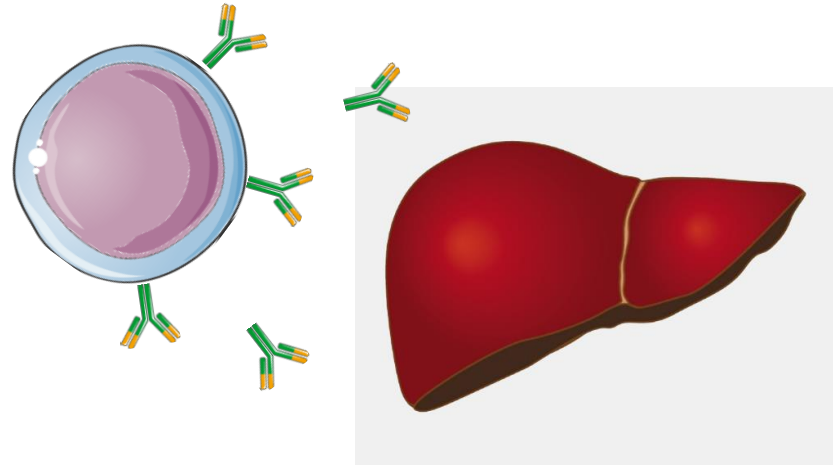


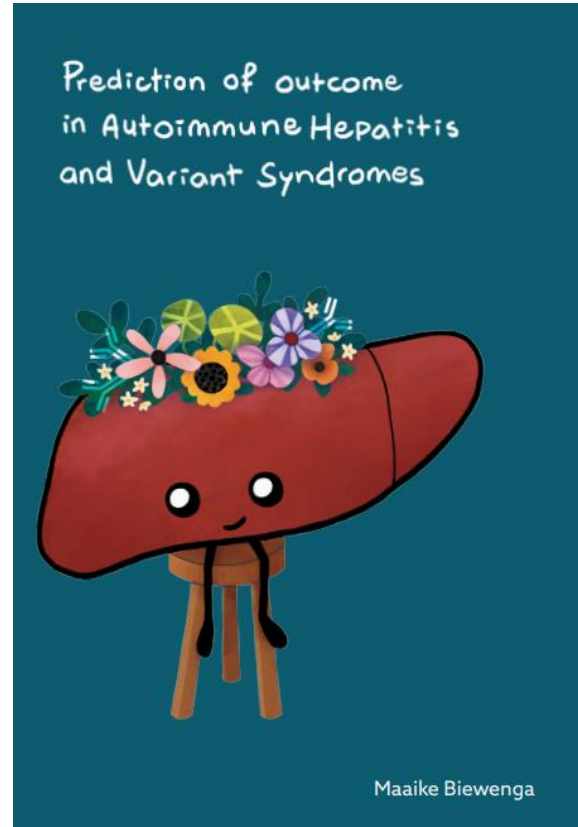
Autoimmuun hepatitis: diagnostiek en behandeling

Dr. M. Biewenga



Wie ben ik?

- Promotieonderzoek naar AIH in LUMC
- Heden werkzaam als AIOS
Medische Microbiologie
Erasmus MC/RdGG

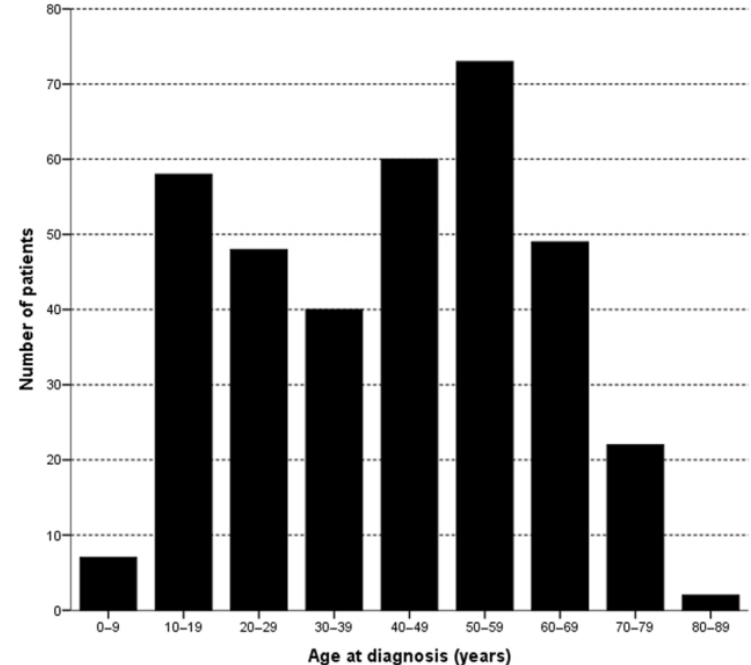


Presentatie & Diagnostiek



Autoimmuun hepatitis

- Zeldzame oorzaak van leverontsteking
- Voornamelijk bij vrouwen
- Kan zich presenteren op elke leeftijd
- Gekenmerkt door:
 - Verhoogd AST/ALT
 - Verhoogd IgG
 - Autoantistoffen
 - Interface hepatitis op het leverbiopt



Presentatie

- Symptomen
 - Acute hepatitis
 - Chronische aspecifieke symptomen
 - Asymptomatisch

Presentatie

- Symptomen
 - Acute hepatitis
 - Icterus
 - Tekenen van leverfalen
 - Verlengd INR
 - Ascites
 - Encephalopathie
 - Chronische aspecifieke symptomen
 - Asymptomatisch



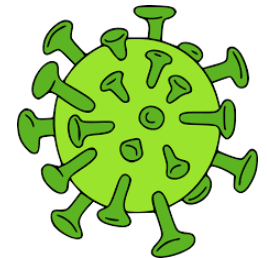
Presentatie

- Symptomen
 - Acute hepatitis
 - Icterus
 - Tekenen van leverfalen
 - Chronische aspecifieke symptomen
 - Vermoeidheid
 - Aspecifieke buikpijn
 - Gewrichtsklachten
 - Asymptomatisch
 - Verhoogde leverenzymen door de huisarts

Diagnose

- Hepatitis heeft een brede differentiaal diagnose

- Alcohol
- Virale hepatitis
- Leververvetting
- Toxisch medicamenteus
- Autoimmuun hepatitis



Aanvullend onderzoek middels lab en leverbioptie

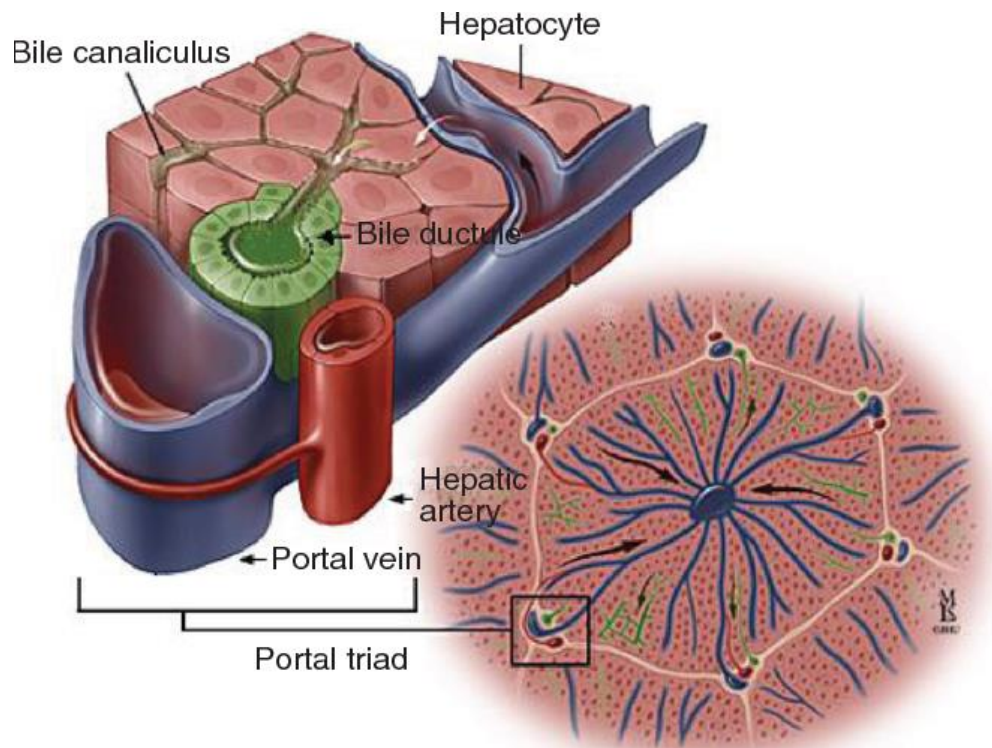
Laboratoriumafwijkingen

TABLE 1 Baseline characteristics of derivation and validation cohort

	Derivation cohort	n = 396
Female (%)	303 (77%)	396
Median age in years (range)	46 (5-84)	396
Blood tests (median [range])		
Serum IgG level in g/l	22 (6.7-92)	371
Anti-SMA positive (%)	220 (64%)	346
ANA positive (%)	244 (69%)	355
Anti-SLA positive (%)	21 (6%)	332
Bilirubin in $\mu\text{mol/L}$	38 (3-596)	244
ALT in IU/l	404 (13-3478)	359
AST in IU/l	462 (19-4388)	253
AP in IU/l	150 (27-2197)	355
GGT in IU/l	152 (2-1317)	245
Albumin in g/l	38 (13-53)	298
Creatinine in $\mu\text{mol/L}$	71 (27-561)	302
Platelets in $\times 10^9/\text{l}$	192 (37-649)	229
PT in seconds	14.6 (9.7-35.2)	217
INR	1.1 (0.9-4.3)	154

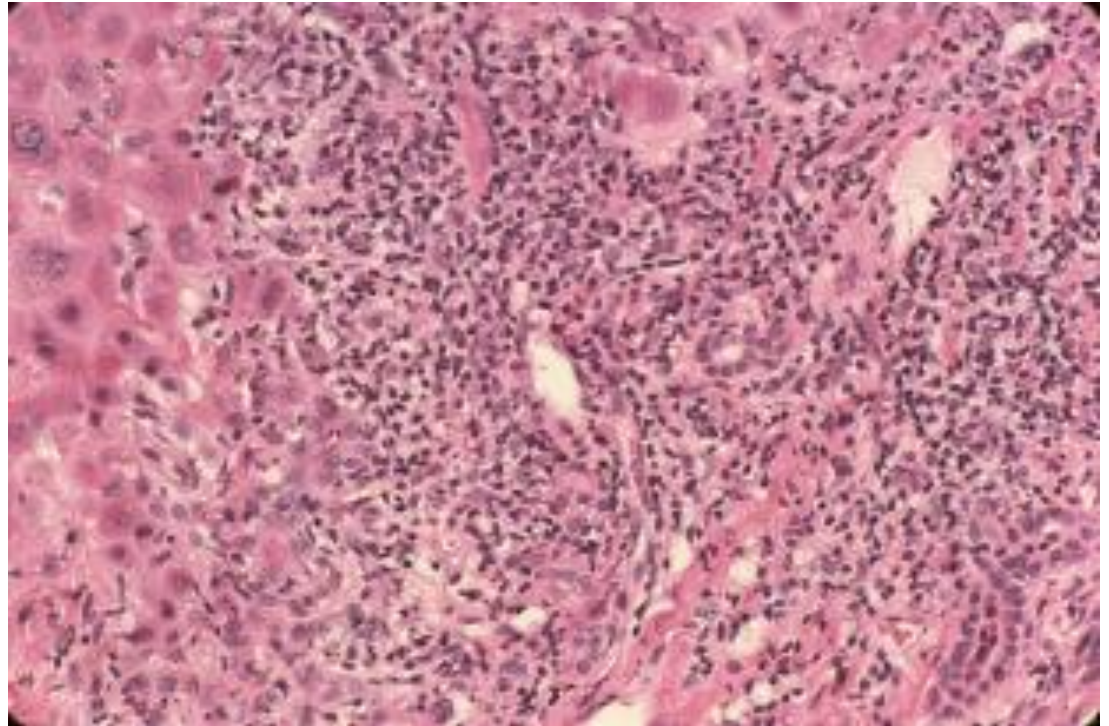
Ref: Development and validation of a prognostic score for long-term transplant-free survival in AIH type 1; UEGJ jul 2021

Leverbiopsie



Leverbiopsie

- Interface hepatitis
- Plasmacellen
- Relatieve sparing van de galwegen
- Mate van fibrose



Simplified criteria AIH

Feature/parameter	Discriminator	Score
ANA or SMA+	$\geq 1:40$	+1*
ANA or SMA+	$\geq 1:80$	+2*
Or LKM+	$\geq 1:40$	
Or SLA+	Any titre	
IgG or immunoglobulin level	>Upper limit of normal	+1
	>1.1 \times Upper limit	+2
Liver histology	Compatible with AIH	+1
	Typical of AIH	+2
Absence of viral hepatitis	No	0
	Yes	+2

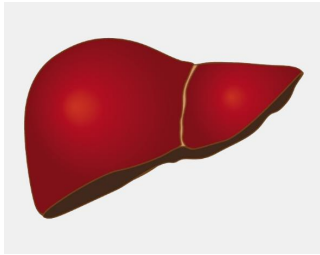
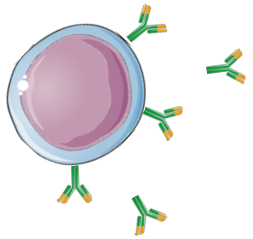
≥ 6 points: probable AIH; ≥ 7 points: definite AIH.

*Addition of points achieved for all antibodies (maximum 2 points).

ANA, antinuclear antibody; LKM, liver kidney microsomal antibody; SLA, soluble live antigen; SMA, smooth muscle antibody.

Levercirrose

Levercirrose



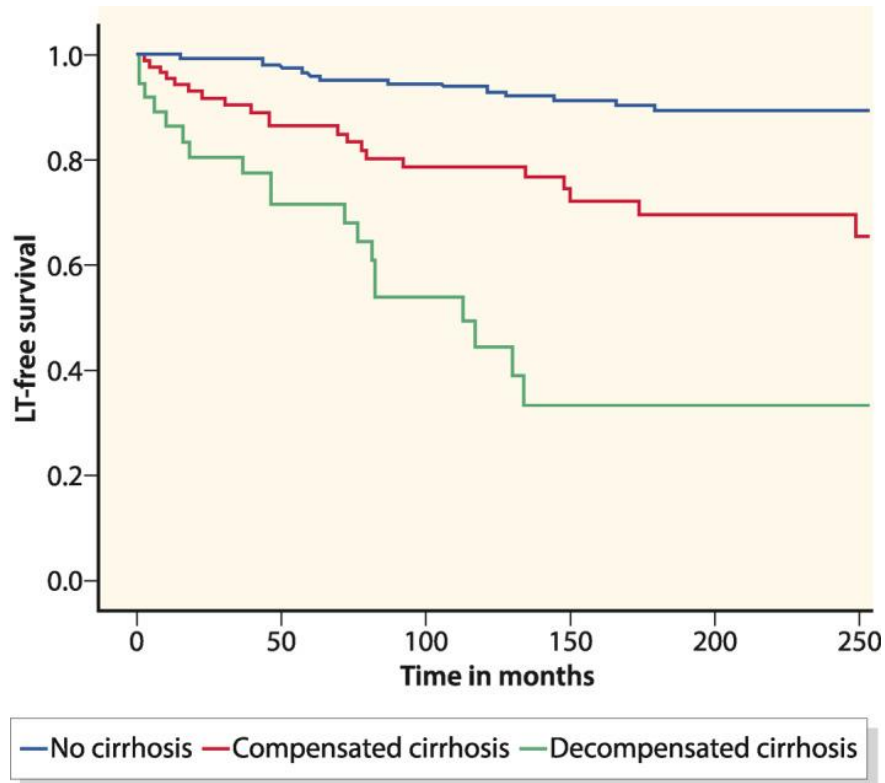
- Ongeveer 1 op de 3 patiënten heeft levercirrose bij diagnose
- Levercirrose kan leiden tot decompensatie
 - Ascites
 - Varices
 - Hepatocellulair Carcinoom
 - Encephalopathie
 - Hepatopulmonaal syndroom
 - Enz.

Fibrose en cirrose bepalen

- Gouden standaard: leverbioptie
- Non-invasieve alternatieven
 - Fibroscan
 - Bloedmarkers
 - Fibrosemarkers: PIIINP, TIMP-1, MMPs
 - ELF score (PIINP, hyaluronzuur, TIMP-1)
 - FIB-score (Leeftijd, AST, ALT, platelets)
 - AST/Platelet ratio
 - AST/ALT ratio



Invloed van cirrose op overleving



Retrospectieve studie
Cohort n=396 AIH patiënten

Ref: Development and validation of a prognostic score for long-term transplant-free survival in AIH type 1; UEGJ jul 2021

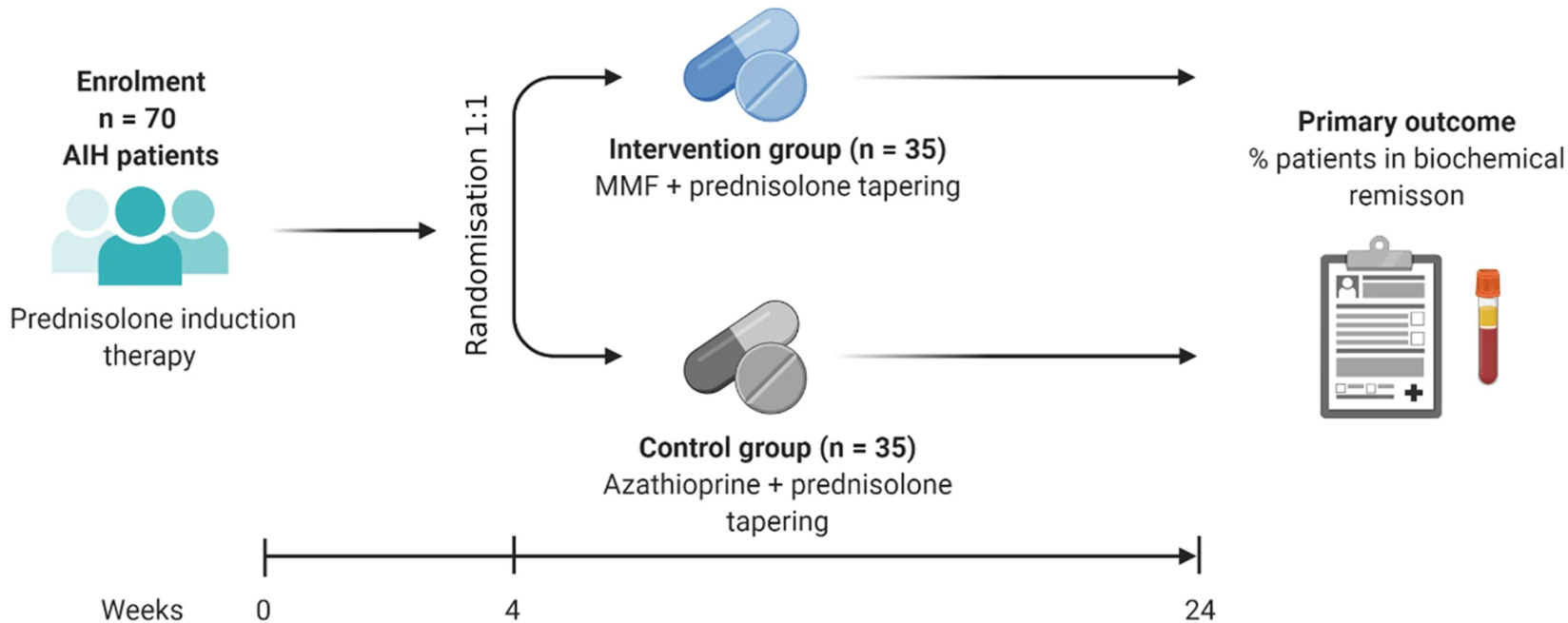
Behandeling



Behandeling

- Inductiebehandeling
 - Hoge dosering prednison of budesonide
- Onderhoudsbehandeling
 - Azathioprine
 - Bij onvoldoende effect of bijwerkingen
 - 6-TG
 - Mycophenolaat
 - Tacrolimus
- Levertransplantatie als laatste optie

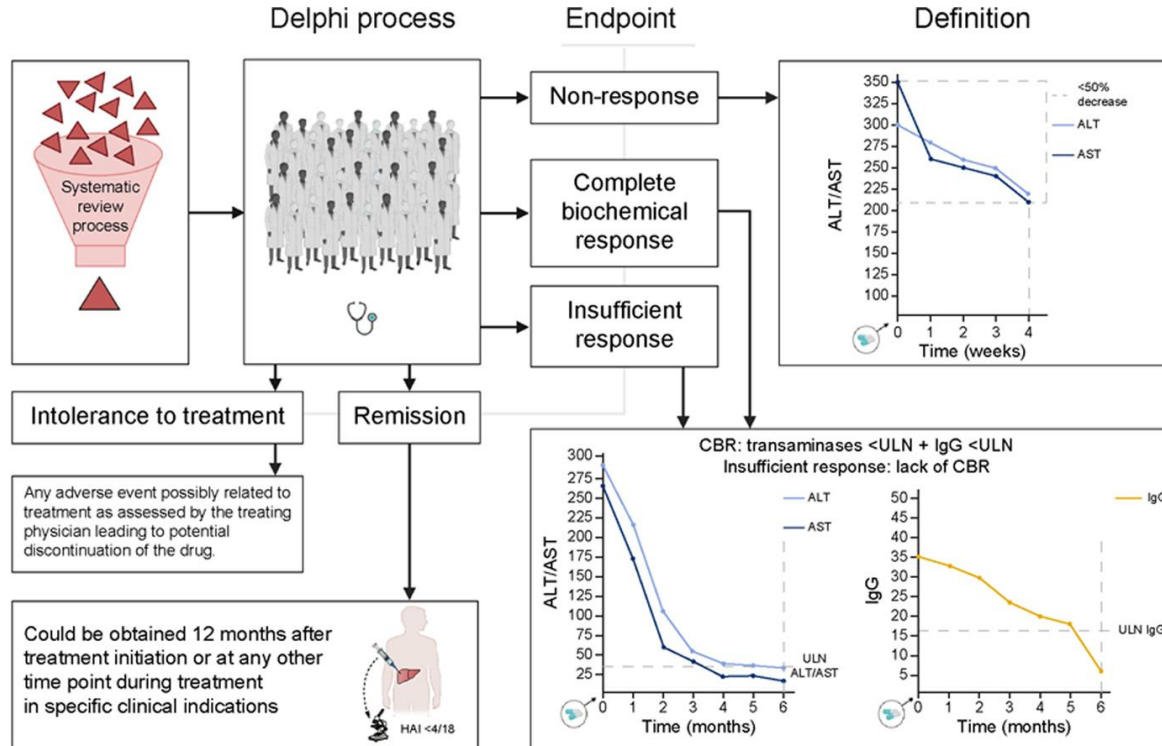
CAMARO studie: verbetering 1^e lijns behandeling



Behandeling

- *“Treatment of AIH should be aimed to obtain complete biochemical and histological resolution of the disease in order to prevent further progression of liver disease” - EASL guidelines AIH 2015*
- Complete biochemische remissie
- Partiële biochemische remissie
- Loss of remission
- Relapse

Definitives responsecriteria

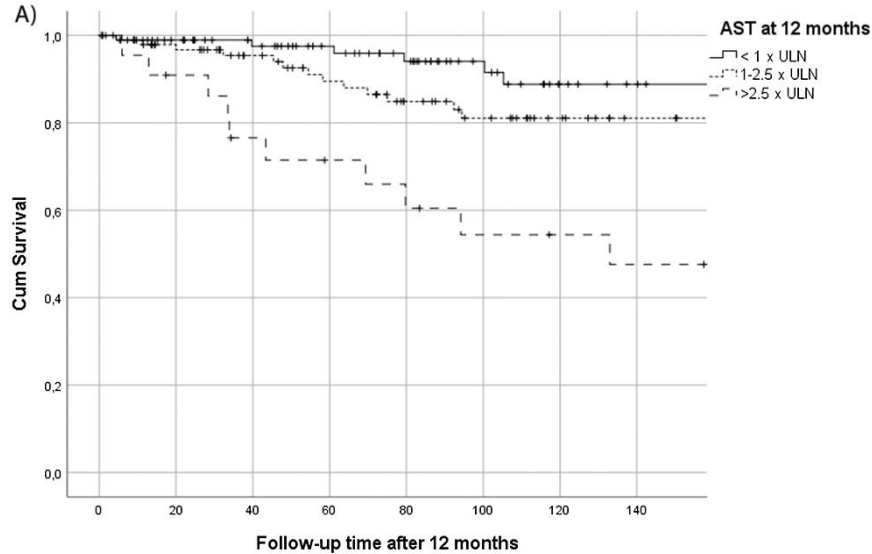


Ref: Systematic review of response criteria and endpoints in autoimmune hepatitis by the International Autoimmune Hepatitis Group; Journal of Hepatology 2022

Effect van behandeling

Cohort n=301

Effect van AST na 12 maanden op overleving



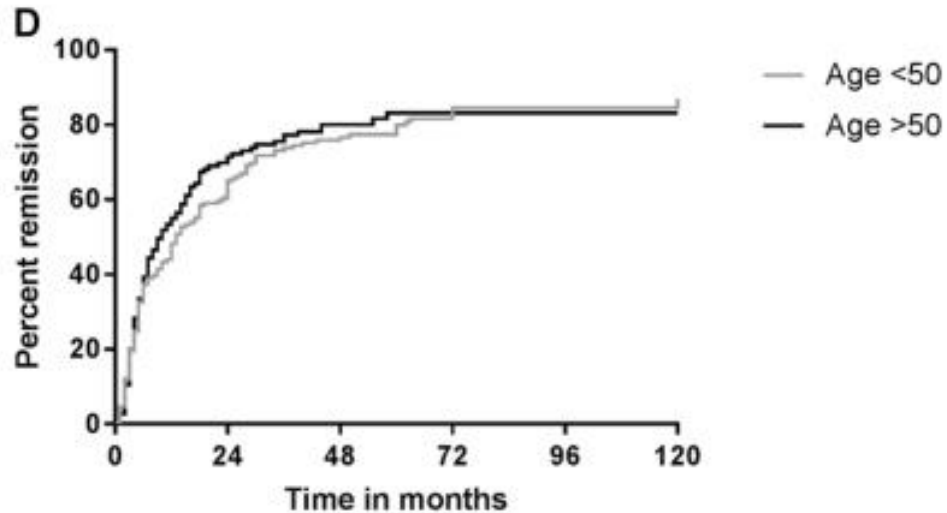
Months	0	20	40	60	80	100	120	140
N at risk								
< 1 x ULN	97	81	70	60	51	37	26	22
1-2.5 x ULN	96	83	69	59	49	41	32	25
> 2.5 x ULN	22	19	15	13	11	9	8	7

Ref: Aminotransferases during treatment predict long-term survival in patients with autoimmune hepatitis type 1: a landmark analysis; Clin Gas Hep 2022

	Hazard Ratio (95% CI)	P Value
6 mo		
Age	1.04 (1.02–1.05)	<.001
Cirrhosis at diagnosis	3.09 (1.62–5.89)	.001
Ln AST × ULN at diagnosis	0.66 (0.48–0.90)	.010
Ln AST × ULN at 6 mo	2.61 (1.47–4.61)	.001
12 mo		
Age	1.03 (1.02–1.05)	<.001
Cirrhosis at diagnosis	2.42 (1.21–4.87)	.013
Ln AST × ULN at diagnosis	0.64 (0.47–0.86)	.004
Ln AST × ULN at 12 mo	2.13 (1.46–3.11)	<.001

Effect gecorrigeerd voor leeftijd,
cirrose en AST bij diagnose

Verdubbeling AST → 69% (!)
toename van HR



	Time	0	24	48	72	96	120
Age <50	<i>N</i> at risk	174	52	30	16	15	12
	<i>N</i> in remission	0	108	125	134	134	135
Age >50	<i>N</i> at risk	143	35	15	8	6	4
	<i>N</i> in remission	0	97	107	109	109	109

Behalen van remissie

Na 1 jaar 50% remissie

Uiteindelijk 80% remissie

Ref: Role of age in presentation, response to therapy and outcome of autoimmune hepatitis; Clin Trans Gastroenterol 2018

- Gedegen onderzoek naar 2^e lijns behandeling hard noodzakelijk
- Kan alleen bij goede (inter)nationale samenwerking



Complement

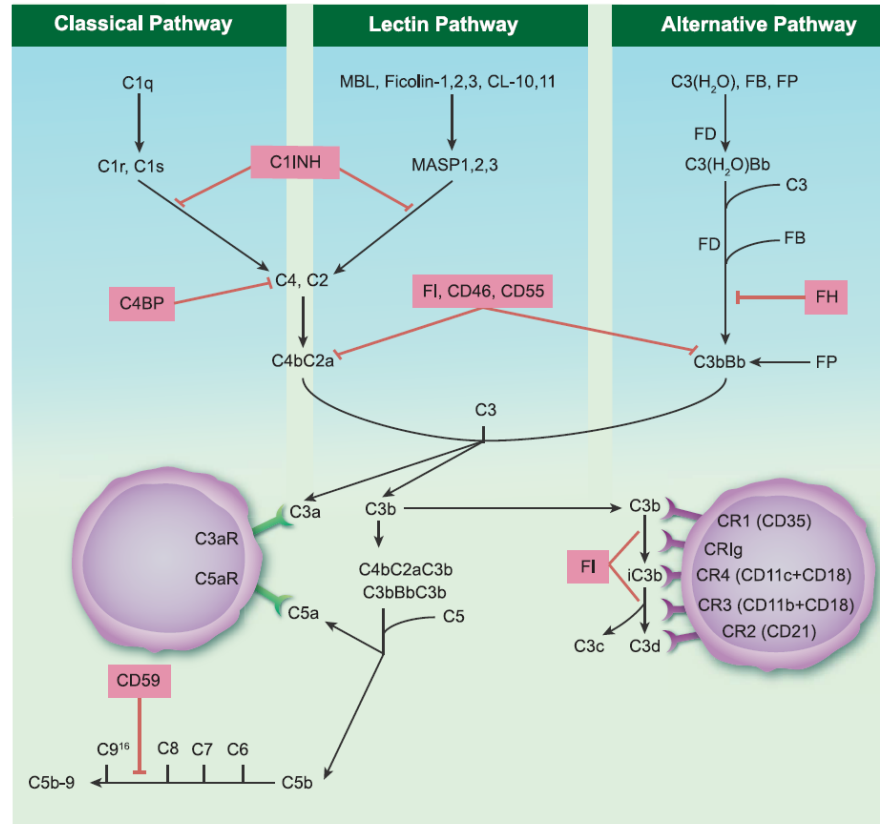
Autoimmune hepatitis

- Chronic autoimmune disease of the liver
- Exact pathophysiology unknown
- Characterized by:
 - Raised total IgG
 - Autoantibodies
 - Interface hepatitis and plasma cells on liver biopsy

Is damage to hepatocytes mediated by complement?

Complement

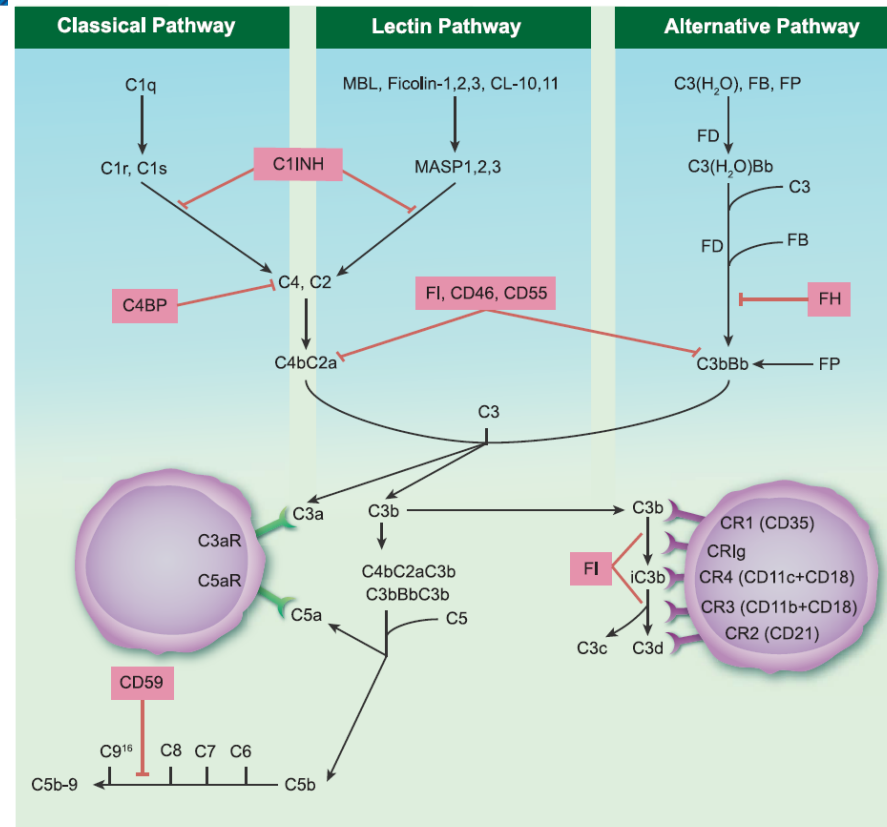
- Proteins of the innate immune system
- Mainly produced by the liver
- Activation results in forming of membrane attack complex and damage of the pathogen/cell

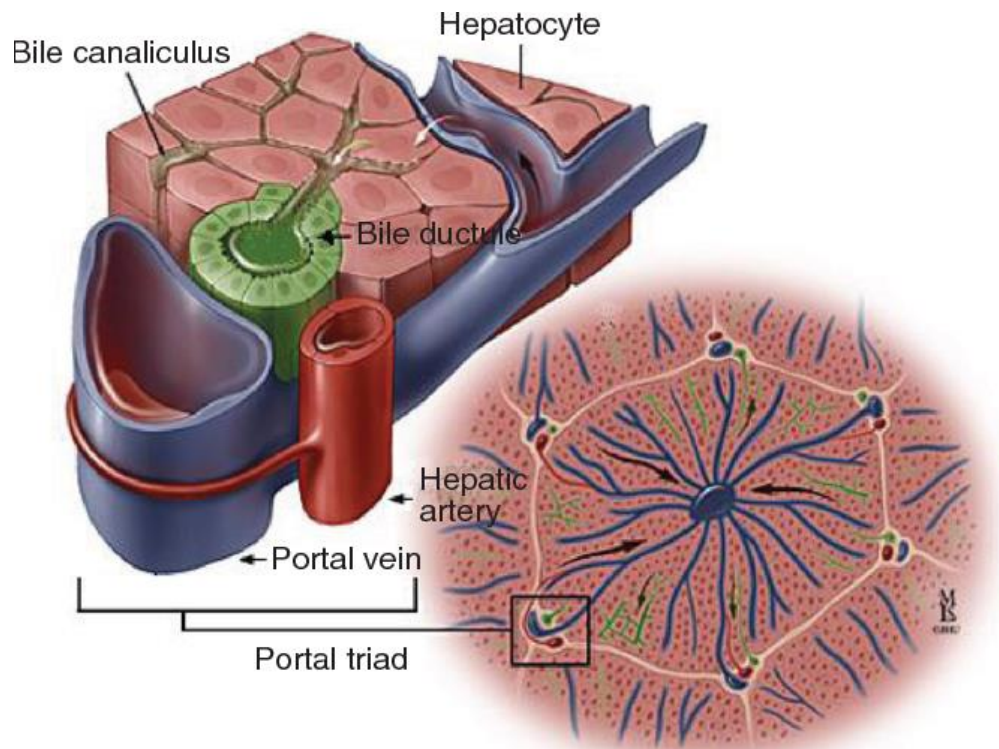


Lubbers et al. 2017 J translation immunology

Methods

- IHC on liver biopsies:
 - N=9
 - IgG
 - C1Q
 - C3D
 - C4D
 - C5b9
- Healthy and positive controls



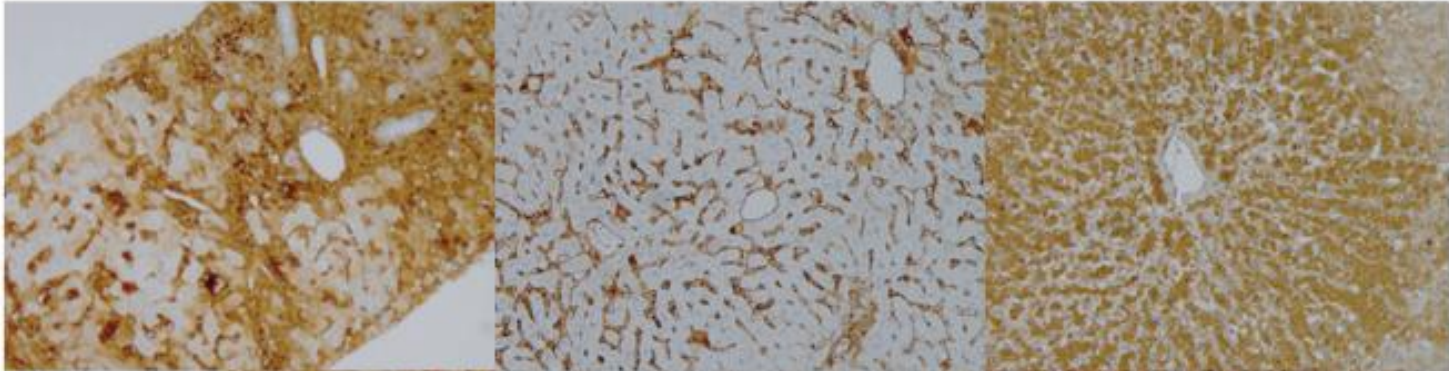


AIH

Healthy control

Acute liver failure

IgG



C1q



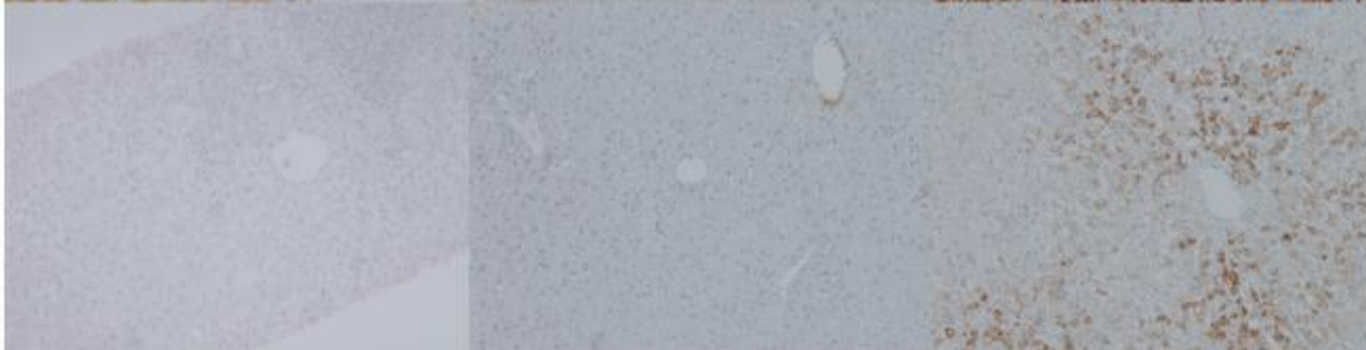
C3d



C4d



C5b9



Conclusie

- Productie van complement vind plaats in de lever
- Ondanks aanwezigheid van IgG en auto-antistoffen geen activatie van complement
- Suggereert dat schade niet via complementactivatie maar via andere routes ontstaat



Leids Universitair
Medisch Centrum

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Prof. dr. L.A. Trouw
Prof. dr. H. Putter



Afdeling MDLZ LUMC
Nederlandse AIH werkgroep
Internationale AIH werkgroep



Dutch working group
Auto-immuun hepatitis