State-of-the-Art

Autoimmune Hepatitis

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12th Paris Hepatology Conference, Paris, 14 January 2019

Acknowledgements

Richard Taubert

Elmar Jaeckel

Disclosure of Interest

Falk Phama GmbH, Freiburg, Germany

Novartis, Basel, Switzerland

AASLD PRACTICE GUIDELINES June 2010

Diagnosis and Management of Autoimmune Hepatitis

Michael P. Manns,[1] Albert J. Czaja,[2] James D. Gorham,[3] Edward L. Krawitt,[4] Giorgina Mieli-Vergani,[5] Diego Vergani,[6] and John M. Vierling[7]

AASLD Practice Guidelines: Hepatology 2010

October 2015

Clinical Practice Guidelines

CrossMark

EASL | JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Autoimmune hepatitis☆

European Association for the Study of the Liver*

www.easl.eu; Journal of Hepatology 2015

Diagnosis of Autoimmune Hepatitis

- Clinical Symptoms
- Biochemistry: ALT, AST, IgG
- Immunological Tests: Autoantibodies
- Genetics
- Histopathology
- Scoring Systems
- Differential Diagnosis

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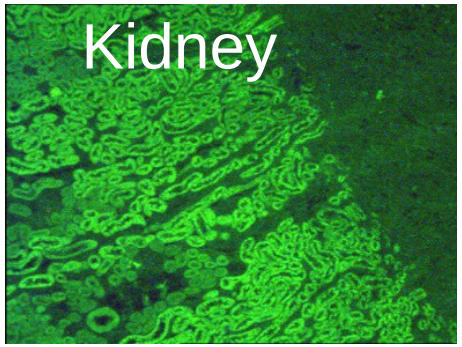
DIAGNOSIS OF AUTOIMMUNE HEPATITIS

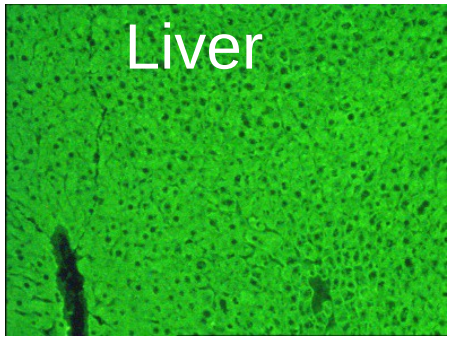
- Female gender
- Extrahepatic autoimmune syndromes
- Hypergammaglobulinia (IgG)
- Autoantibodies: ANA, LKM-1, SMA, SLA/LP
- Genetics: HLA DR 3 , DR 4, AIRE
- Histology
- Immunsuppressive Therapy

Diagnosis of AIH

Autoantibody Testing by Immunofluorescence

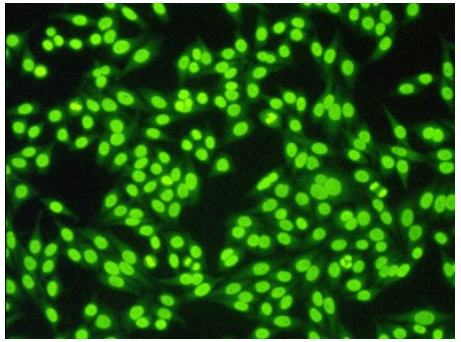
3 rodent tissue sections





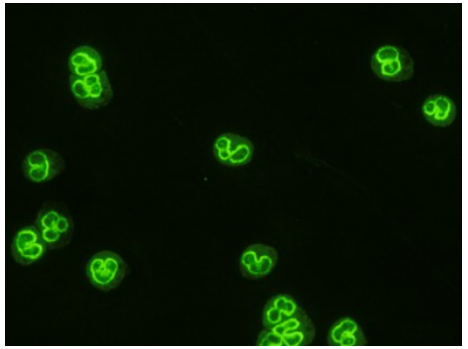
ANA, SMA, AMA, LKM, LC1

Hep2 cells



ANA pattern

Neutrophils



pANCA/pANNA

others: SLA, ASGPR

Manns et al. AASLD guidelines 2010, EASL CPG 2015
Hennes et al. Hepatology 2008, Alvarez et a. J Hepatol. 1999

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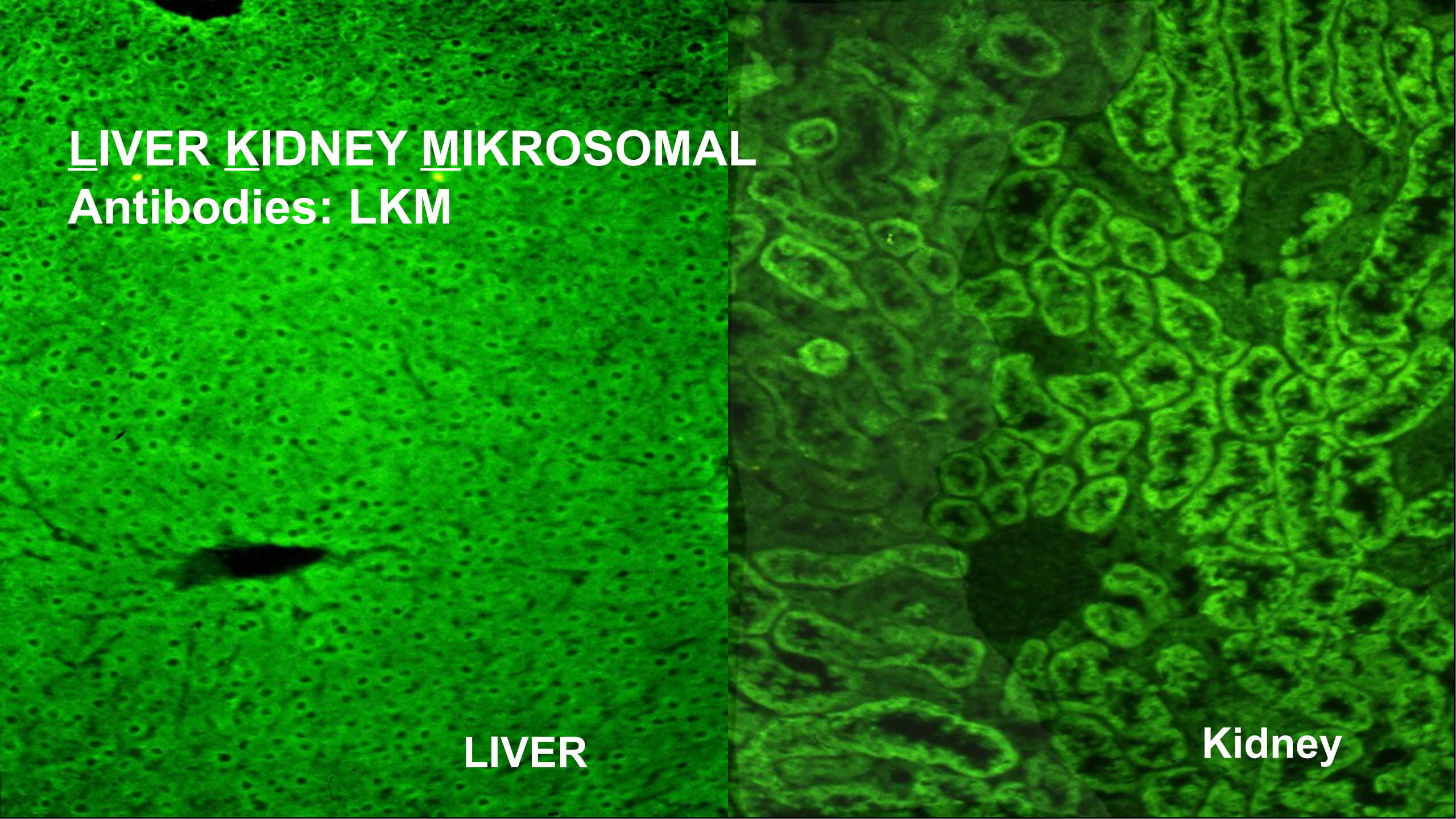
LIVER KIDNEY MIKROSOMAL
Antibodies: LKM
LIVER
Kidney

Autoantibodies in Liver Diseases

Autoantibodies	Target	Disease association
ANA	multiple nuclear antigens	AIH, SLE, MTCD etc.
AMA	2-oxo-acid-dehydrogenase complex	PBC
pANCA	h-Lamp-2, proteinase 3,	AIH, PSC, PBC
SMA	Actin, troponin, tropomysin	AIH 1
LKM 1	**CYP 2D6**	**AIH 2, HCV**
LKM 2	CYP 2C9	Tienilic acid-induced hepatitis
LKM 3	**UGT1A**	**AIH 2, hepatitis D**
LKM	**CYP 2A6**	**APS-1, hepatitis C**
LC1	**FTCD**	**AIH 2**
SLA/LP	tRNP(Ser)Sec	AIH 3
LM	**CYP 1A2**	**Dihydralzine-induced hepatitis, APS-1**
ASGP-R	Asialoglycoproteinrezeptor	Autoimmune liver disease, HCV

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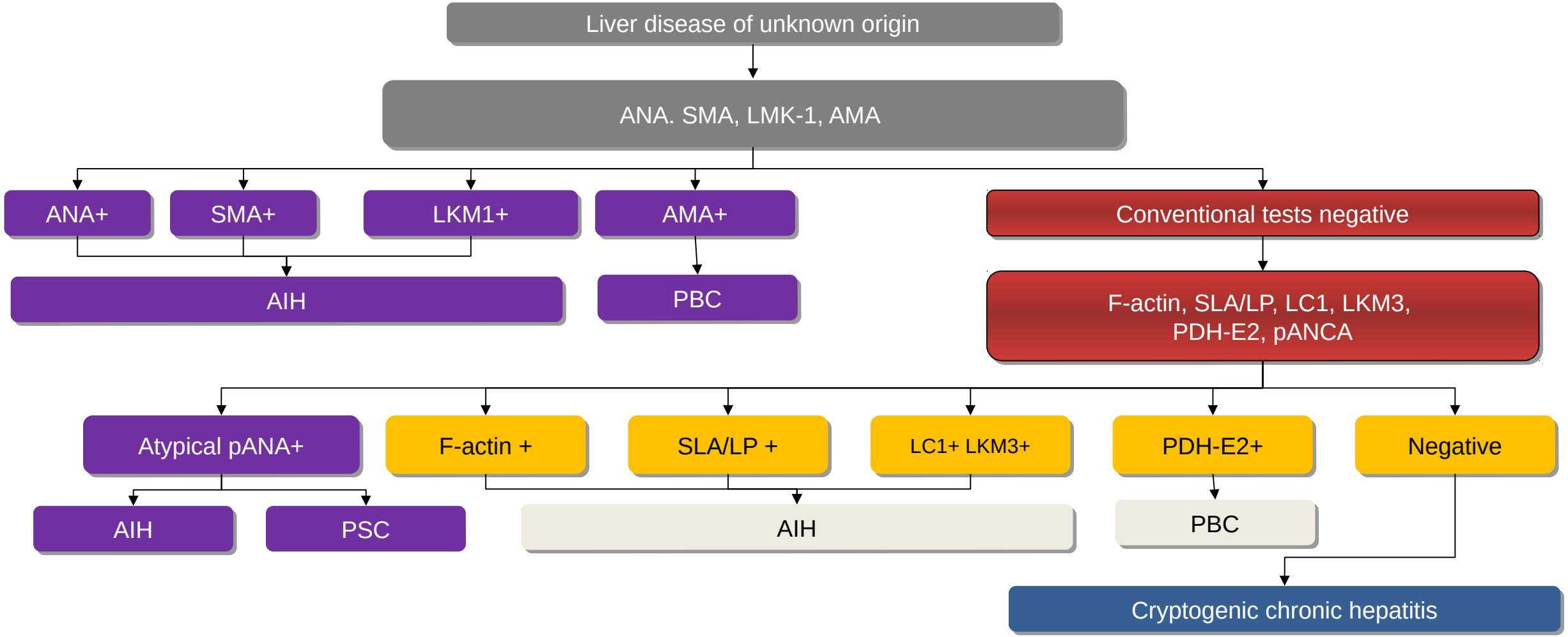
Autoantibodies in the Diagnosis of AIH



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

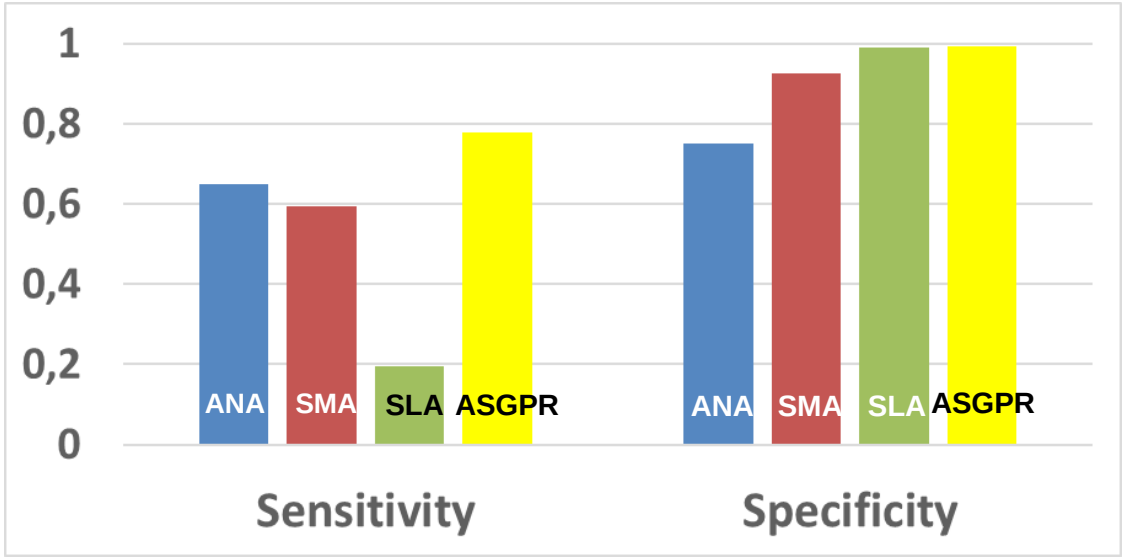
Limitations of Autoantibodies in AIH

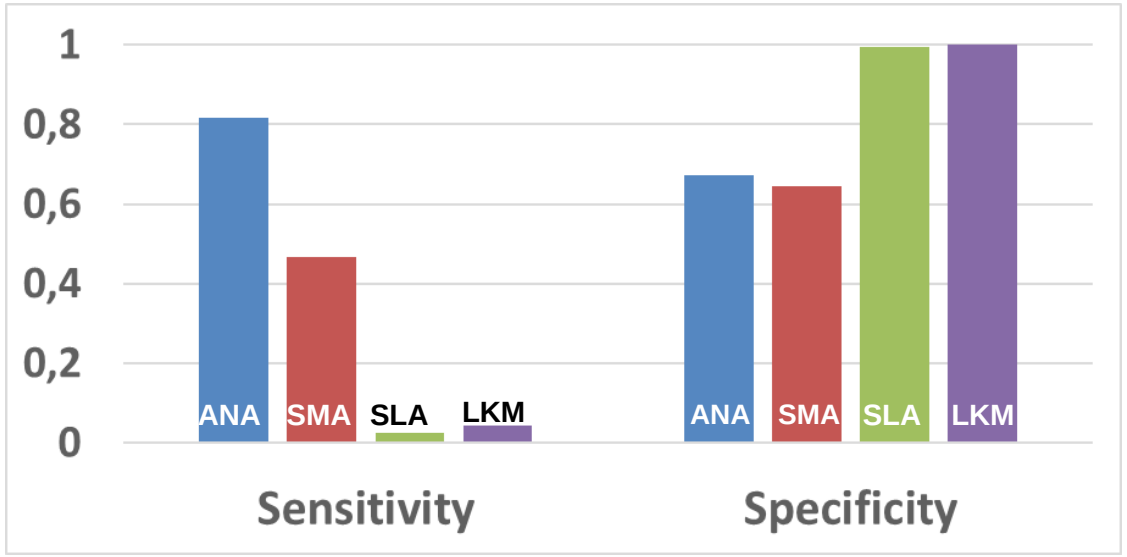
	ANA	SMA
AIH	60-85%	60-80%
NAFLD	12-40%	3-7%
NASH	20-40%	6-9%
HBV	15-30%	20-25%
HCV	9-40%	5-60%
PBC	20-50%	10%
PSC	7-70%	13-20%

Meta-Analysis
Zhang et al.
PloS One 2014

Hausdorf et al.
Clinica Clinica Acta 2009

Hannover
retrospective
Cohort
n=237-270

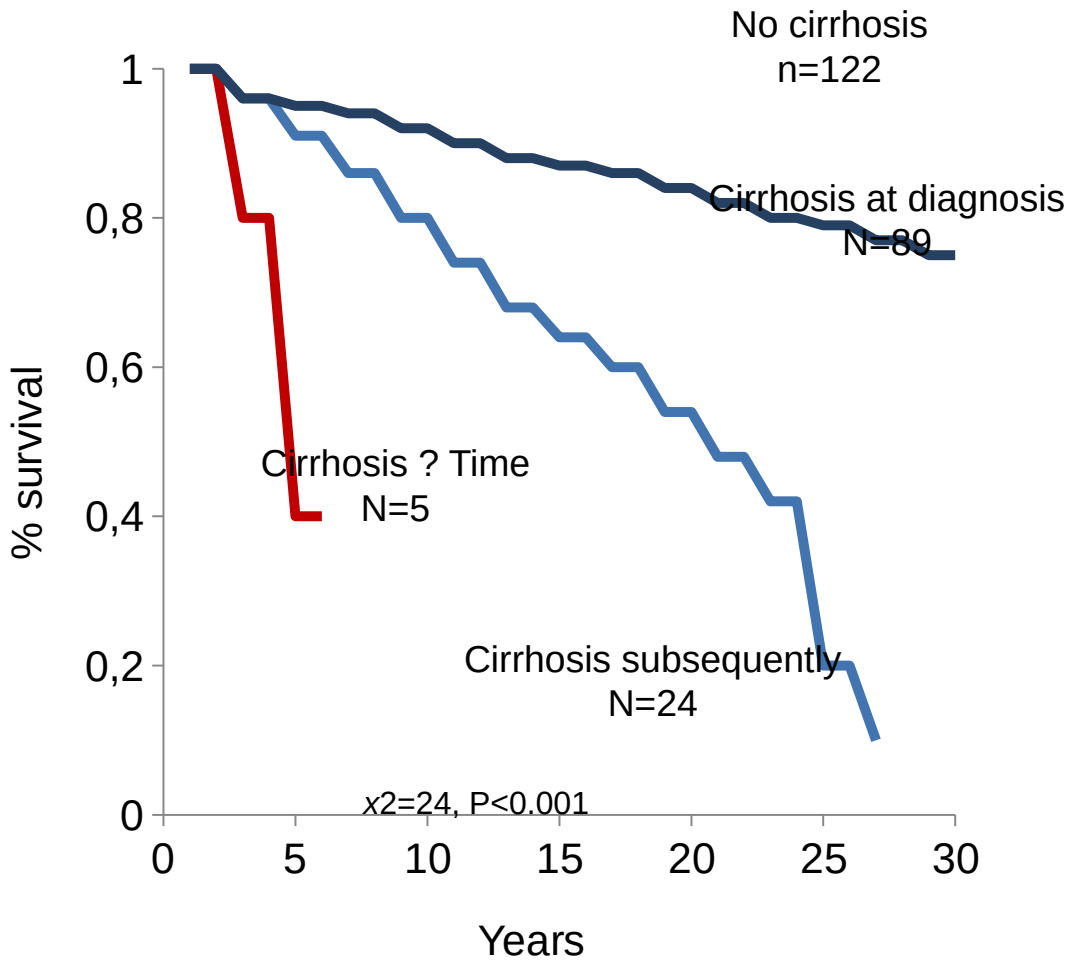




Manns et al. AASLD guidelines 2010, EASL CPG 2015; Zhang et al. Plos One 2014; Hausdorf et al. Clinica Chemica Acta 2009

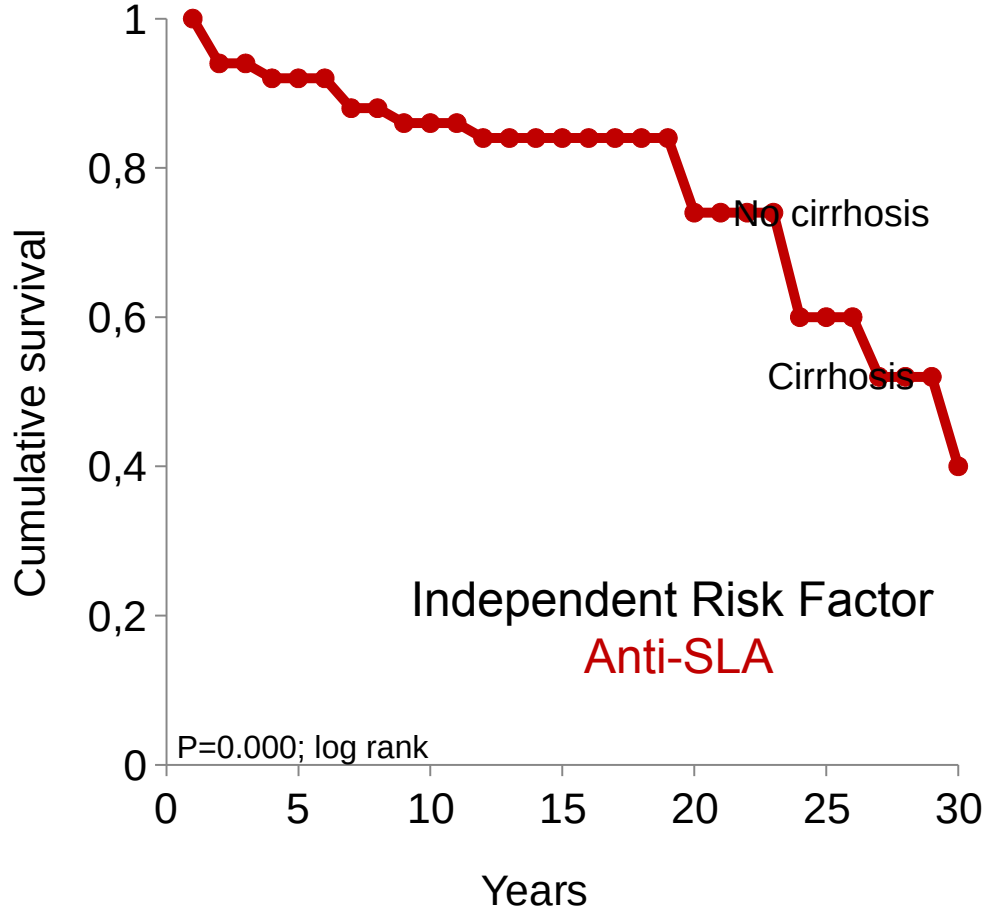
Severity Of Autoimmune Hepatitis

Association of liver-related death or transplantation, n=240



Hoeroldt B, et al. *Gastroenterology*. 2011 Jun;140(7): 1980-9.

Overall and LT-free Survival, n=354

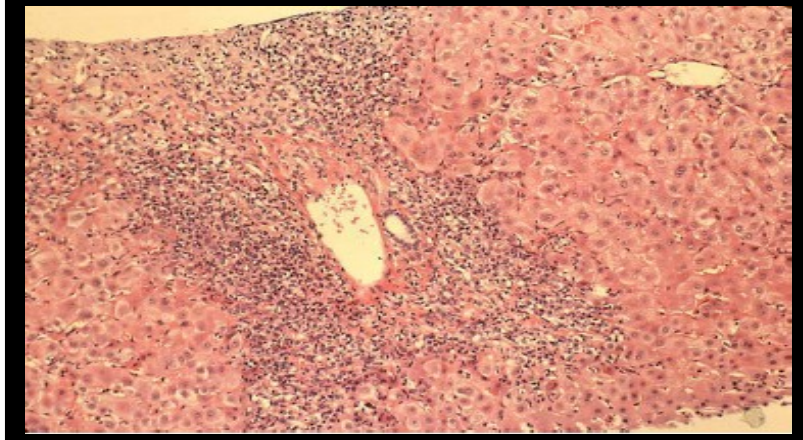


Kirstein MM, et al. *Hepatology.* 2015 Nov;62(5): 1524-35.

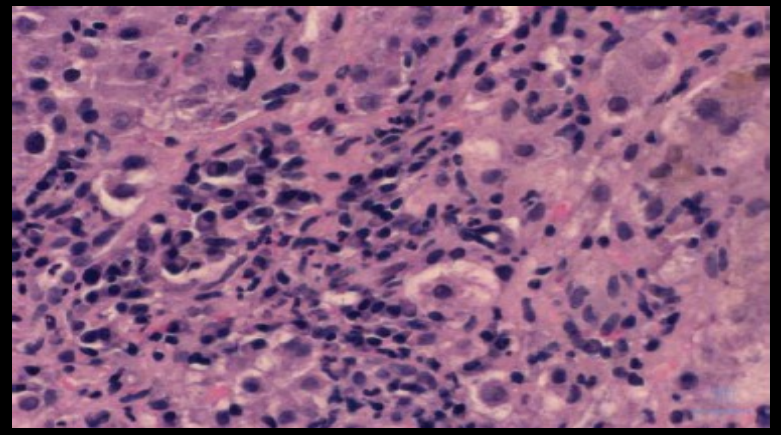
Classification Of Autoimmune Hepatitis Based On Autoantibodies

Autoimmune hepatitis Type 1	**ANA, SMA**	• 80% of cases • age: 16-30 years • slow onset
Autoimmune hepatitis Type 2	**LKM-1, LKM-3, LC-1**	• 20% of cases • age: around 10 • also fulminant cases
Autoimmune hepatitis Type 3	**SLA/LP**	• similar to type 1 • more relapse, • more difficult to treat

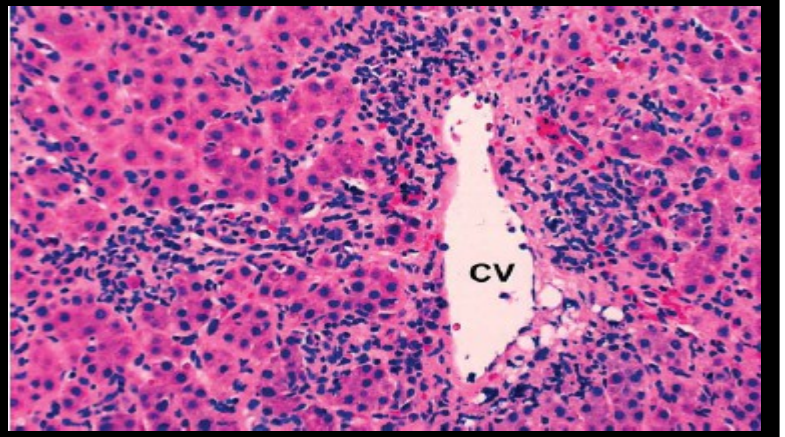
Diagnosis of Autoimmune Hepatitis: Histology



Interface hepatitis.
Limiting plate of the portal tract is disrupted by a lymphoplasmacytic infiltrate.



Plasma cell infiltration.



Median centrilobular zone 3 necrosis.
Centrilobular zone 3
necrosis associated with a mononuclear inflammatory infiltrate.

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Autoimmune Hepatitis: Histopathology

- **Interface hepatitis**
- **Plasmacellular infiltrates**
- **Hepatocyte rosetting**
- **Emperipolesis**

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Autoimmune Hepatitis: Histopathology

- **Alone not sufficient for AIH diagnosis**
- **But essential for diagnosis of AIH**
  - Presence of characteristic features
  - Exclusion of other diseases
- **Important for Grading and Staging**
- **Very important before stopping therapy**

Czaja et al. *Hepatology* 2002 | Manns and Strassburg, *Gastroenterology* 2001

AIH – Scores

Alvarez et al. J Hepatol. 1999

Hennes et al. Hepatology 2008

Feature/parameter	Discriminator	Score
Antibodies (max 2 points)		(0–2 points total)
ANA or SMA+	≥1:40	+1
ANA or SMA+	≥1:80	+2
or LKM+	≥1:40	+2
or SLA/LP+	Any titre	+2
IgG or γ-globulins level	>ULN	+1
	>1.1x ULN	+2
Liver histology (evidence of hepatitis is required)	Compatible with AIH	+1
	Typical of AIH	+2
	Atypical	0
Absence of viral hepatitis	No	0
	Yes	+2

Score ≥7 = Definite AIH

Score ≥6 = Probable AIH

Hennes EM, et al. Hepatology 2008;48:169–76; EASL CPG AIH. J Hepatol 2015;63:971–1004

Mieli-Vergani et al. JPGN 2017

For paediatric AIH und AISC

- Lower auto-antibody titer
- Cholangiogram
- Family history for autoimmune diseases

Diagnosis of Autoimmune Hepatitis

- Clinical Symptoms
- Biochemistry: ALT, AST, IgG
- Immunological Tests: Autoantibodies
- Genetics
- Histopathology
- Scoring Systems
- **Differential Diagnosis**

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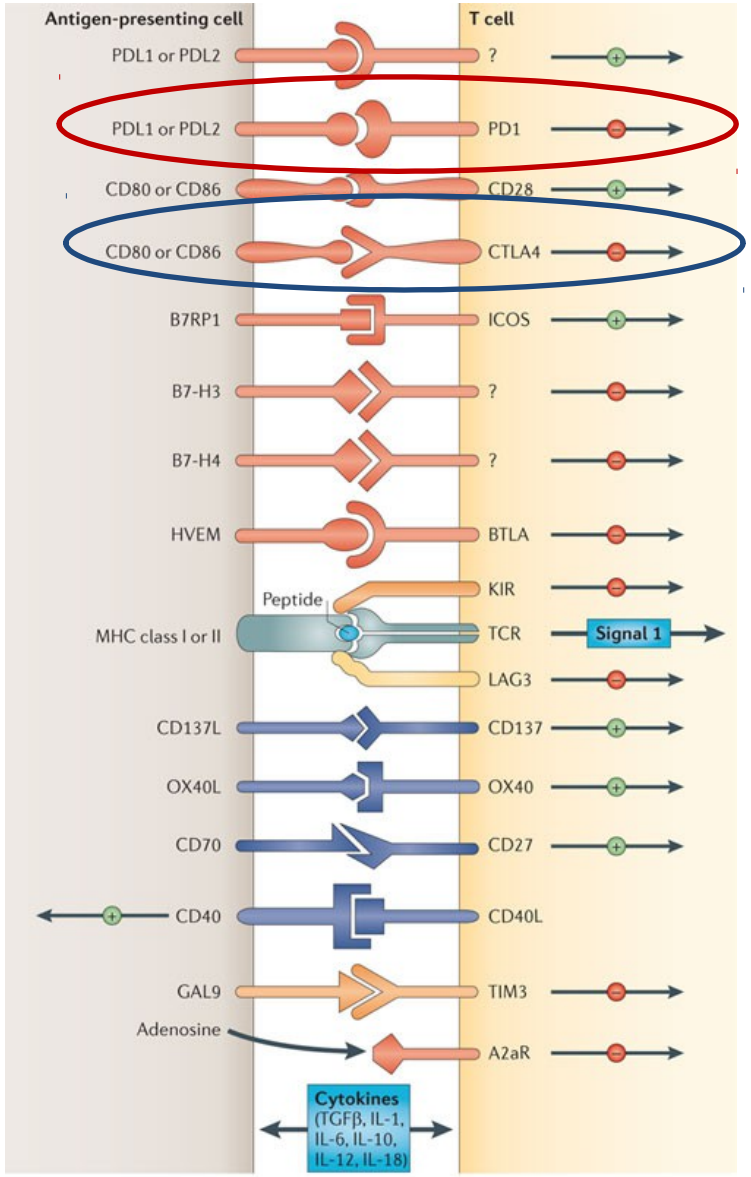
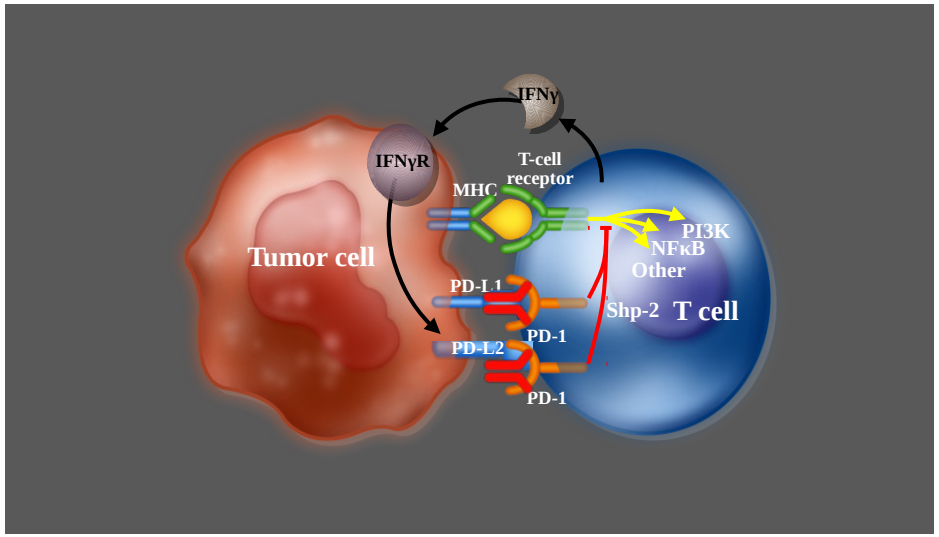
immune check points – therapeutic targets



- Nivolumab
- Pembrolizumab
- Pidilizumab

- Ipilimumab
- Tremelimumab



Nivolumab: Anti-PD-1

Nivolumab is a monoclonal immunologically active antibody (IgG4), binding to the Immune-Checkpoint-Receptor (programmed death-1) PD-1 leading to Restoration of T-Cell-Activity

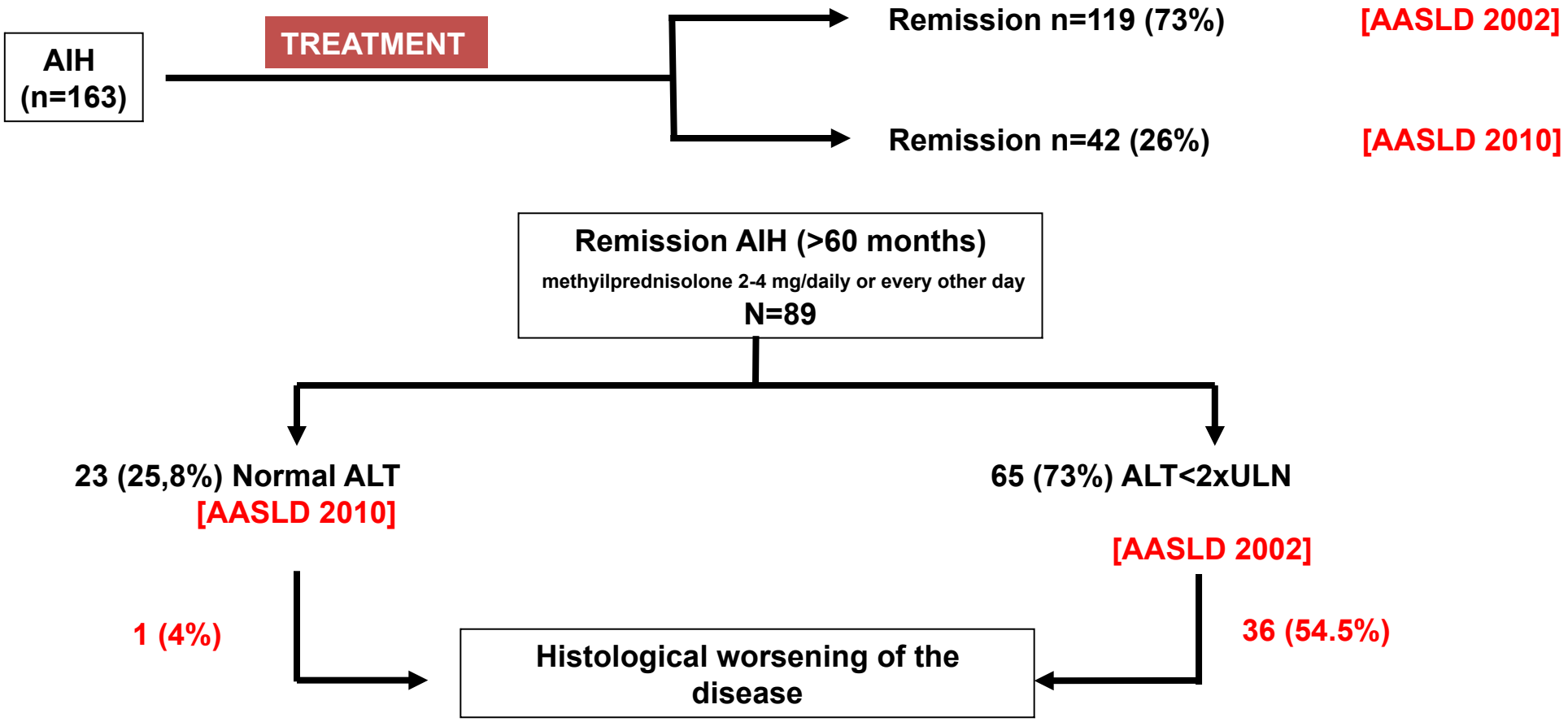
Pardoll et al. 2012, Nature Reviews

Treatment of AIH: Endpoints

Endpoints	Criteria	Recommendations
Remission	**Disappearance** of clinical symptoms, **Normalization** of aminotransferases (ALT, AST), bilirubin und γ-globulins Normal liver histology or inactive liver cirrhosis	Slow **Reduction** of steroids within 6 weeks **Control** of serum AST, ALT, total-bilirubin, and γ-globulins in 3-week intervals during and 3 months after withdrawal, then every 6 months for 2 years, then every year

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

Application of the 2010 AASLD criteria of remission to a cohort of Italian patients with autoimmune hepatitis

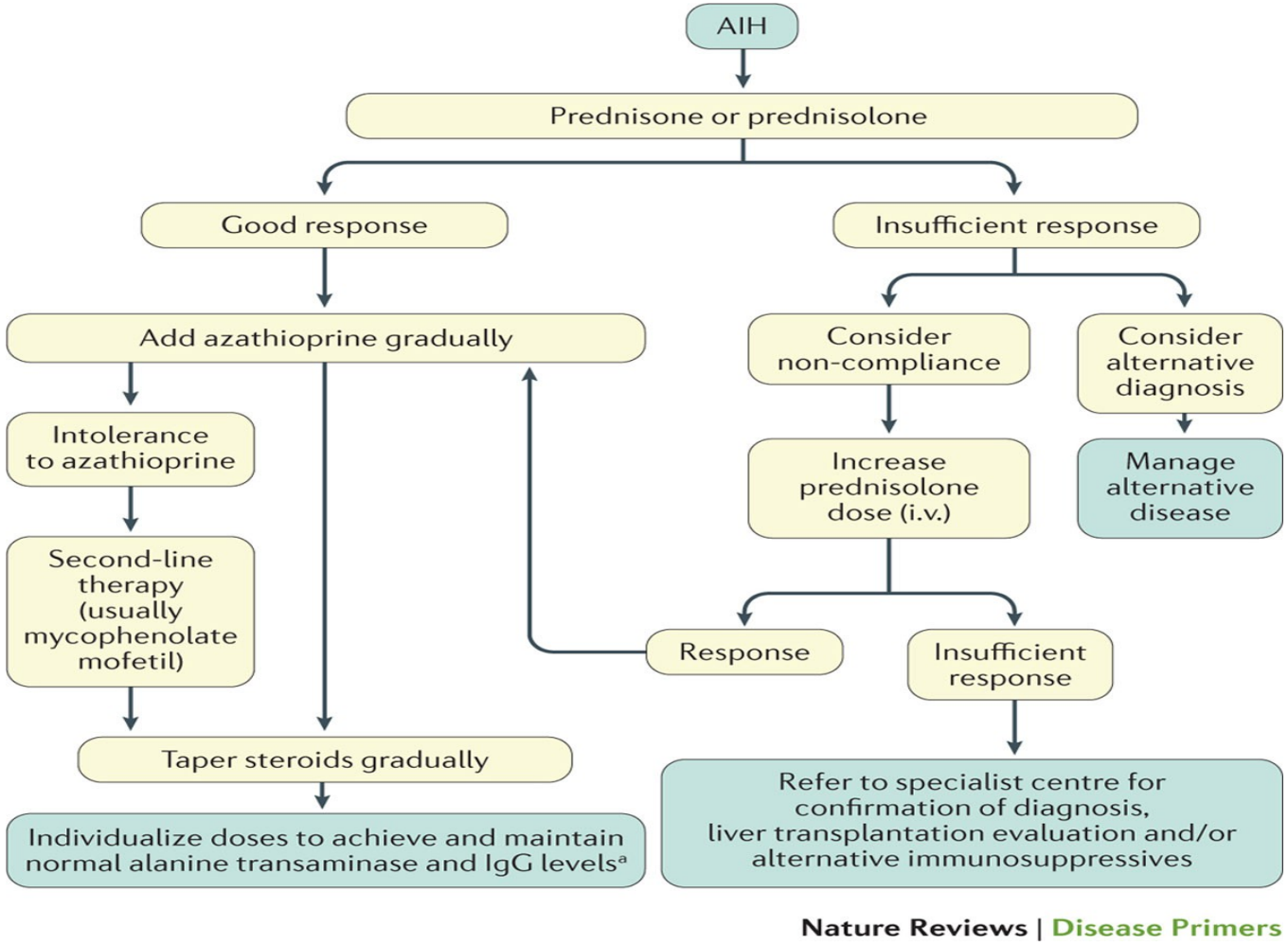


AASLD CPG: First Line Treatment of AIH (adults)

	Monotherapy	Combination Therapy		
	Prednisone	Prednisone	Azathioprine	
	(mg/ day)	(mg/ day)	USA (mg/ day)	EU (mg/ kg/ day)
Week 1	60	30	50	1 - 2
Week 2	40	20	50	1 - 2
Week 3	30	15	50	1 – 2
Week 4	30	15	50	1 – 2
Maintenance-Therapy	20 and less	10	50	1 - 2
Reasons for Choice of Therapy	Cytopenia Thiopurinmethyl-transferase-Deficiency Pregnancy Tumors Therapy ≤6 Mo	Postmenopausal Osteoporosis uncontrolled Diabetes, Hypertension, Obesity Acne Emotional Instability		

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

Management of AIH in adults



Adapted with permission from European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. *J. Hepatol.* **63**, 971–1004 (2015), Elsevier.

Mieli-Vergani, G. et al. (2018) Autoimmune hepatitis
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2018.17

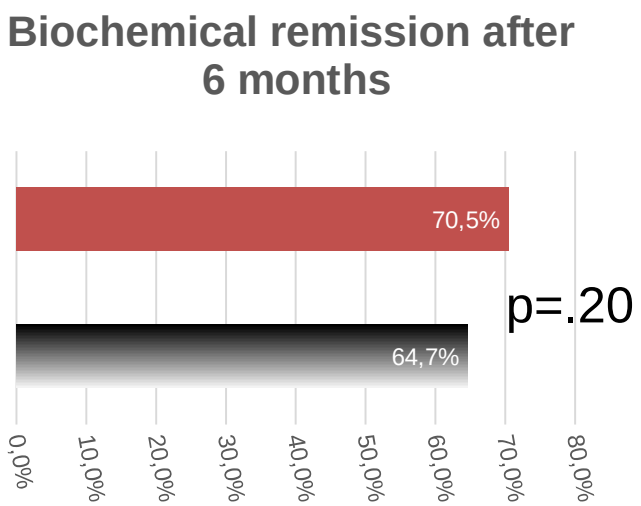
Management of AIH in adults

Differences of high (≥0.5mg/kg) and low (<0.5mg/kg) dose prediso(lo)ne regimen during first line therapy

451 AIH patients from 9 centers in 5 European countries treated between 1978 and 2017

≥0.5mg/kg/day
(n=281)

<0.5mg/kg/day
(n=170)



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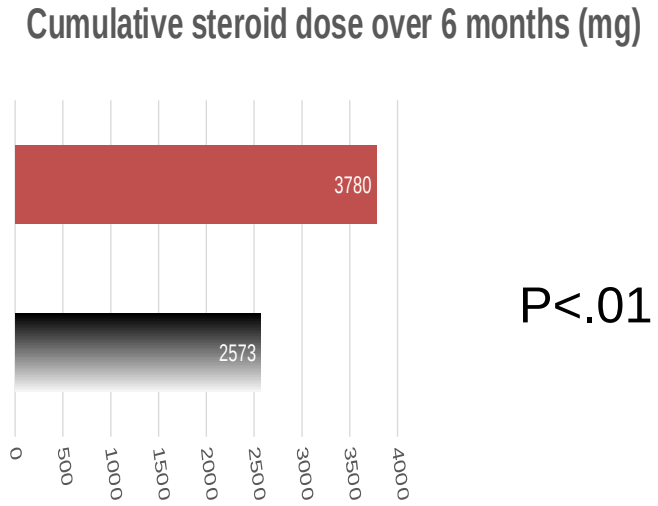

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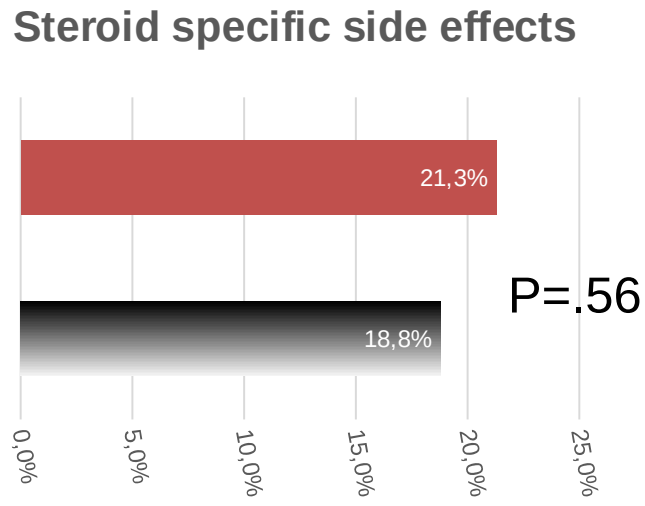

P=.56

Pape et al. Clin Gastroenterol Hepatol 2019 Jan 5.

Second Line Therapy for AIH: Alternative Drugs

Safety (Intolerance) versus Efficacy

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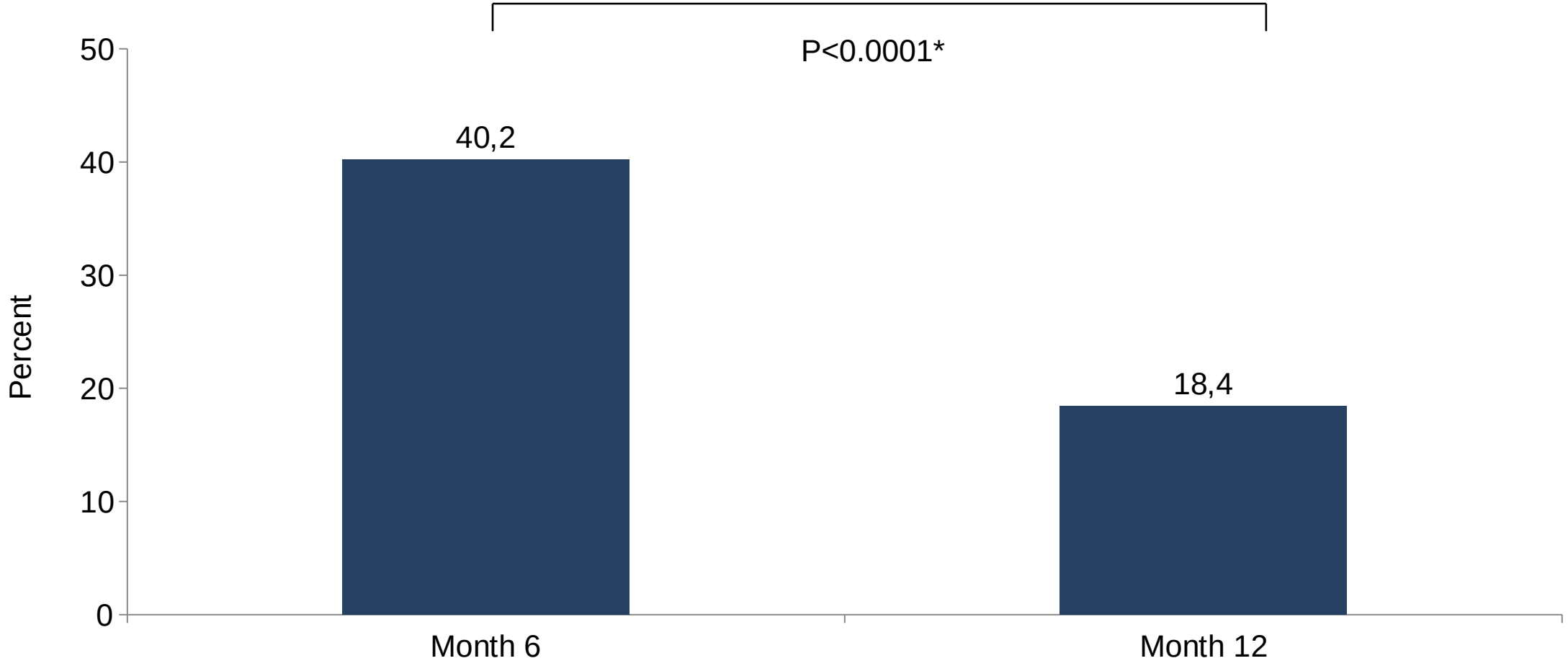
Frequency and Nature of Side Effects (Adults)

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):2193-2

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

Role of Budesonide

- Instead of Predniso(lo)ne to reduce side effects in combination with Azathioprine
  - Induction of remission in risk patients for steroid specific side effects (SSSE)
  - Long-term maintenance of remission

- Approved for AIH in 23 European and 13 Non-European countries

Budesonide Versus Prednisone: Limitations

- Bu
  -
  -
- Lo eeded
  -
- Lim e
  -

EDITORIAL:

The right drug at the right time for the right patient

Manns, Jaeckel, Taubert, Clin Gastroenterol Hepatol, 2018

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Routine assessment of thiopurine methyltransferase (IPMT) ?

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

Mycophenolate Mofetil (MMF) as Second Line Therapy – Retrospective Analysis

- MMF in n = 36 patients
  - n = 27 due to AZA intolerance
  - n = 09 due to AZA insufficiency

- Remission : < 2x ULN
- Total Remission to MMF: 14/36 (38 %)
- Remission in AZA intolerant pts: 12/28 (~ 43 %)
- Remission in AZA failure pts: 02/08 (~ 25 %)

- **MMF should be considered in AZA intolerant patients**

Hennes et al, Am J Gastro, 2008

Second Line Therapy for AIH: Alternative Drugs

Safety (Intolerance) versus Efficacy

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Second Line Therapy for Treatment Failures: Alternative Drugs

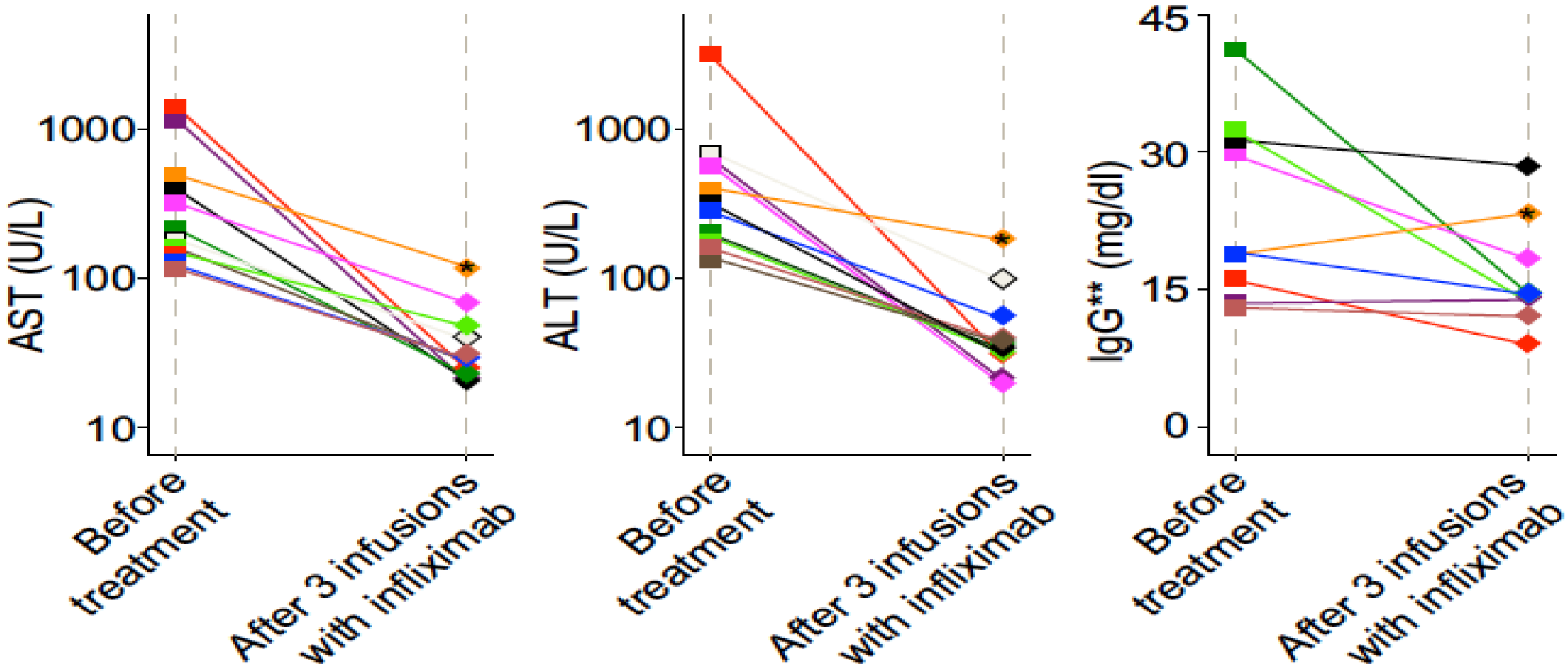
	Dose	Side effects
Cyclosporine A	3-5 mg/kg kg/qd	hypertension renal insuffiency
Tacrolimus	3 mg bid	hypertension
Everolimus	0.75-1.5mg bid (3-6ng/ml)	Proteinuria, lipid disturbance, ulcera

NONE OF THESE SECOND LINE THERAPIES IS APPROVED !

Management of failures to standard of care

- Biologicals
  - Anti TNF
  - Anti CD 20 (Rituximab)
  - Anti B cell and anti BAFF-R (VAY736)

Treatment of refractory AIH with anti-TNF



Weiler-Norman et al. J Hepatol 2013

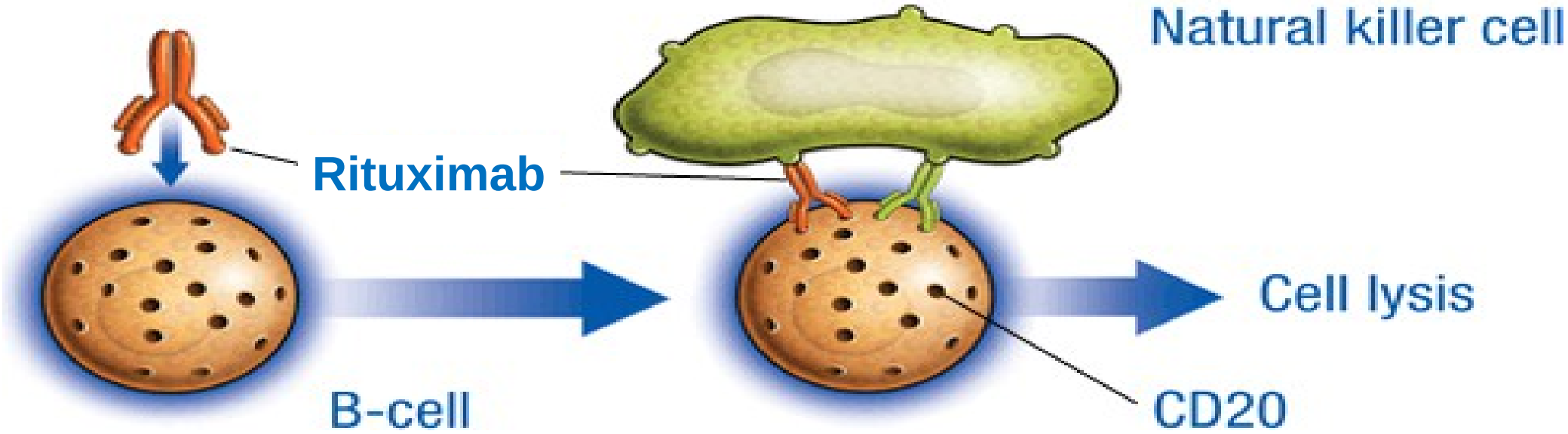
Anti-TNF alpha may cause AIH

- **Induction of AIH following TNF alpha antagonists:**

  - **Harada K et al. Clin Rheumatol 2008** AIH Exacerbation following Etanercept in patients with rheumatoid arthritis
  - **Ozorio G et al. Med J Aust 2007** AIH following infliximab therapy of ankylosing spondylitis.
  - **Cravo M. BioDrugs 2010** AIH induced by Infliximab in a patient with Crohn‘s disease, no relapse after switch to adalimumab

Rituximab Treatment of AIH

Chimeric monoclonal antibody against B cell marker CD20



PLoS ONE 6(10): e26358

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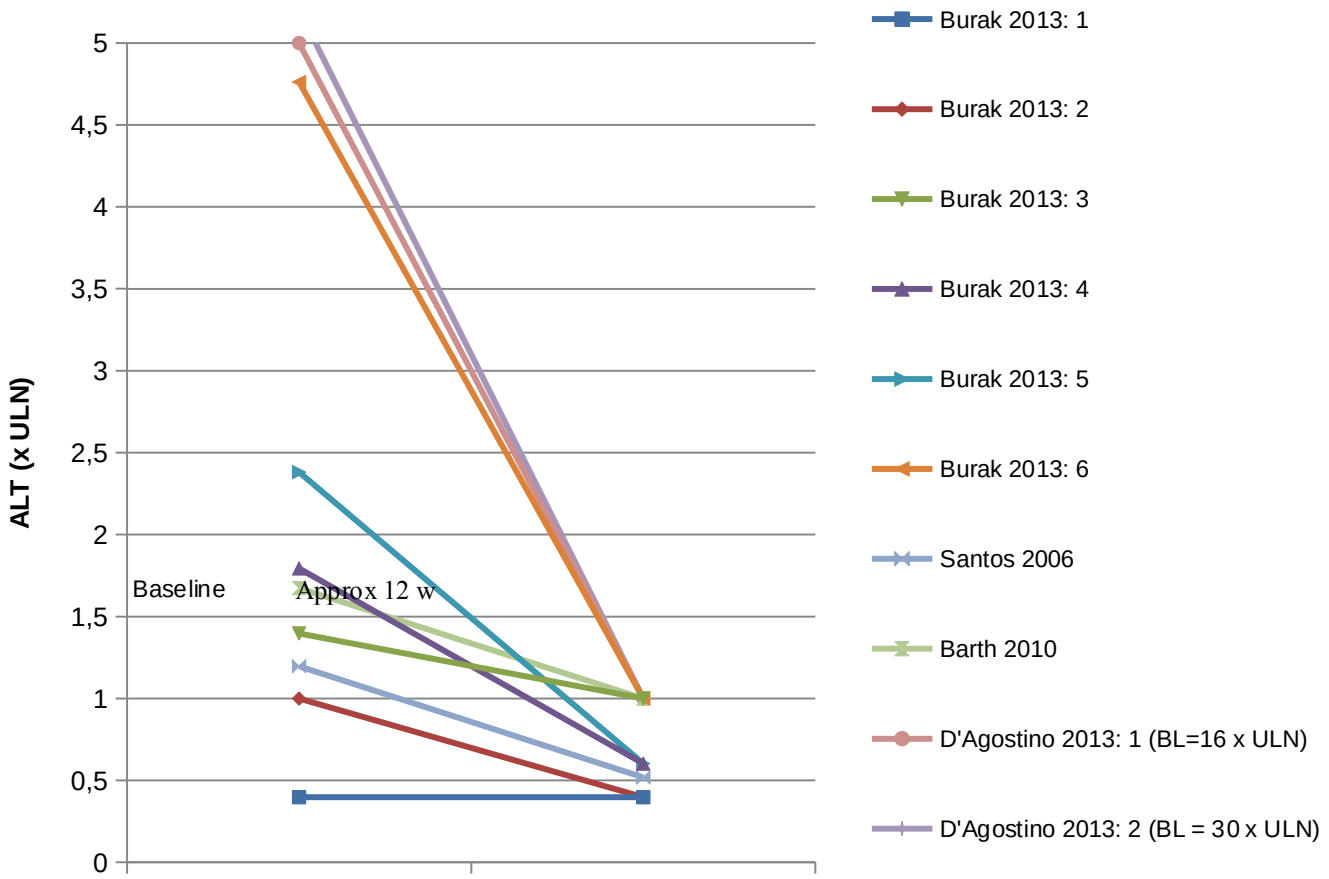
Rituximab response: case reports



Rituximab treatment experience in patients with complicated type 1 autoimmune hepatitis in Europe and North America

- 22 patients, retrospective analysis, UK, Canada Germany
- Befere and 24 months after RTX
- Reduction of Predniso(lo)ne and freedom of flares
- Improvement of ALT, AST and sustained for 24 months, ($p < 0.0010$)

- ALT 167 IU/L to 32 IU/L ($p< 0.001$)
- AST 127 IU/L to 29 IU/L
- IgG 18.9 g/l to 13.2 g/L ($p< 0.001$)

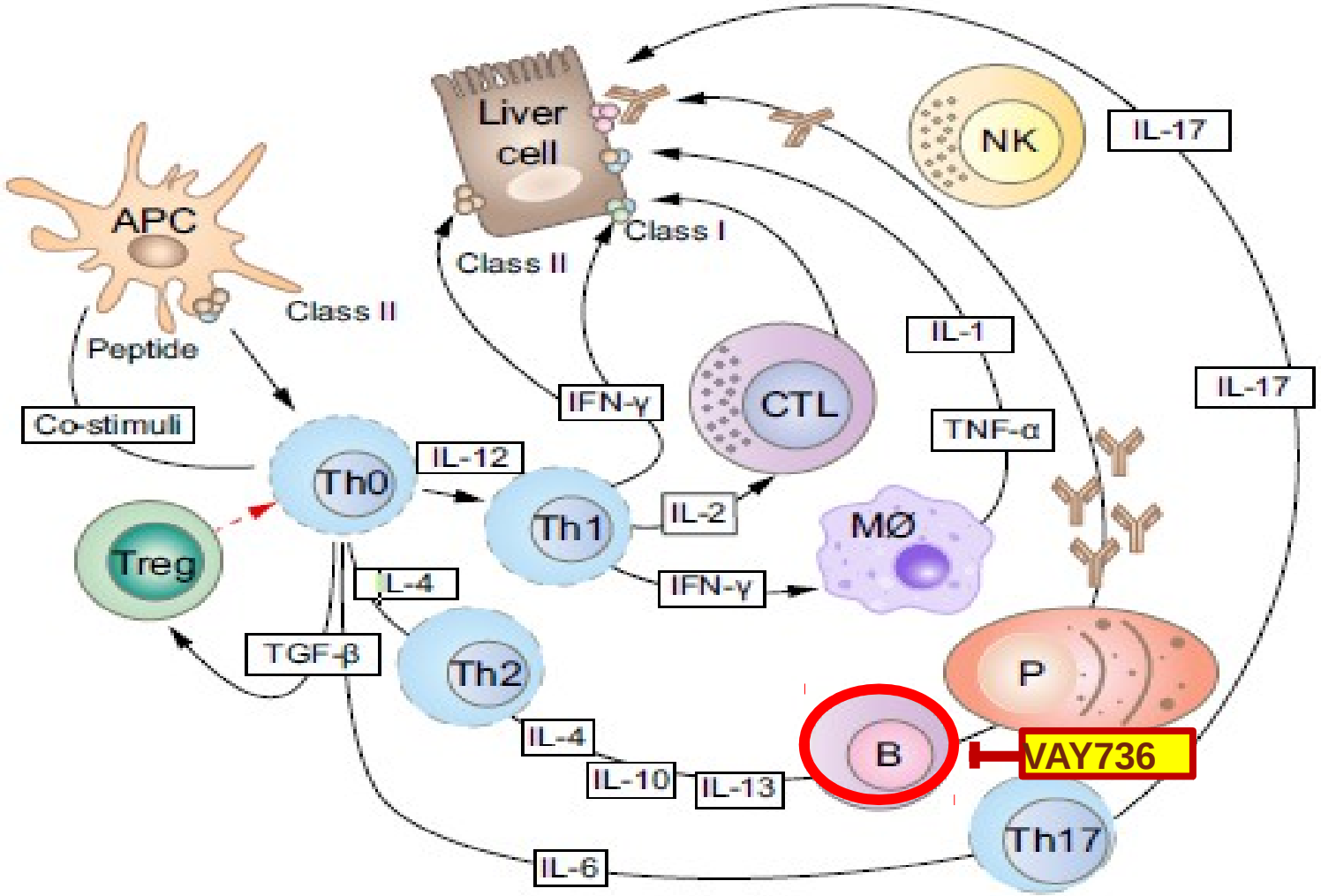
Than et al, EASL 2018, J Hepatol, 68, S217-8, 2018

Rituximab – Complications and Adverse Events

- **Usually mild, infrequent:**
  - Infusion reactions, bacterial infections, neutropenia, anemia, rash, fever, diarrhea, reactivation of viral infections

- **But include:**
  - Late onset neutropenia, rheumatic disease, HBV reactivation, activation of a latent polyoma virus (JC virus) with multifocal leucoencephalopathy

Molecular pathogenesis of autoimmune hepatitis



Manns et al., Journal of Hepatology, 2015

VAY736 = lanalumab

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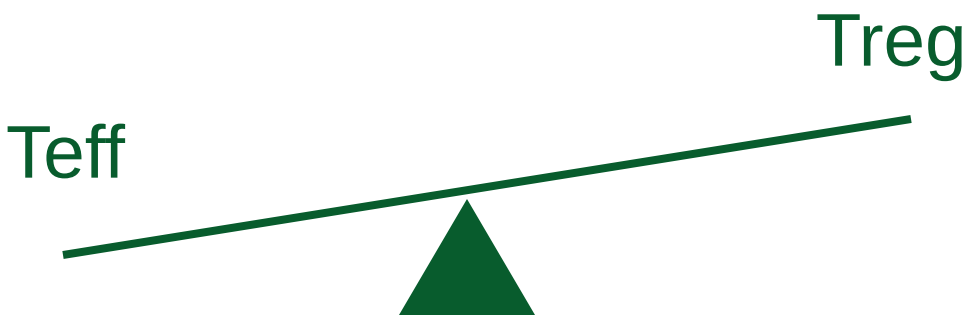
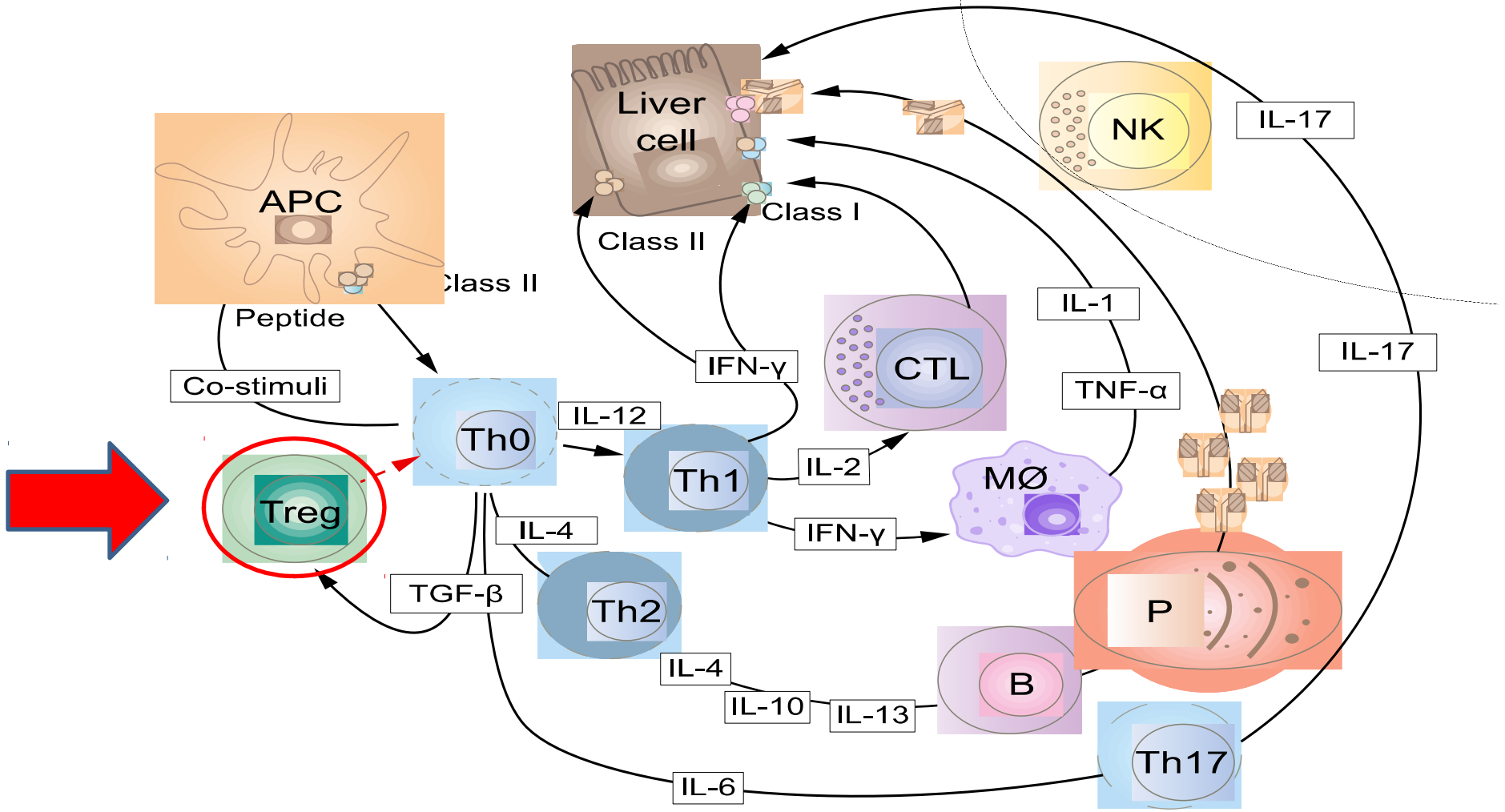
AIH: Future Therapies

- Can we increase therapeutic response by strengthening immunoregulation ?

- Anti CD 3
- Low dose IL-2
- Adoptive transfer of Tregs ?



Molecular pathogenesis of autoimmune hepatitis



Manns et al., Journal of Hepatology, 2015

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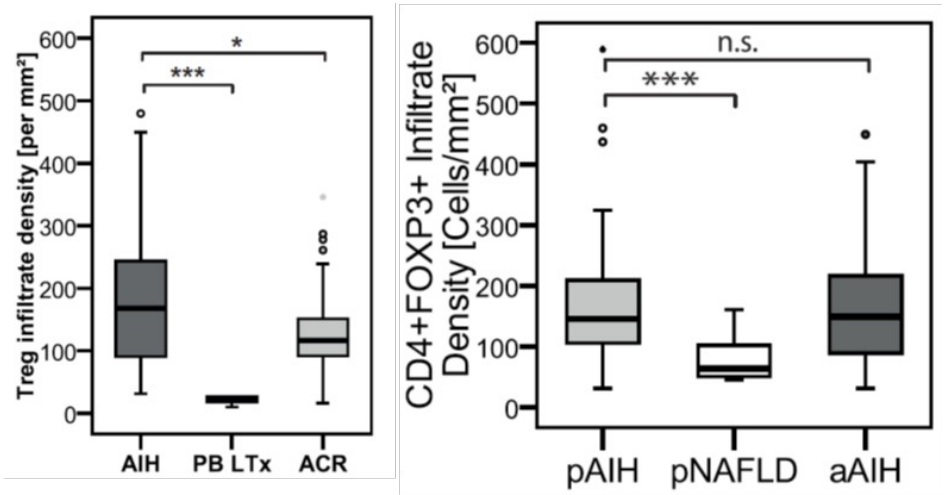
Regulatory T cells (Treg): Numbers and function

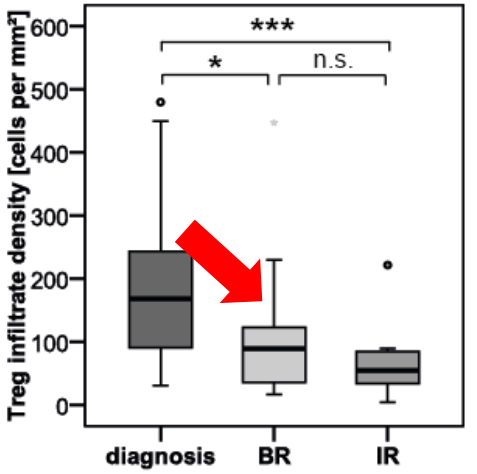
No numerical Dysfunction of intrahepatic Treg



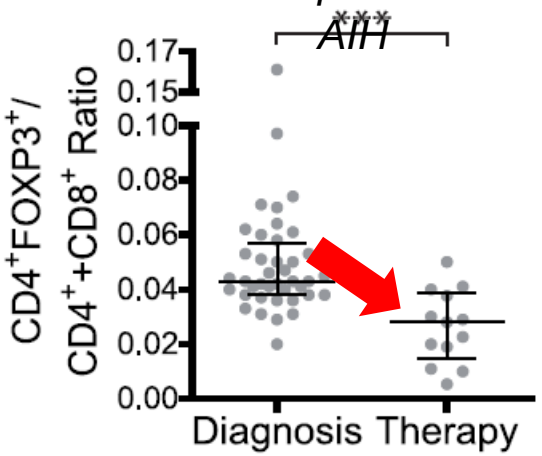
modified from Taubert et al. J Hepatol. 2014;61(5):1106-14
Diestelhorst et al. PLoS One. 2017;12(7):e0181107

Selective Treg depletion under standard therapy

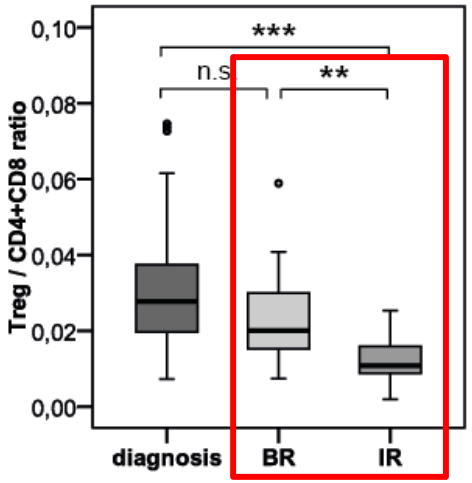
adult AIH



pediatric AIH



Higher intrahepatic Treg in remission

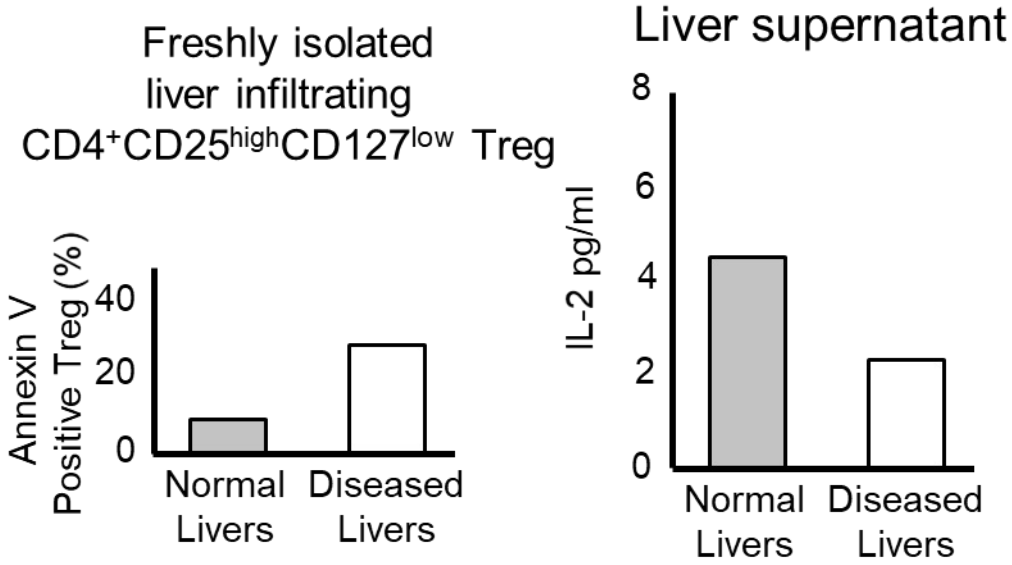


modified from Taubert et al. J Hepatol. 2014;61(5):1106-14
Diestelhorst et al. PLoS One. 2017;12(7):e0181107

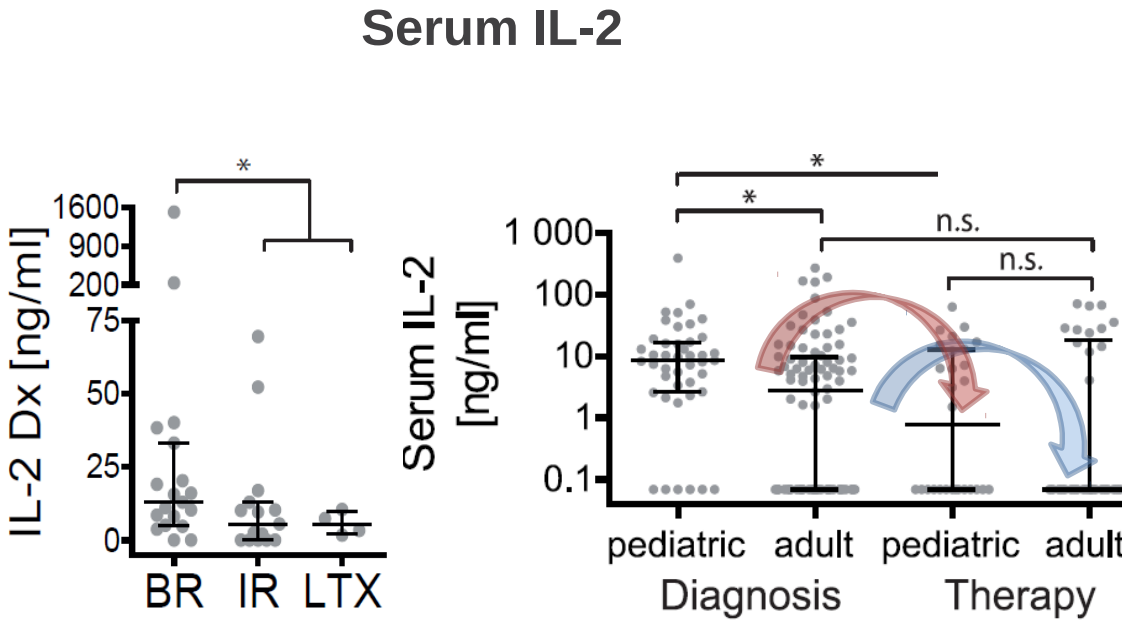
Similar findings by multiple centers

Oo et al. JI 2010; Peiseler et al. J Hepatol 2012
Renand et al. Hepatol. Commun. 2018

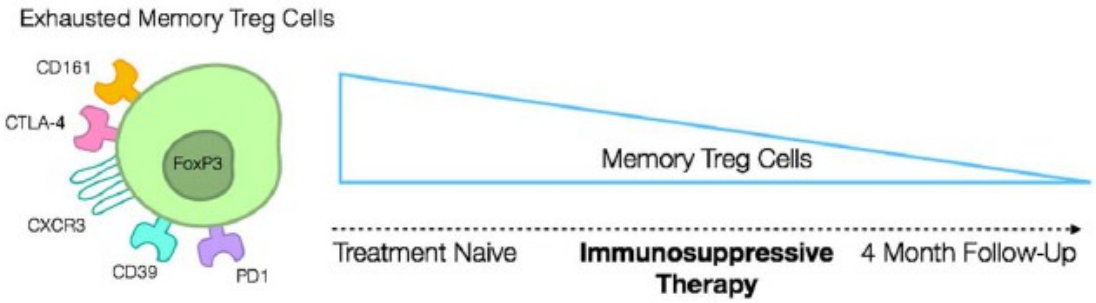
Regulatory T cells (Treg): Numbers and function



Chen et al. Hepatology. 2016 Jul;64(1):138-50



Diestelhorst et al. PLoS One. 2017;12(7):e0181107
Diestelhorst et al. Sci Rep. 2018 Jan 11;8(1):419.

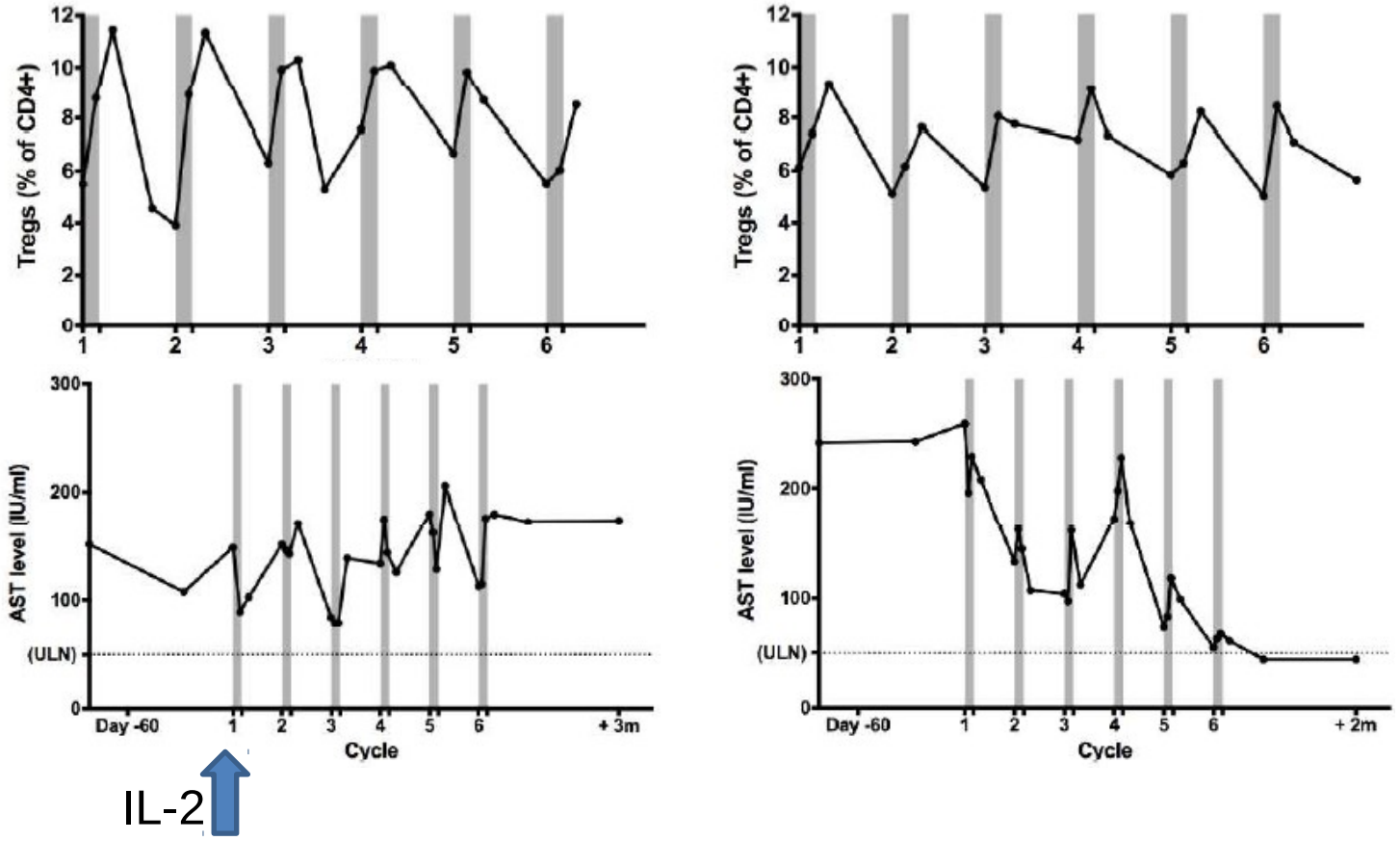


modified from: Jeffery et al. HEPATOLOGY COMMUNICATIONS, Vol. 2, No. 4, 2018

Low dose IL-2 in refractory AIH

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

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



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

Modified from Lim et al., Hepatolgy, 2018

Treatment withdrawal and relapse

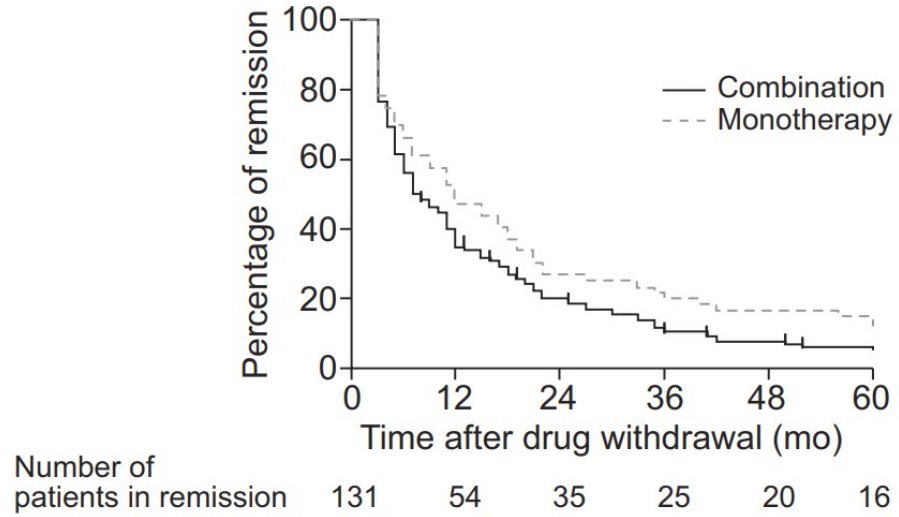
Relapse occurs rapidly after treatment withdrawal

- Incidence of relapse or loss of remission
  - 59% after 1 year
  - 73% after 2 years
  - 81% after 3 years

In patients with combination therapy at start of withdrawal

- Risk of relapse was higher
- Time to relapse was shorter

Probability of remission after drug withdrawal*



Relapse is almost universal on withdrawal of immunosuppressive therapy

*All patients had been in remission for at least 2 years prior to drug withdrawal

Van Gerven et al. J Hepatol 2013;58:141–7
EASL CPG AIH. J Hepatol 2015;63:971–1004

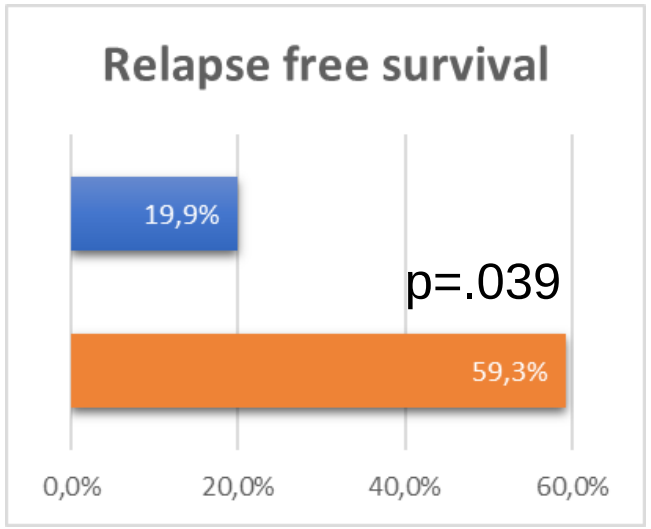
Chloroquine for Maintenance of Remission in AIH (single center RCT in Brazil)

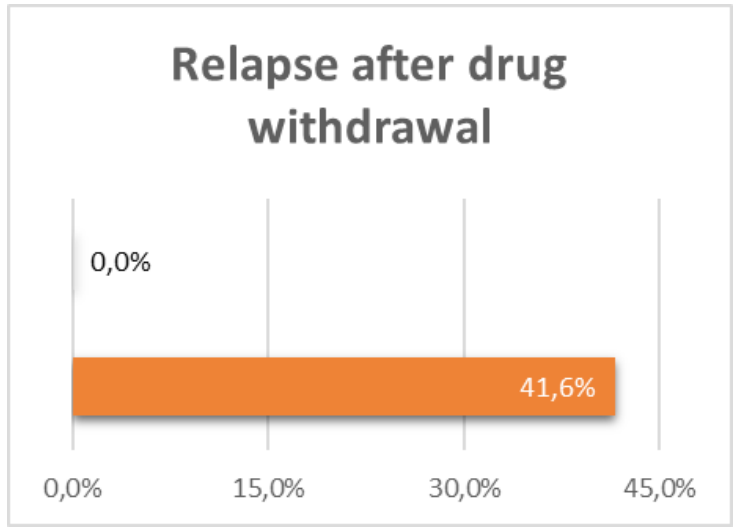
61 AIH pts. with histologic Remission (HAI<4)

30 pts. Placebo 24 pts.

36 months

31 pts. CQ 250mg/d 23 pts.



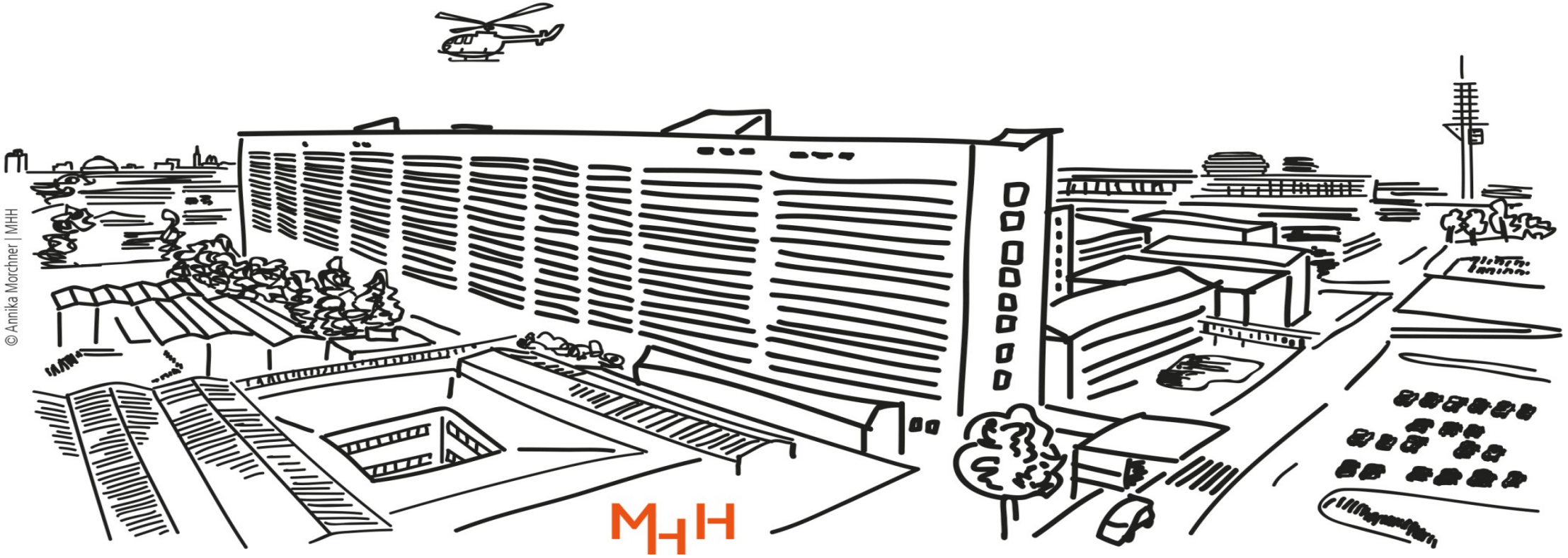


Adverse Event	Chloroquine (n = 31) n (%)	Placebo (n = 30) n (%)
Any AE	17 (54.8)	5 (16.7)
Discontinuation due to AE	6 (19.3)	3 (10)
Classification according to Naranjo algorithm	Definite (0)	Definite (0)
	Probable (4)*	Probable (0)
	Possible (12)†	Possible (3)
	Doubtful (1)‡	Doubtful (2)
Grade 3/4	0	0

Terrabuio et al., Hepatol Commun, 2019

Thank you for your attention

Hannover Medical School



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14.01.2019