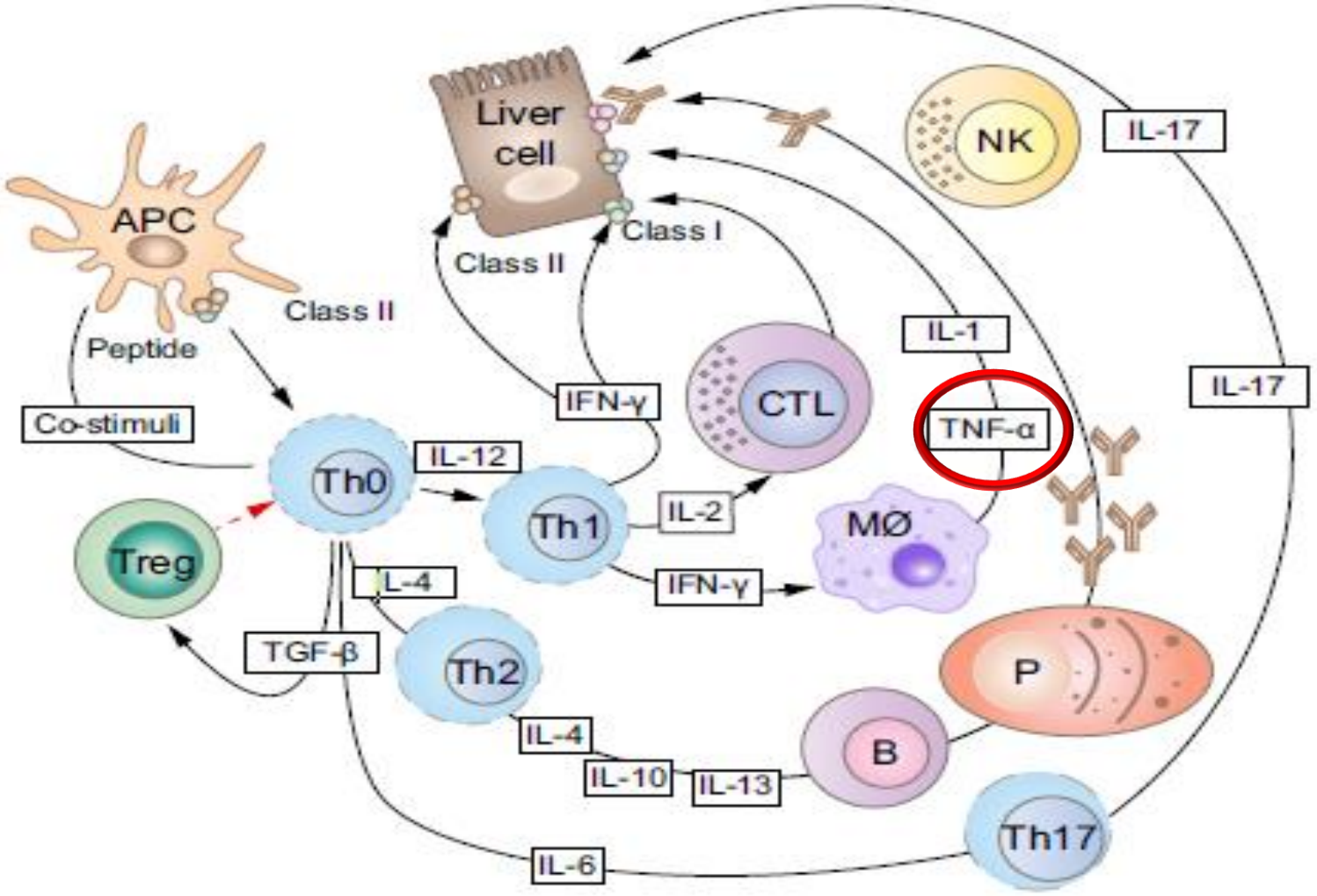
Third Line Therapy

Molecular Pathogenesis of autoimmune hepatitis



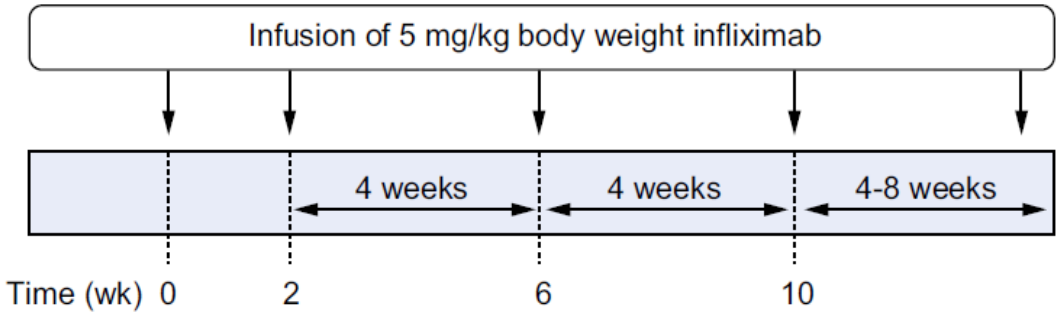
Manns et al., Journal of Hepatology, 2015

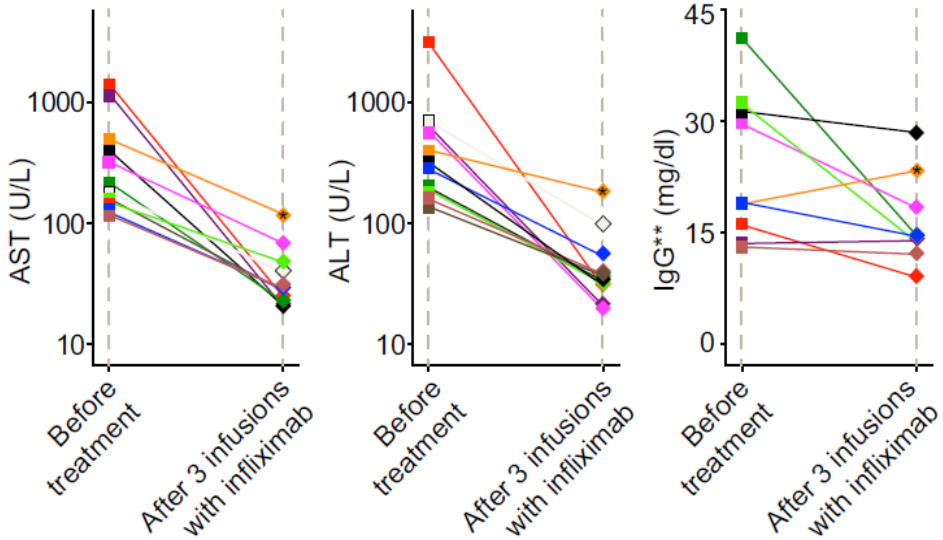
Molecular Pathogenesis of autoimmune hepatitis



Manns et al., Journal of Hepatology, 2015

Infliximab for difficult to manage AIH





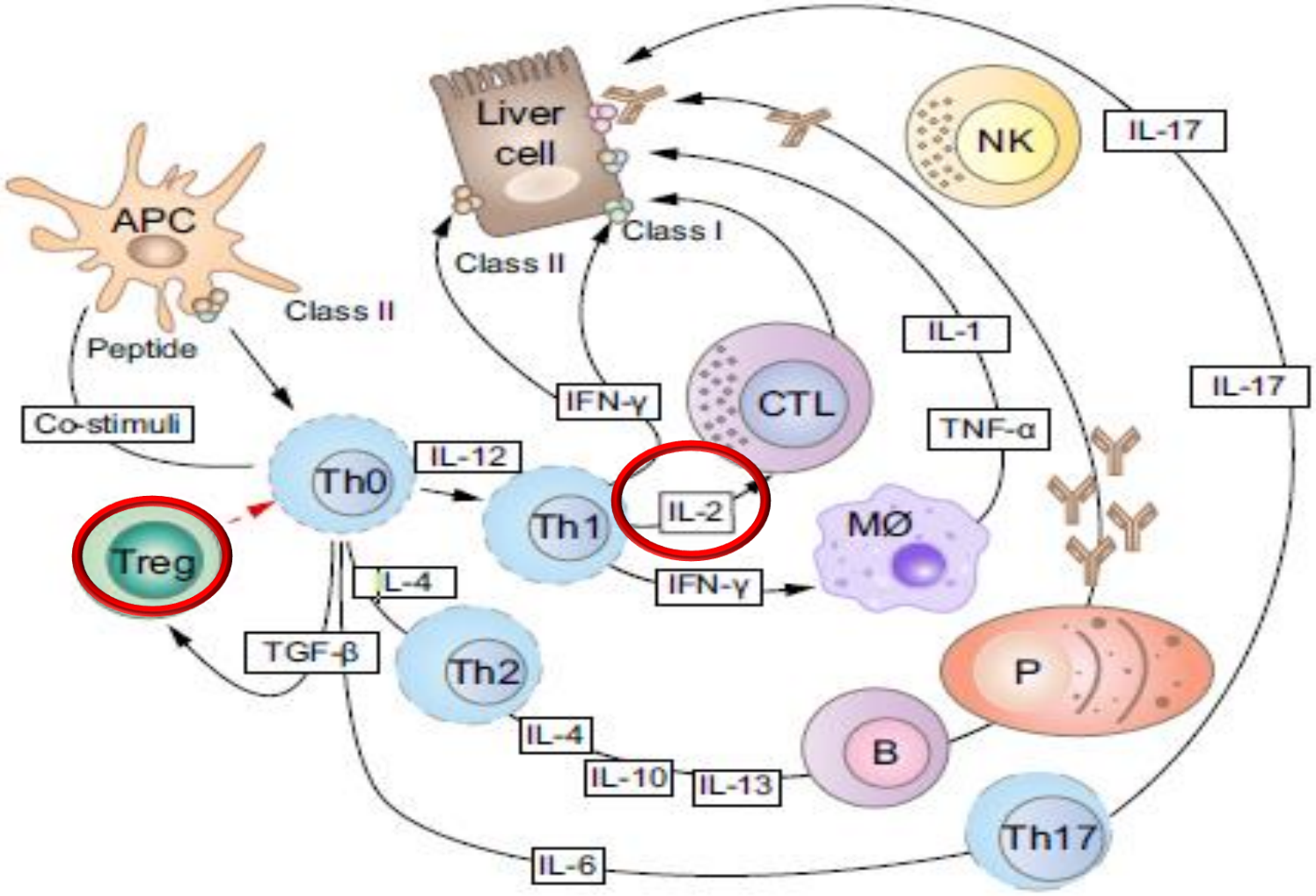
Single center study

- 11 pts. (64% cirrhosis)
- Infections in 55% of pts. (in 67% of cirrhotic pts.)

- 6/11 full remission
- 2/11 inomplete response
- 2/11 repeated full remission (on/off therapy)
- 1/11 flare after initial remission

Weiler-Normann et al. J Hepatol 2013 Mar;58(3):529-34.

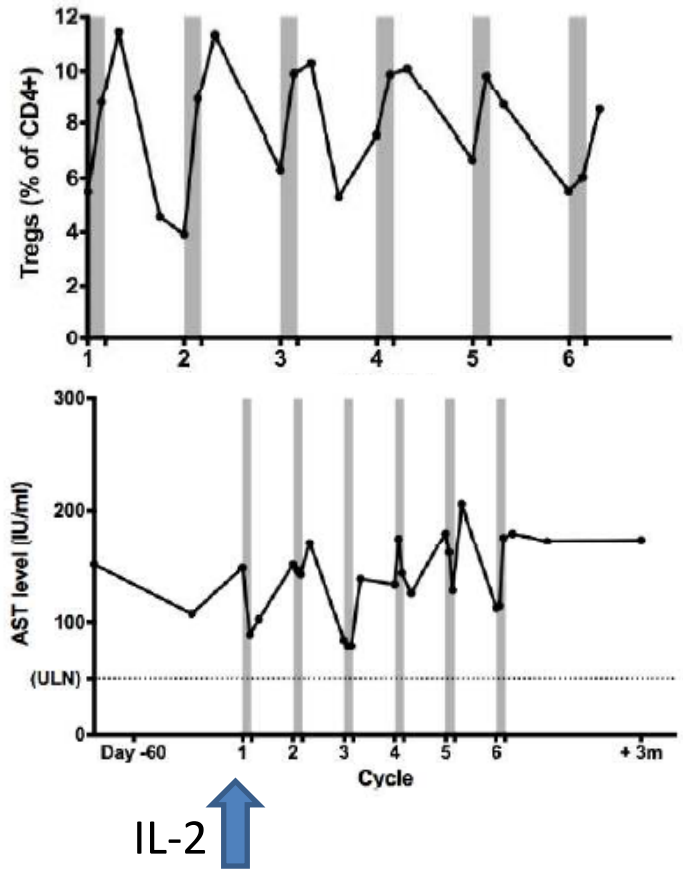
Molecular Pathogenesis of autoimmune hepatitis



Manns et al., Journal of Hepatology, 2015

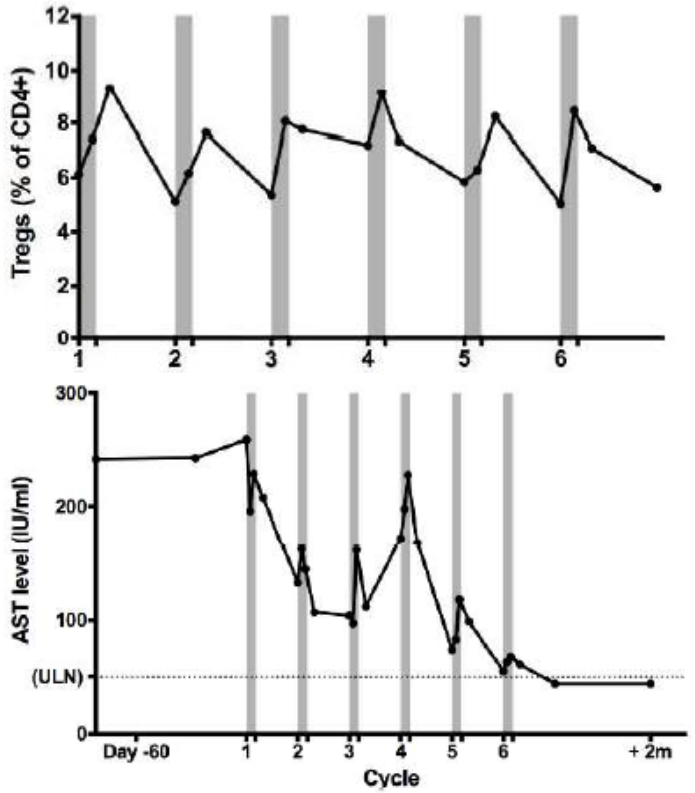
Low dose IL-2 in AIH

female 20 yrs. with cirrhosis
(pediatric AIH-1)



IL-2

female 56 yrs. with bridging fibrosis
(adult AIH-3)



Effect of RO7049665 on the Time to Relapse Following Steroid Tapering in Participants With Autoimmune Hepatitis (AIH) - NCT04790916 (Hoffmann-Roche)

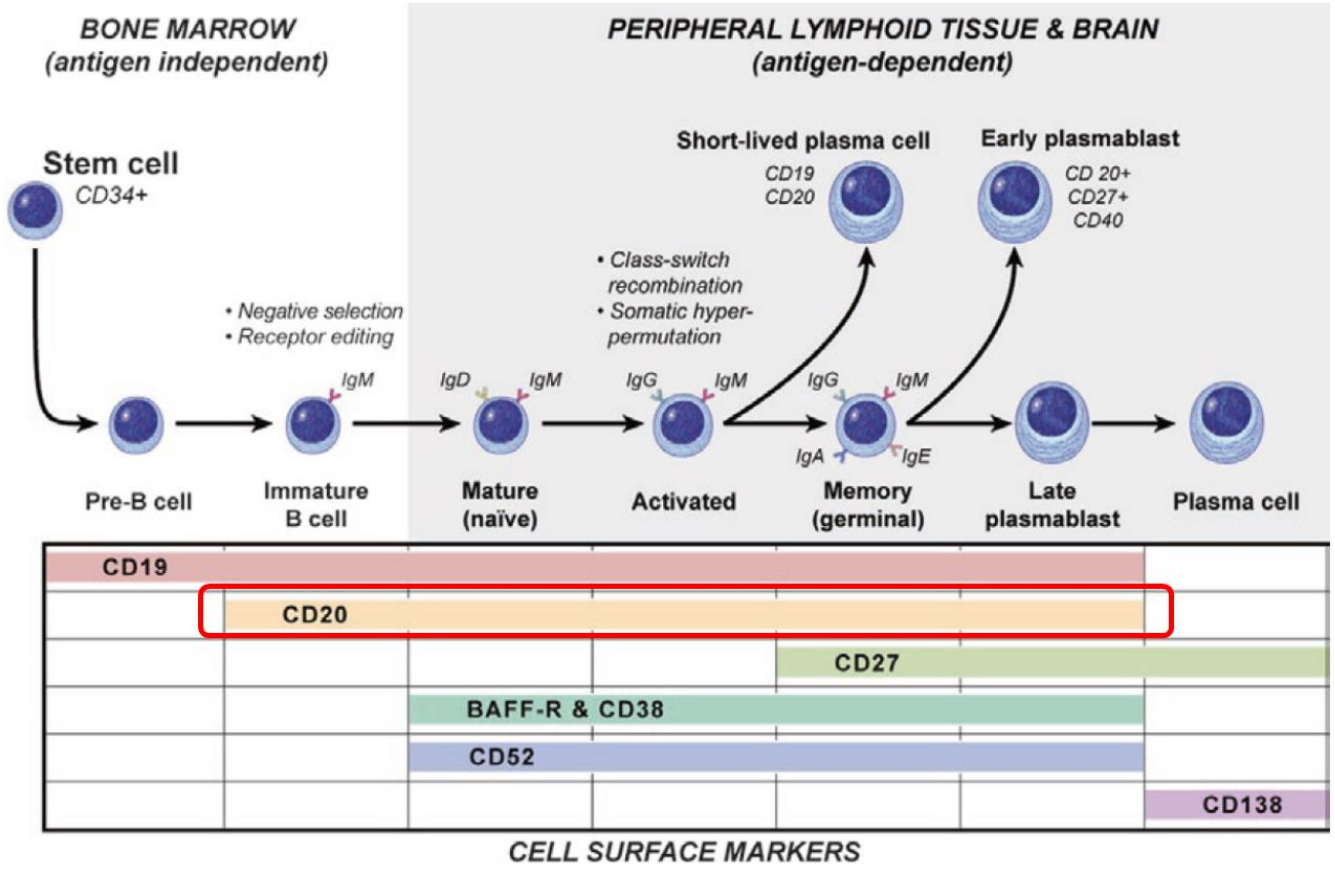
First study on IL-2/mutein for maintenance of AIH remission after end of therapy.

(1 Mio. Units s.c. 5x/month over 6 months)

Modified from Lim et al., Hepatolgy, 2018

Role of B cell depletion in Autoimmune Hepatitis

B cell depletion – anti-CD20 (rituximab)



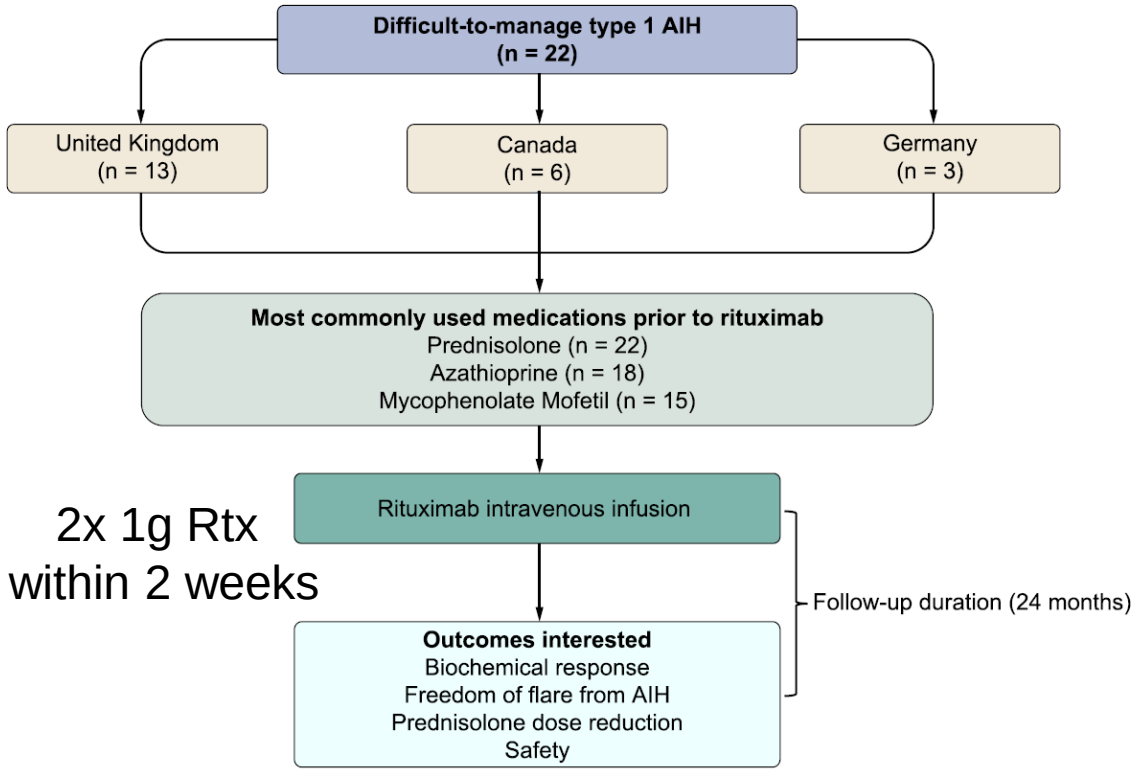
- Good safety profile with regard to infections
  (anti-HBc testing obligative !!!!)
- Low infection rate e.g. protective antibodies after vaccination usually not affected
- No overall hypogammaglobulinemia

Joscelyn et al. 2020 Clinical Neuroimmunology, Current Clinical Neurology, https://doi.org/10.1007/978-3-030-24436-1_2
Ghilardi et al. Annu. Rev. Immunol. 2020.38:249-287

Rituximab for difficult to manage AIH

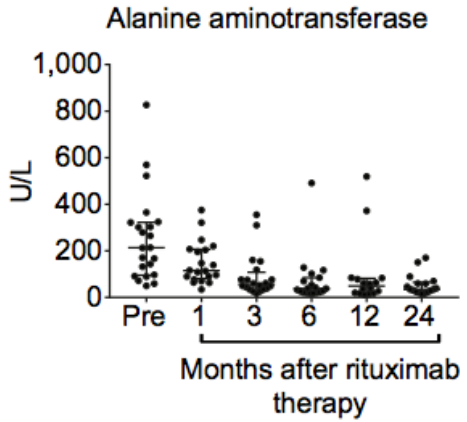
retrospective **IAIH group study**

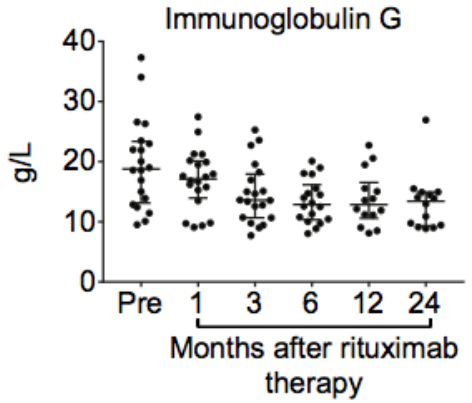
incl. 3x Cirrhosis (2x CP A; 1x CP C)

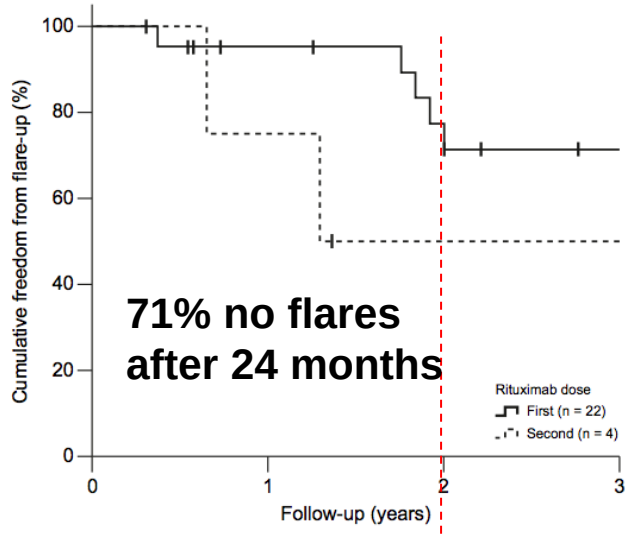


2x 1g Rtx
within 2 weeks

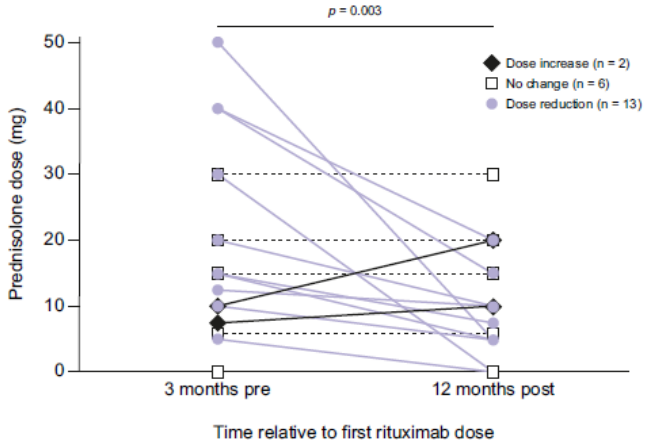
No serious adverse event





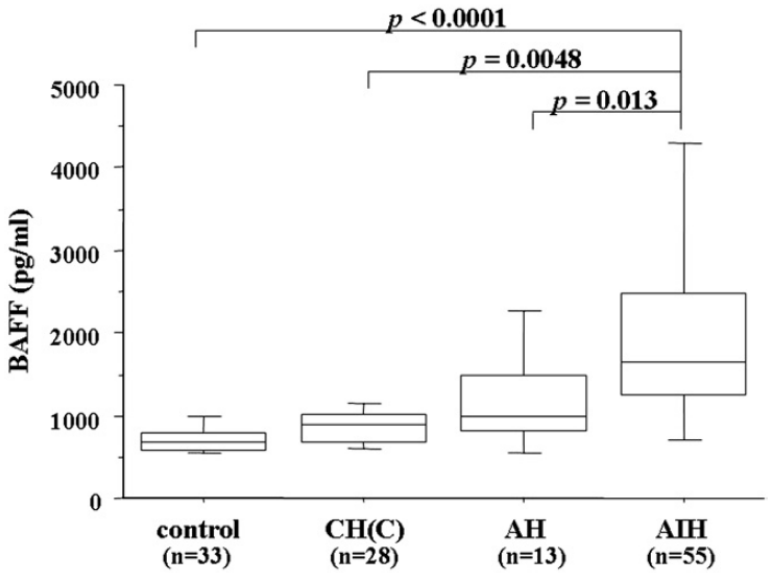


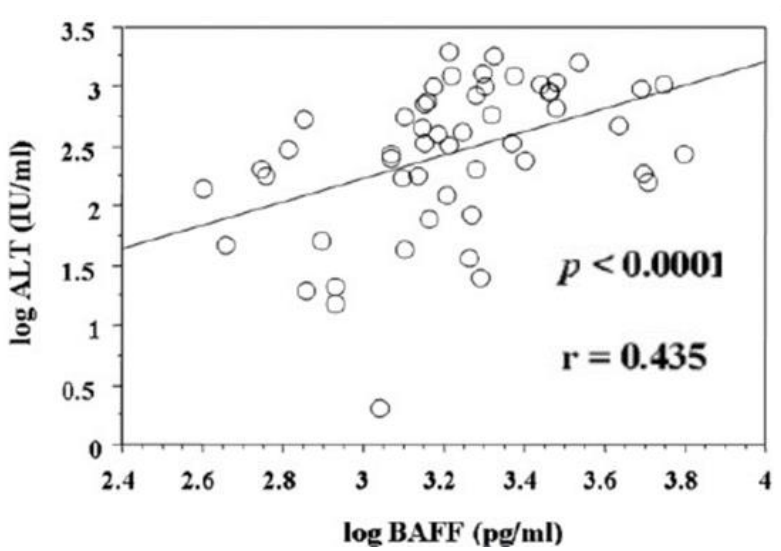
62% Steroid dose reduction

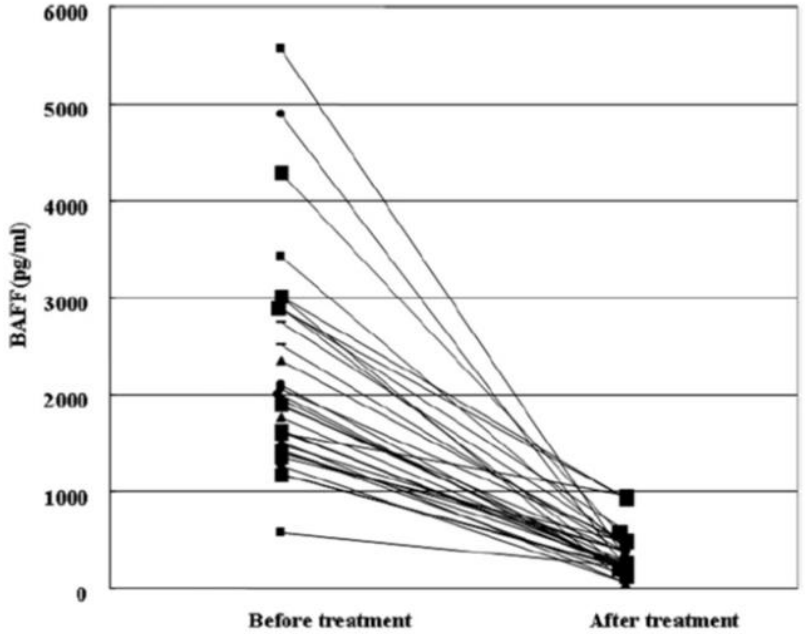


Modified from Than NN, …. Taubert R … Manns MP, … et al. JHEP Reports 2019; 1: 437 - 445

BAFF in AIH







Joscelyn et al. 2020 Clinical Neuroimmunology, Current Clinical Neurology, https://doi.org/10.1007/978-3-030-24436-1_2

BAFF and IL-21 in AIH

66 untreated AIH patients (Netherlands)

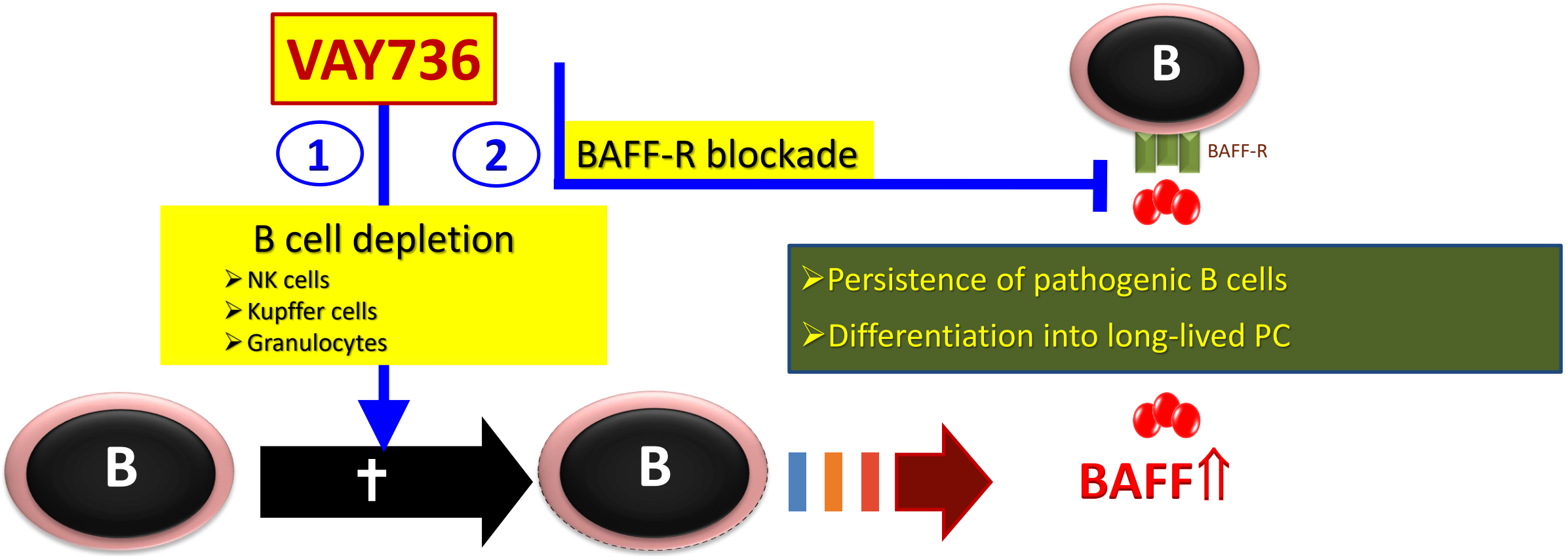
Groups of untreated patients with AIH		Remission after 1-year treatment	Outcome
 Normal BAFF and IL-21 (41%)	Normal BAFF	54%	
 High BAFF and normal IL-21 (41%)	High BAFF	34%	Higher bilirubin, indicating more severe liver dysfunction
 High IL-21 (18%)	High IL-21	0%	AIH-PSC variant syndrome developed in 25% of patients

Autoimmune-associated B cells were elevated, and BAFF levels correlated with certain B cells

Biewenga et al. JHEP Rep. Volume 4, Issue 5, May 2022, 100460

VAY736 (Ianalumab): Anti-BAFF-R antibody with dual action

1) ADCC mediated B cell depletion; 2) Functional BAFF-R blockade



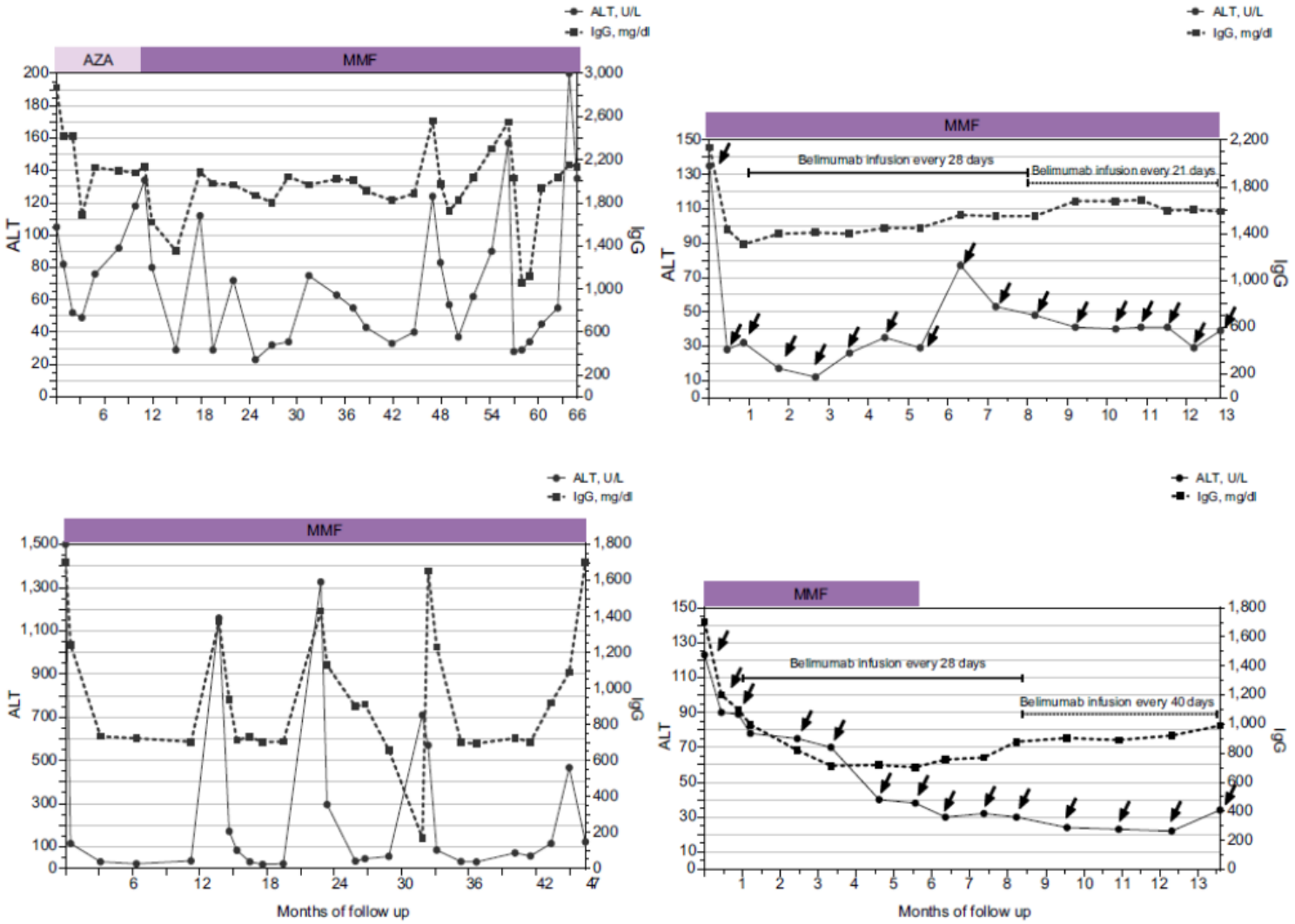
Rapid and profound B cell depletion | Prevention of BAFF-induced hardening of autoimmunity

www.clinicaltrials.gov: NCT03217422

Anti-BAFF-mAb (Belimumab) in difficult to treat AIH

Single center experience:

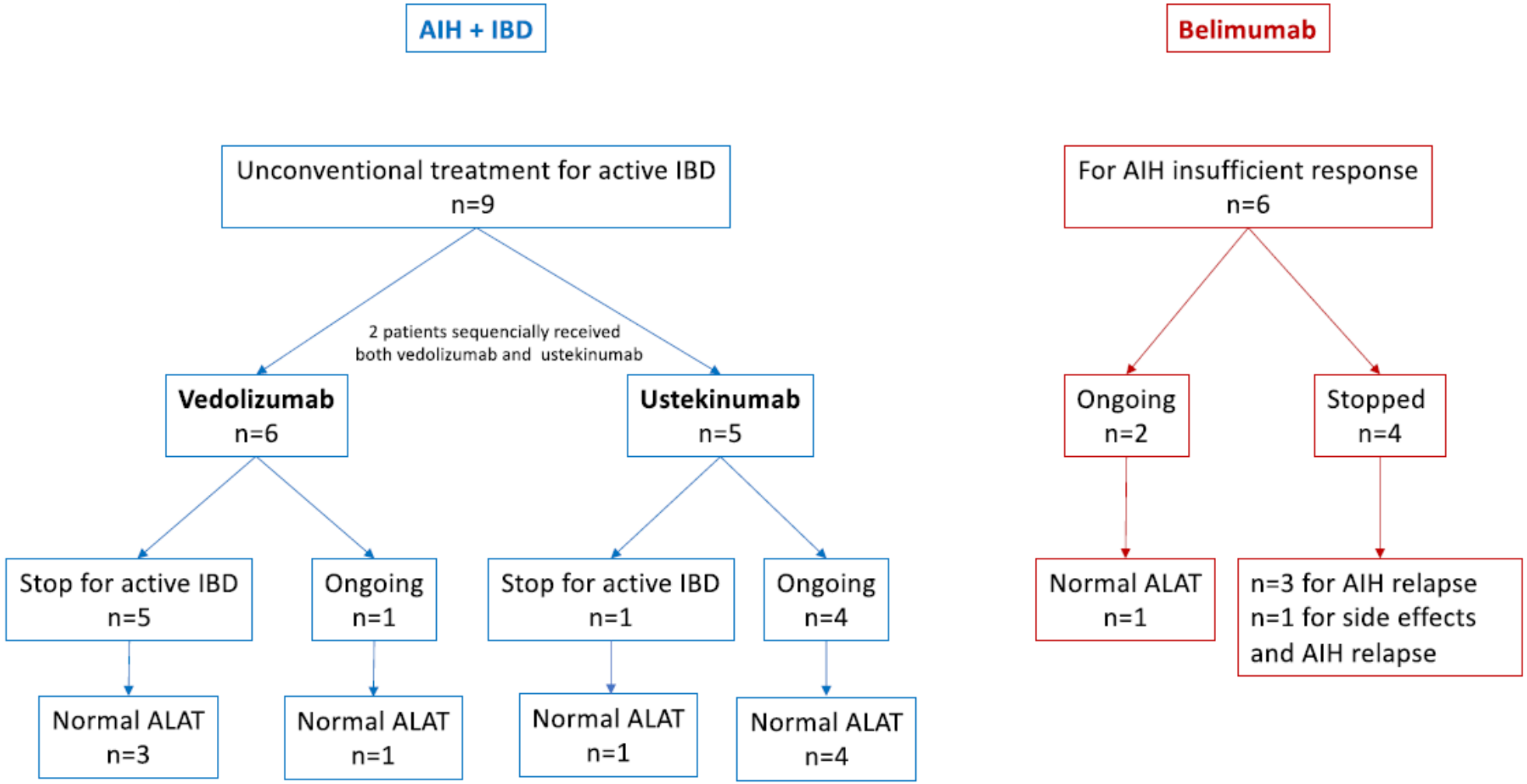
- 2 cirrhotic pts.
- complete response in both pts. with reduced steroids
- no adverse events
- improved liver stiffness
- histological response documented in one patient



Arvaniti et al. JHEP Rep. 2020 May 29;2(4):100123.

European Reference Network
for rare or low prevalence complex diseases

Immunmodulatory drugs in AIH



Beretta-Piccoli et al. Journal of Autoimmunity 140 (2023) 103113

Summary – B cell depletion in AIH

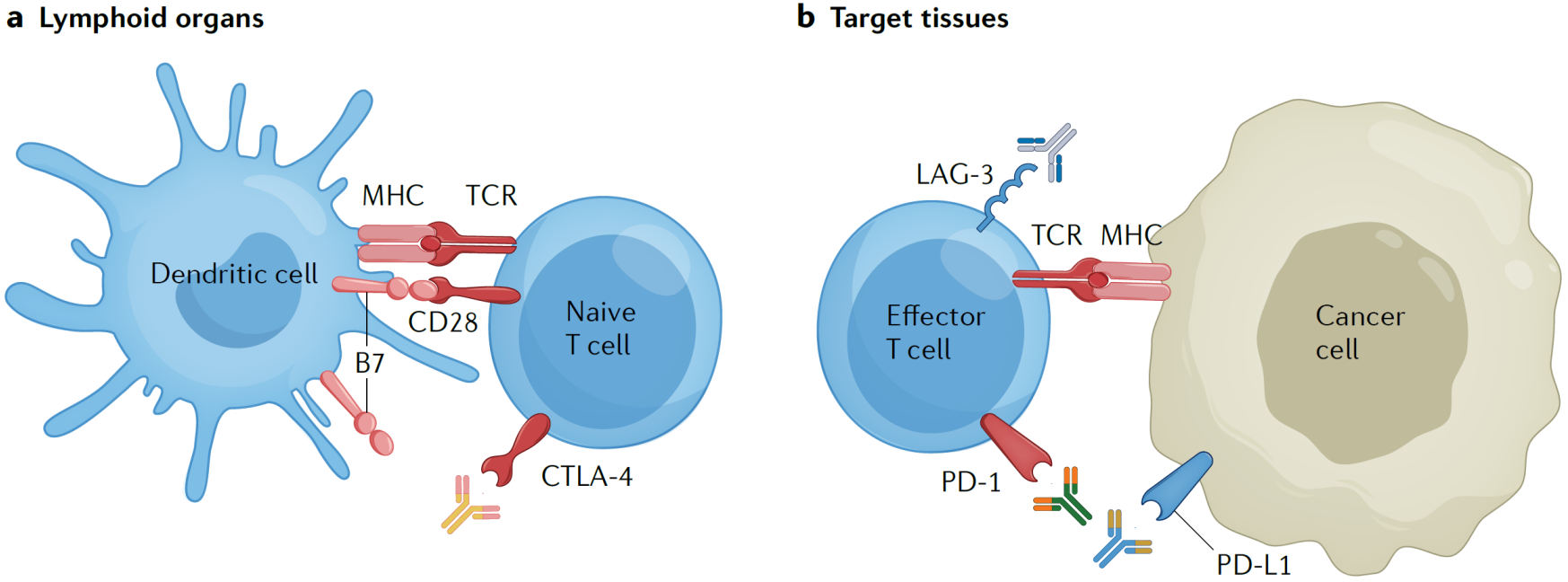
- Feasible and rather safe (low infectious complications compared to other biologicals in AIH) in the setting of salvage therapy
  - Rituximab – anti- CD20
  - Belimumab – anti-BAFF
- only small retrospective studies/case reports
- Long term application of B cell depletion not published yet
- RCT with ianalumab (anti-BAFF-R) ongoing: AMBER

Autoimmune Hepatitis (AIH)
versus
Drug-Induced Autoimmune-Like Hepatitis (DI-ALH)

Drug-Induced Autoimmune Like Hepatitis (DI-ALH)

- Immunotherapy of malignancies has improved the therapeutic armamentarium for solid tumors
- Immune check point inhibitors (ICI): anti PD-1/PD-L1 alone or in combination with anti CTLA-4
- DILI can mimic (almost) all liver disorders
- Since the advent of ICI in cancer therapy immune related adverse events (irAEs) are of increasing importance
- irAE can affect all organs including the liver
- irAE of the liver - CHILI: cholestatic, hepatitic, mixed

Mechanisms of action of immune check point inhibitors



Tison, A., Garaud, S., Chiche, L. et al. Immune-checkpoint inhibitor use in patients with cancer and pre-existing autoimmune diseases. Nat Rev Rheumatol 18, 641–656 (2022). https://doi.org/10.1038/s41584-022-00841-0

DI-ALH vs. AIH

	DI-AILH $n = 28$	AIH $n = 39$	p value
Gender			
Female: Male (% female)	21:7 (76)	29:10 (74)	0.96
Age at presentation			
Median (IQR)	49 (21–60)	53 (40–63)	0.27
Other autoimmune disease (no.)	8	9	0.65
Symptoms at presentation (no.)			
Jaundice/Pruritus	20	13	0.004
Antibody (no.)			
ANA	20	13	0.003
ASMA	8	21	0.04
SLA/LP	0	2	0.34
LKM	0	1	0.58
Seronegative	5	1	0.05

Ishak score	DI-AILH $n = 28$	AIH $n = 39$	p value
Periportal interface hepatitis	2.4 (±1.2)	3.0 (±0.8)	0.05
Confluent necrosis	2.5(±2.6)	2.3 (±2.2)	0.78
Focal lytic necrosis	2.3 (±0.9)	2.5 (±1.1)	0.51
Portal inflammation	2.1 (±0.7)	2.5 (±0.6)	0.07
Fibrosis	1.9 (±1.1)	3.5 (±1.4)	<0.0001
Plasma cell aggregates	61%	97%	<0.001
Eosinophil aggregates	18%	3%	0.031

Chung et al. United European Gastroenterol J .2024 Feb;12(1):66-75. doi: 10.1002/ueg2.12499.

Distinction of idiopathic AIH from drug-induced autoimmune-like hepatitis (DI-ALH)

	Idiopathic AIH	**DI-ALH**
ALT, AST	++	++
IgG	+++	+/-
autoantibodies	ANA, SMA, LKM-2 & 3, SLA	ANA, SMA, (LKM-1, LKM)
autoantibody titers	+++	+
response to steroids	++	+
relapse after steroid therapy	+	-
drug as trigger	?	+
histology	plasma cells, B cells, CD4	T cells: CD8

Seminar

JOURNAL
OF HEPATOLOGY

Nomenclature, diagnosis and management of drug-induced autoimmune-like hepatitis (DI-ALH): An expert opinion meeting report

Raúl J. Andrade[1,2,*,†], **Guruprasad P. Aithal**[3,†], **Ynto S. de Boer**[4,†], **Rodrigo Liberal**[5,6,†], Alexander Gerbes[7], Arie Regev[8], Benedetta Terziroli Beretta-Piccoli[9], Christoph Schramm[10], David E. Kleiner[11], Eleonora De Martin[12], Gerd A. Kullak-Ublick[13,33], Guido Stirnimann[14], Harshad Devarbhavi[15], John M. Vierling[16], Michael P. Manns[17], Marcial Sebode[18], Maria Carlota Londoño[2,19], Mark Avigan[20], Mercedes Robles-Diaz[1,2], Miren García-Cortes[1,2], Edmond Atallah[3], Michael Heneghan[21], Naga Chalasani[22], Palak J. Trivedi[23], Paul H. Hayashi[24], Richard Taubert[25], Robert J. Fontana[26], Sabine Weber[7], Ye Htun Oo[27], Yoh Zen[28], Anna Licata[29], M Isabel Lucena[1,2,30,*,#], Giorgina Mieli-Vergani[31,#], Diego Vergani[31,#], Einar S. Björnsson [32,#], on behalf of the IAIHG and EASL DHILI Consortium

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Journal of Hepatology, **September 2023**. vol. 79 | 853–866

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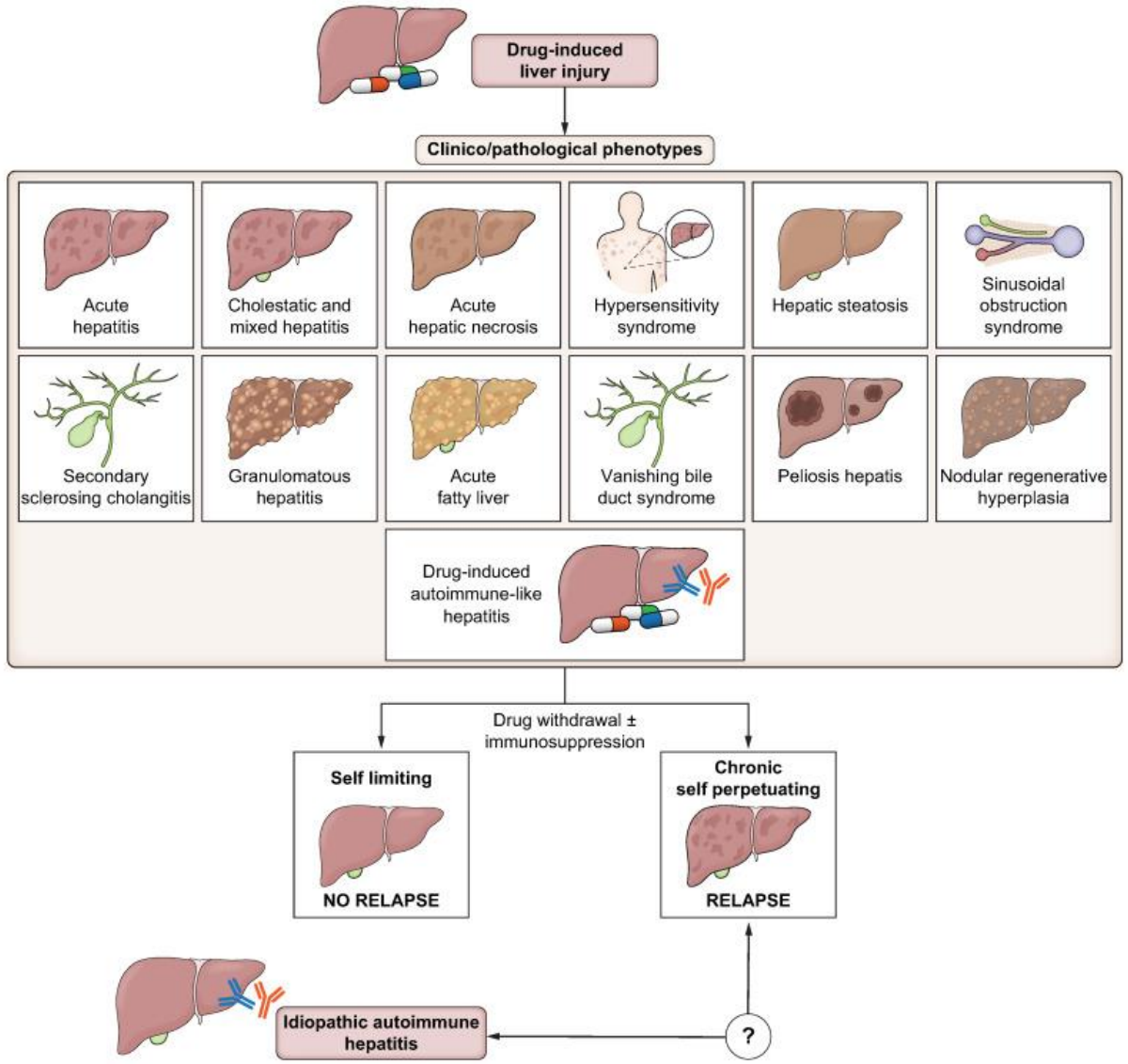
Drug-induced Autoimmune Like Hepatitis



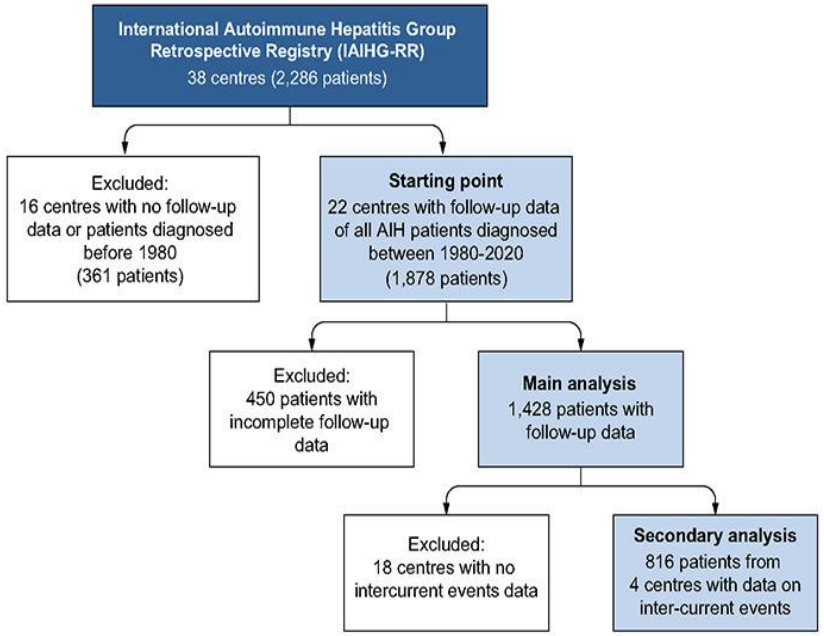
Andrade et al. Journal of Hepatology 2023 Sep;79(3):853-866.
doi: 10.1016/j.jhep.2023.04.033

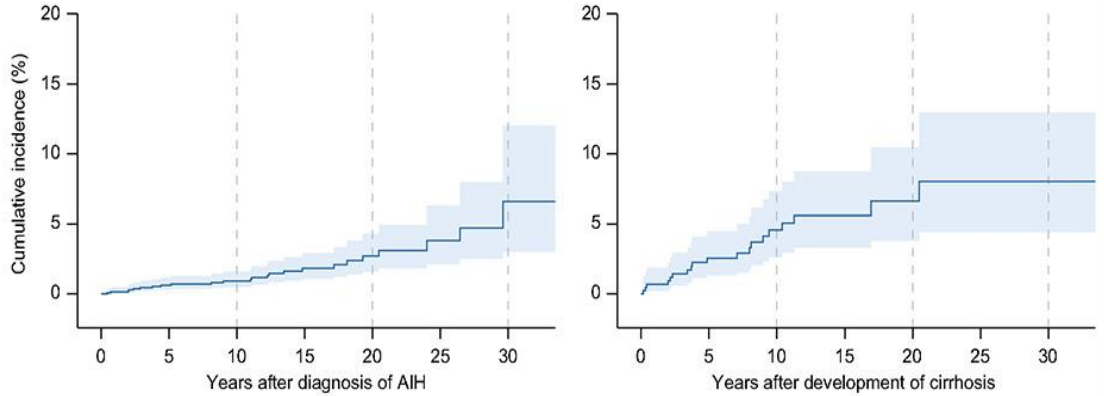
Autoimmune liver disease (AILD) and immune check point inhibitors (ICI)

- AILD (AIH, PBC, PSC) are at risk to develop liver cancer

Incidence and predictors of hepatocellular carcinoma in patients with autoimmune hepatitis

International Autoimmune Hepatitis Group (IAIHG) Retrospective Registry



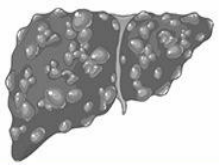


Patients at risk	1,428	1,090	828	418	217	93	32
HCCs (cumulative)	0	8	11	17	20	22	24

Patients at risk	453	279	161	88	45	24	13
HCCs (cumulative)	0	10	15	17	18	19	19‡

	Patients	5-year	10-year	15-year	20-year	25-year	30-year
Cumulative incidence of HCC after diagnosis of AIH (%) (95% CI)	1,428	0.6 (0.3-1.2)	0.9 (0.5-1.6)	1.8 (1.1-2.9)	2.7 (1.6-4.3)	3.8 (2.1-6.3)	6.6 (3.0-12.1)
Cumulative incidence of HCC after development of cirrhosis (%) (95% CI)	453	2.6 (1.3-4.5)	4.6 (2.6-7.3)	5.6 (3.3-8.8)	6.6 (3.8-10.5)	8.0 (4.4-13.0)	8.0 (4.4-13.0)

- HCC incidence in AIH patients is low even after cirrhosis development.
- Risk of HCC development in AIH is associated with obesity, cirrhosis, and AIH/PSC variant syndrome at AIH diagnosis.



PSC

Colapietro et al. Journal of Hepatology 2024 8053-61
DOI: (10.1016/j.jhep.2023.09.010)

Autoimmune liver disease (AILD) and immune check point inhibitors (ICI)

- AILD (AIH, PBC, PSC) are at risk to develop liver cancer
- HCC in AIH and PBC at cirrhotic stage
- CCC in PSC develops independent of cirrhosis, highest risk 1st year after diagnosis
- Liver and non-liver tumors develop in AILD patients
- AILD are regarded as increased risk for irAE, therefore excluded from trials with ICI

What do we know on safety of ICI in **non liver** autoimmune disorders ?

Pre-existing rheumatic disease	Flare[a]
Rheumatoid arthritis	55–56%
Polymyalgia rheumatica	57–64%
Psoriatic arthritis	50–79%
Spondyloarthritis	23–31%
Sarcoidosis	19–20%
Systemic lupus erythematosus	27–31%
Systemic sclerosis	11–25%
Sjögren syndrome	25–43%
Myositis	33–50%
Vasculitis	17–46%

De novo irAE in 16 – 90 %

Tison, A., Garaud, S., Chiche, L. et al. Immune-checkpoint inhibitor use in patients with cancer and pre-existing autoimmune diseases. Nat Rev Rheumatol 18, 641–656 (2022). https://doi.org/10.1038/s41584-022-00841-0

European Reference Network Rare Liver (ERN Rare-Liver)

- Retrospective

- 22 AILD
  - 4 x AIH, 12 x PBC, 5 x PSC, 1 x AIH/PSC overlap
  - 11 x hepatobiliary cancer, 11 x non-hepatic tumors
  - 5 different anti PD1/PD-L1 monotherapy
  - Atezolizumab (n=7), durvalumab (n=5), pembrolizumab (n=4), nivolumab (n=4), spartalizumab (n=1)
  - 1 nivolumab/ipilimumab
  - No anti LAG-3 (relatlimab)

- ***Safety***:
- 8/22 with irAE
- 3/8 DI-ALH, 2 AIH, 1 PBC, within 2 months after ICI start, no discontinuation
- all grade 1 or 2, no decompensation

Kocheise et al, Frontiers in Immunology, 2024

Recommendations for the use of ICIs in cancer patients with pre-existing AILD

- No contraindication to use ICI +/- anti CTLA-4 in liver and non-liver tumors in patients with underlying preexisting AILD
- Sofar favorable safety profile
- Lack of data on efficacy
- Decision based on individual benefit risk evaluation
- Close follow up, highest risk for AIH with cirrhosis not in stable remission

Thank you for your attention