Hepatitis Autoinmune: De las Guías a la Práctica Clínica

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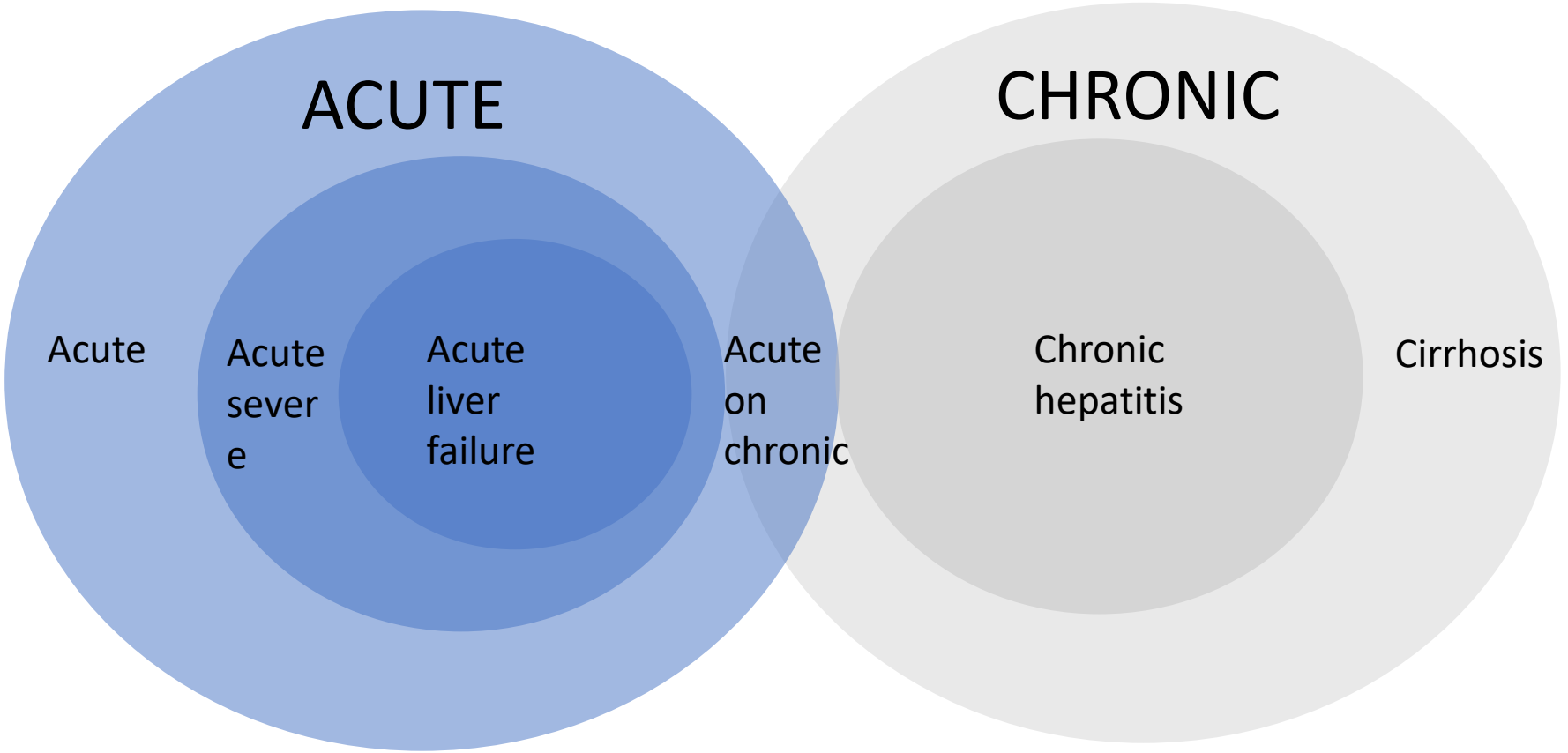
Considerations

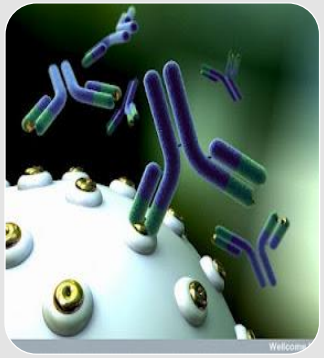


- ✓ Age
- ✓ Sex/gender
- ✓ Comorbidities
- ✓ Concomitant medication
- ✓ Desire for pregnancy

EASL guidelines AIH. J Hepatol 2015; 63 (4):971-1004

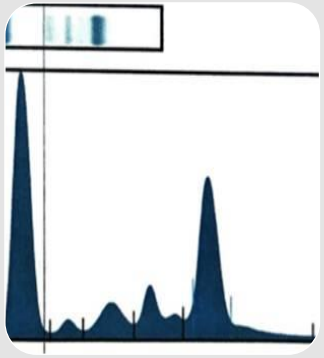
Diagnosis

Increase in transaminase levels



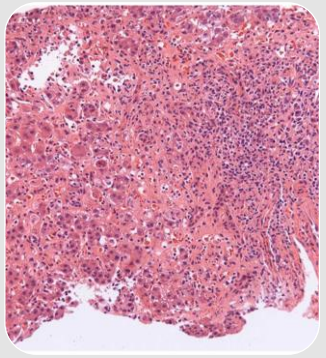
Autoantibodies

- ANA, SMA
- Anti-LKM
- Anti-LC1
- Anti-SLA
- 75% of the patients



Elevated IgG levels

- 85% of the patients
- It could be negative at the time of initial presentation.



Liver biopsy

Interfase hepatitis

- ✓ None of these characteristics is specific or pathognomonic for the diagnosis of AIH.
- ✓ Exclusion of other causes of liver disease

Floreani et al. Aliment Pharmacol Ther 2006; 24: 1051-10577,
Vergani et al. J Hepatol 2004; 41: 677-683

Simplified Criteria

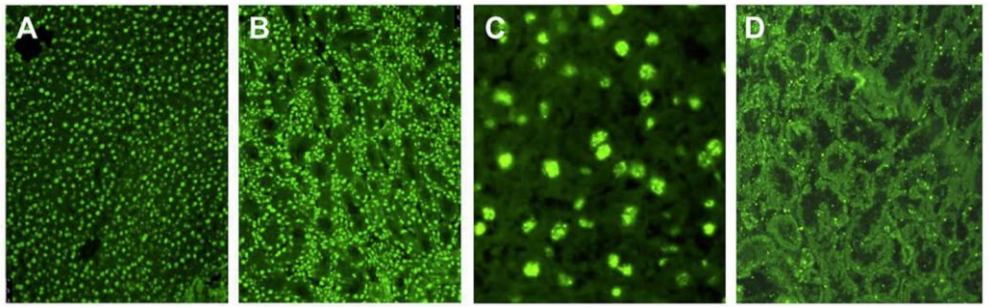
	0	1	2
ANA, SMA	Negative	1:40 ; 1:80	>1:80
IgG	Normal	>Normal	>1.5 ULN
Histology	-	Compatible	Typical
Viral Hepatitis	Yes		No

- 6 → Probable
- >7 → **Definite**

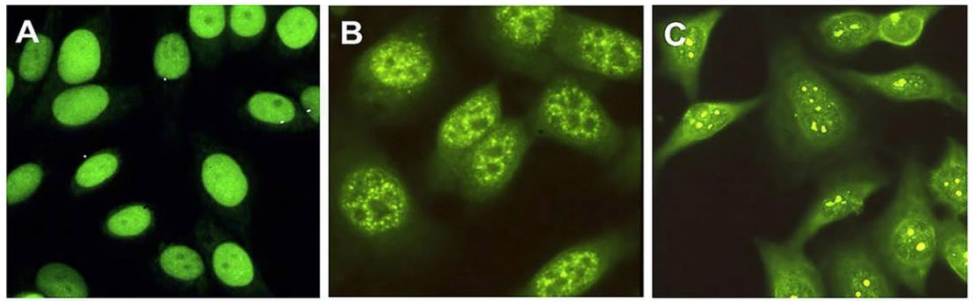
ANA→ S 32%, E 75%
SMA→ S 16%, E 76%

ANA + SMA→ Accuracy 74%

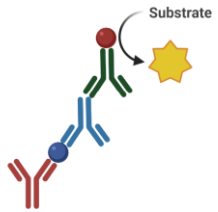
IF in mouse triple tissue sections (liver, kidney, stomach)



IF in Hep-2 cells



ELISA



Hennes et al. Hepatology 2008, Galaski et al. J Hepatol 2020

Simplified Criteria

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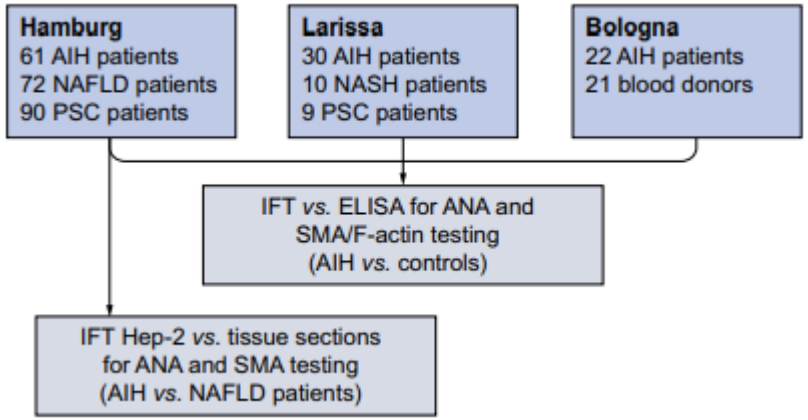

Substrate	Titer	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
HEp-2 cells	1:40	95.1	8.3	46.8	66.7	48.1
	1:80	91.8	36.1	54.9	83.9	61.7
	1:160	75.4	73.6	70.8	77.9	74.4
	1:320	72.1	76.4	72.1	76.4	74.4
	1:640	60.7	87.5	80.4	72.4	75.2
Any tissue positivity (primate liver, rat kidney, rat stomach)	1:40	85.3	65.3	67.5	83.9	74.4
	1:80	73.8	77.8	73.8	77.8	75.9
	1:160	52.5	87.5	78.1	68.5	71.4
	1:320	50.8	91.7	83.8	68.8	72.9
	1:640	37.7	93.1	82.1	63.8	67.7

Hennes et al. Hepatology 2008, Galaski et al. J Hepatol 2020

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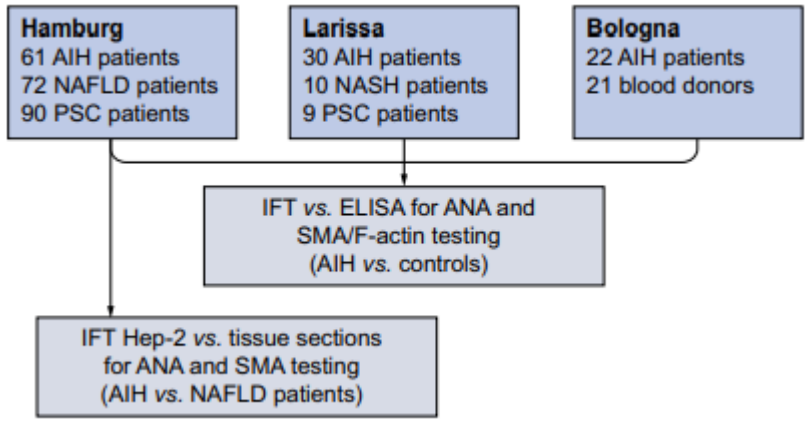

		0	1	2
Antibodies	ANA, SMA	Negative	+	++
				Anti-LKM or Anti-SLA
	IgG	Normal	> Normal	>1.1 ULN
	Histology	-	Compatible	Typical
	Viral Hepatitis	Yes		No

+: >1:40 in tissue (IF), >1:80 in Hep-2; ++: >1:80 in tissue or >1:160 in Hep-2

Hennes et al. Hepatology 2008, Galaski et al. J Hepatol 2020

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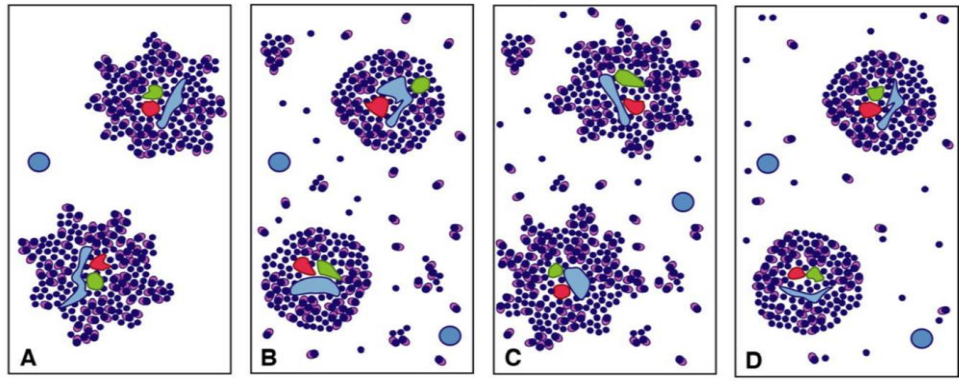
Typical: interfase hepatitis, lymphoplasmacytic infiltrate, emperipolesis, rosette.
Compatible: chronic hepatitis without the typical features.

Concomitant liver diseases?
Acute presentation?

Chronic Hepatitis



Portal inflammation	X	X	X	X
Interfase hepatitis	X		X	
Lobular inflammation		X	X	
Plasma cell groups	X	X	X	
	PROBABLE	PROBABLE	PROBABLE	POSIBLE

Hennes et al. Hepatology 2008, Lohse et al. Liver Int 2022

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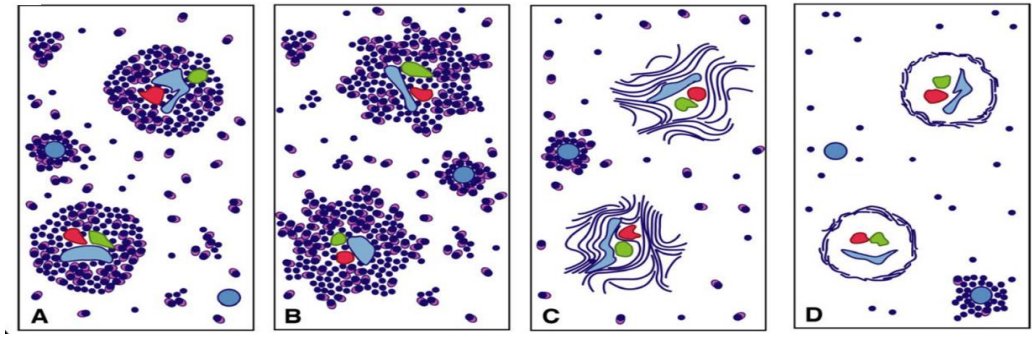
Acute presentation?

Acute Hepatitis



Lobular hepatitis
Central perivenulitis
Plasma cell group
} ± portal inflammation

Hennes et al. Hepatology 2008, Lohse et al. Liver Int 2022

Treatment

- ✓ Aim of treatment: To achieve disease remission and to prevent fibrosis progression.
- ✓ Biochemical response: Normalization of transaminases and IgG levels.
- ✓ Remission: Histological → mHAI < 4/18.
- ✓ Insufficient response: Abnormal transaminases and IgG after 6 months of treatment.
- ✓ Non-response: < 50% decrease in transaminase levels after 4 weeks of starting immunosuppression.

Hennes et al. Hepatology 2008, Pape et al. J Hepatol 2022

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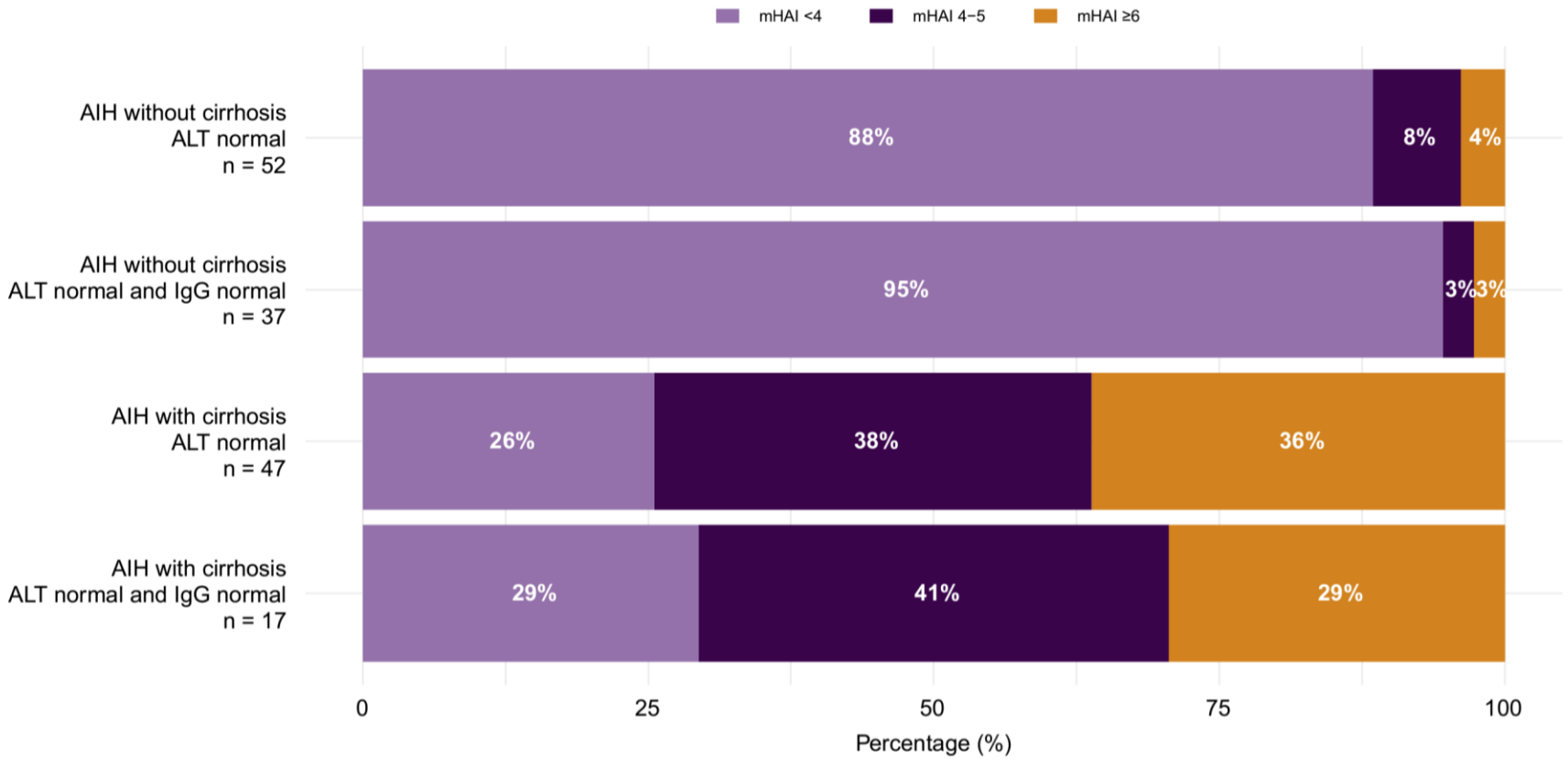
Hennes et al. Hepatology 2008, Pape et al. J Hepatol 2022

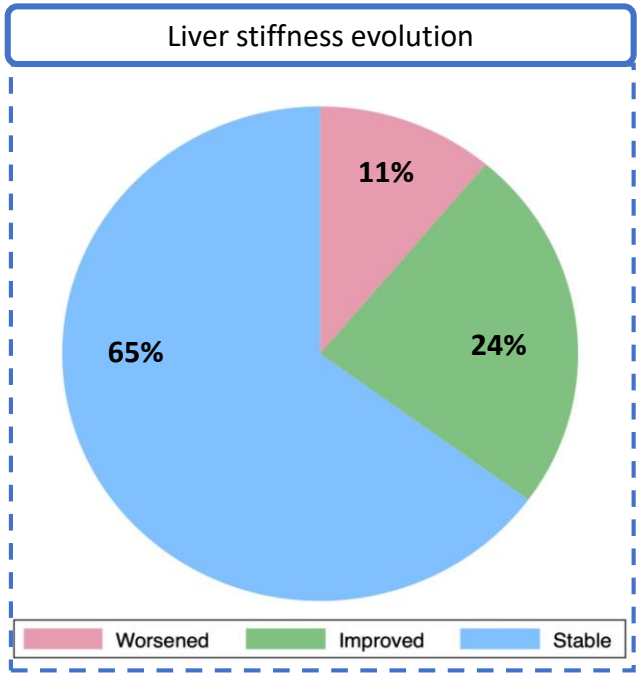
Correlation between histology and ALT/IgG levels. Multicenter study, 125 liver biopsies



Laschtowitz et al. JHEP Rep 2021

Multicenter center study from ColHai Registry, patients with persistently normal transaminases.

Variable	Odds Ratio (IC95%)	p valor
Age	1.01 (0.99 – 1.02)	0,279
Gender (women)	1.37 (0.57 – 3.34)	0.553
Another autoimmune disease	0.89 (0.28 – 2.88)	0.858
ANA	3.91 (0.51 – 30.28)	0.192
ASMA	0.83 (0.29 – 2.37)	0.739
Persistently normal IgG	0.41 (0.14 – 1.13)	0.091
Persistently elevated IgG	1.51 (0.46 – 4.91)	0.489
IgG flares	2.67 (0.80 – 8.89)	0.108
Fibroscan at normalization > 10.5 kPA	**6.71 (1.12 – 40.07)**	**0.037**
Time to normalization > 12 months	**3.22 (1.07 – 9.67)**	**0.037**



Diaz-González & Londoño et al. EASL 2022

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Hennes et al. Hepatology 2008, Pape et al. J Hepatol 2022

Retrospective study from Hannover, 109 patients, 78% achieved biochemical response at some point during the follow-up

Patients with moderate to severe interfase hepatitis and advanced fibrosis are slow-responders

	CBR@M6	CBR>M6	p-value
n	39	39	
female sex	27 (69.2)	25 (64.1)	0.81
age [months]	47 (17 - 83)	60 (20 - 72)	0.109
ferritin [xULN]	2.6 (0.1 - 41.9)	3.0 (0.1 - 16.1)	0.761
iron [xULN]	1.1 (0.2 - 3.7) (n=33)	1.3 (0.1 - 2.3) (n=30)	0.63
transferrinsaturation [%]	47 (16 - 100) (n=30)	51.5 (9 - 98) (n=26)	0.805
CRP [mg/l]	8.5 (1 - 38) (n=38)	8 (1 - 245) (n=37)	0.556
Hb [g/dl]	14 (11.4 - 16.5)	13.5 (11.8 - 16.3)	0.519
IgG [xULN]	1.2 (0.5 - 3.6)	1.5 (0.6 - 4.6)	0.101
ANA	33 (84.6)	34 (87.2)	1
anti-SMA	33 (84.6)	24 (63.2) (n=38)	**0.04**
anti-LKM	0 (0)	0 (0)	n/a
anti-SLA	3 (7.7)	2 (5.4) (n=37)	1
mHAI	9 (5 - 14) (n=33)	9 (4 - 16) (n=23)	0.105
mHAI - A	3 (0 - 4) (n=33)	4 (2 - 4) (n=23)	**0.018**
mHAI - B	0 (0 - 4) (n=33)	0 (0 - 5) (n=23)	0.284
mHAI - C	2 (1 - 4) (n=33)	2 (0 - 4) (n=23)	0.851
mHAI - D	3 (2 - 4) (n=33)	3 (1 - 4) (n=23)	0.083
Ishak F	2 (0 - 6) (n=33)	4 (0 - 6) (n=28)	**0.006**
AST [xULN]	20.6 (1.2 - 113.2)	20.7 (1.7 - 103.6)	0.445
ALT [xULN]	21.3 (0.6 - 124.9)	22.7 (1.9 - 90.6)	0.708
gGT [xULN]	3.4 (1.0 - 34.1)	5.4 (0.5 - 19.4)	0.549
ALP [xULN]	1.4 (0.5 - 5.1)	1.3 (0.3 - 5.5) (n=38)	0.787
bilirubin [xULN]	3.6 (0.3 - 45.2) (n=37)	5.3 (0.3 - 33.7) (n=38)	0.992
PT ratio [%]	78 (38 - 104)	67 (27 - 100) (n=38)	0.427

Engel & Taubert. J Hepatol 2022

Treatment

Before starting

- Determine TPMT activity
- Vaccinate against hepatitis A and B
- Determine the risk of HBV reactivation
- Bone marrow density and vitamin D levels
- Explain treatment and adverse events
- Birth control

Mack et al. Hepatology 2021

EASL guidelines (2015)

Induction

Prednisone
0.5-1 mg/Kg/d

Good response

Maintenance

Add AZA gradually
1-2 mg/kg/d

If AZA intolerance→ second line treatment

Week	Prednisolone (mg/day)	Azathioprine (mg/day)
1	60 (= 1 mg/kg body weight)	-
2	50	-
3	40	50
4	30	50
5	25	100*
6	20	100*
7 + 8	15	100*
8 + 9	12.5	100*
From week 10	10	100*

AASLD guidelines (2021)

AIH
Prednisone 20-40 mg/day or Budesonide 9 mg/día

AIH-cirrhosis
NO budesonide

Prednisone 20-40 mg/día

AIH-acute severe
NO budesonide

Prednisone 60 mg/d

Evaluate response after 4-8 weeks and progressively withdraw within 6 months

Evaluate response 7-14 d

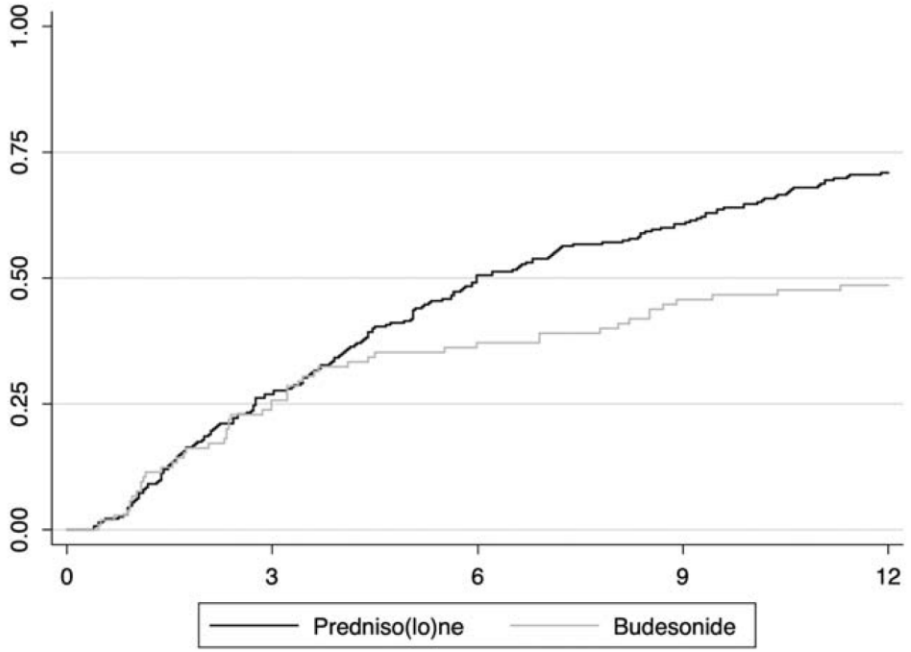
Mack et al. Hepatology 2021

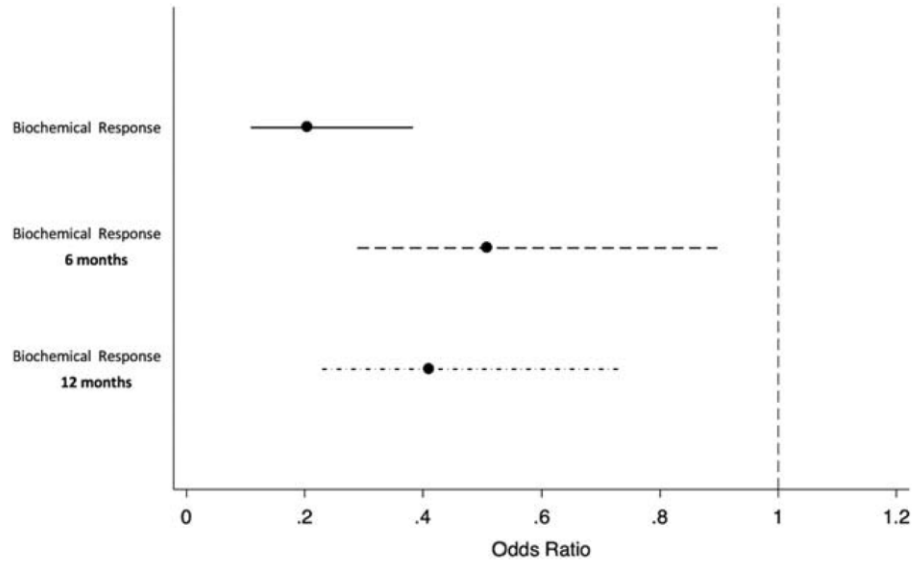
Modificado de EASL guidelines. J Hepatol 2015;

Treatment

Prednisone vs. Budesonide

Multicenter retrospective study from COLHAI registry,
151 patients with budesonide, IPTW-PS





Diaz et al. Hepatology 2023

Treatment

Induction with Low vs. High Prednisone Dose

Design: retrospective análisis of 9 centers in 5 countries in Europe (n=451).
Aim: To compare high or low dose of prednisone in the induction treatment (≥ o < 0,5 mg/Kg/d)
End point: 1) Transaminase normalization at 6 months, 2) biochemical response

100

	<0.50 mg/kg/day (n = 170)	≥0.50 mg/kg/day (n = 281)	*P* value
Female sex, n (%)	125 (73.5)	213 (75.8)	.59
Age at diagnosis, *y* (SD)	52.03 (15.35)	49.67 (17.47)	.13
Simplified IAIHG score, median	6	7	< .01
ALT × ULN, median (IQR)[a]	7.12 (12.69)	13.44 (21.00)	< .01
AST × ULN, median (IQR)[b]	8.52 (17.40)	13.48 (24.27)	< .01
Bilirubin, *μmol/L*, median (IQR)[c]	29 (83)	48 (177)	.01
IgG, *g/L*, median (IQR)[d]	20.79 (10.90)	21.60 (13.00)	.10
Cirrhosis, n (%)	44 (25.9)	42 (14.9)	< .01
AS-AIH, n (%)	18 (10.6)	29 (10.3)	.93

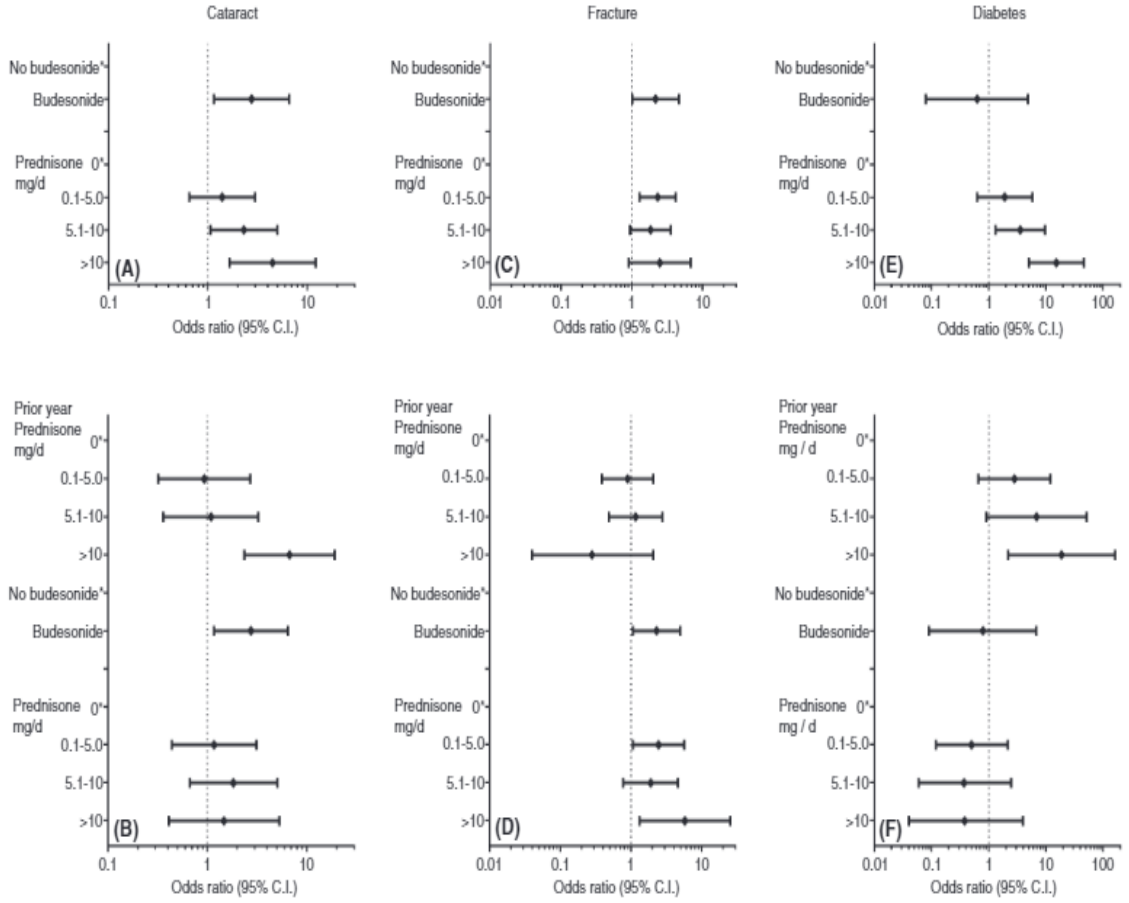
astroenterol Hepatol 2019

Treatment

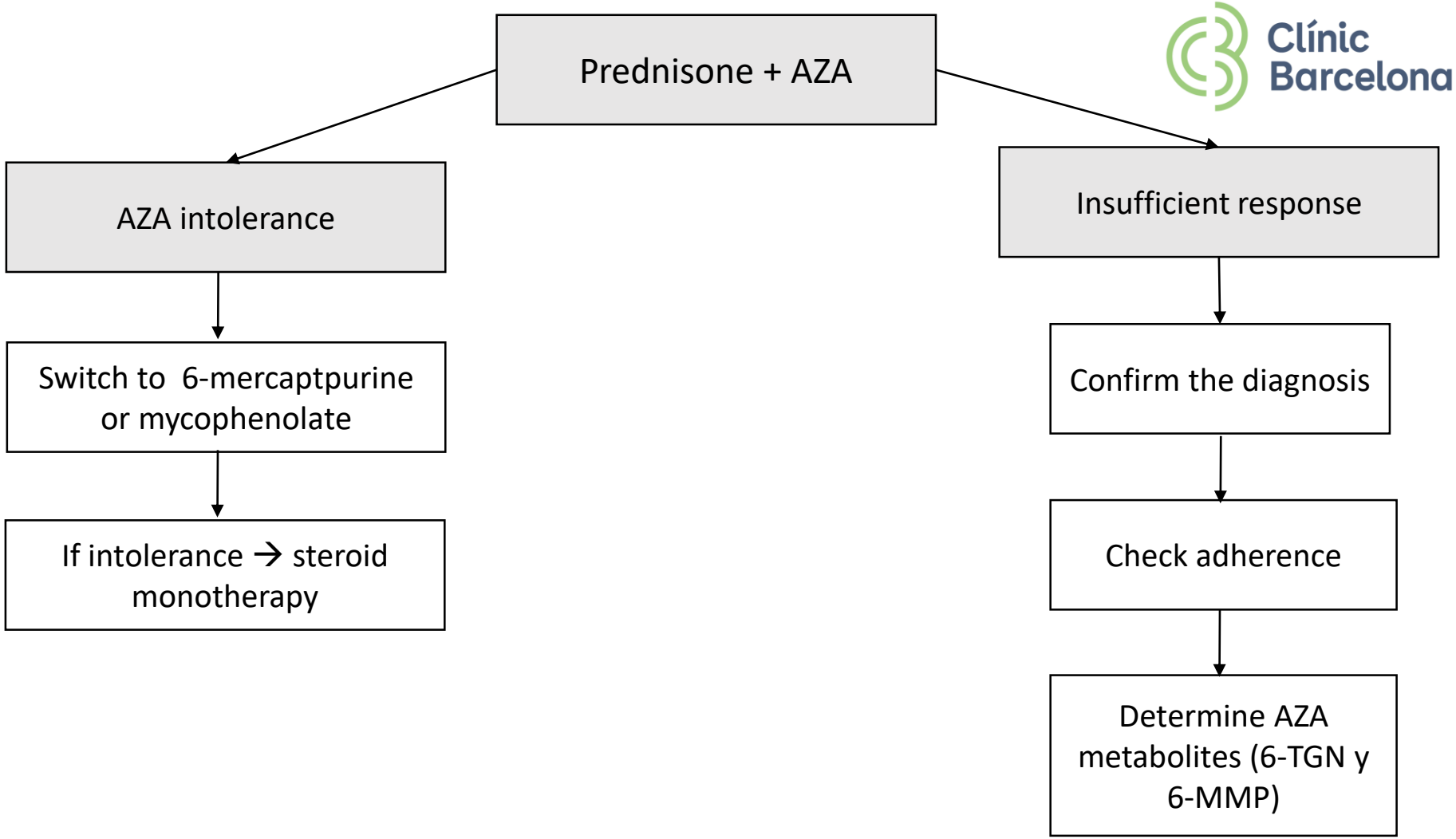
According to guidelines 80 % of patients respond

30% -40% of patients have treatment-related adverse events

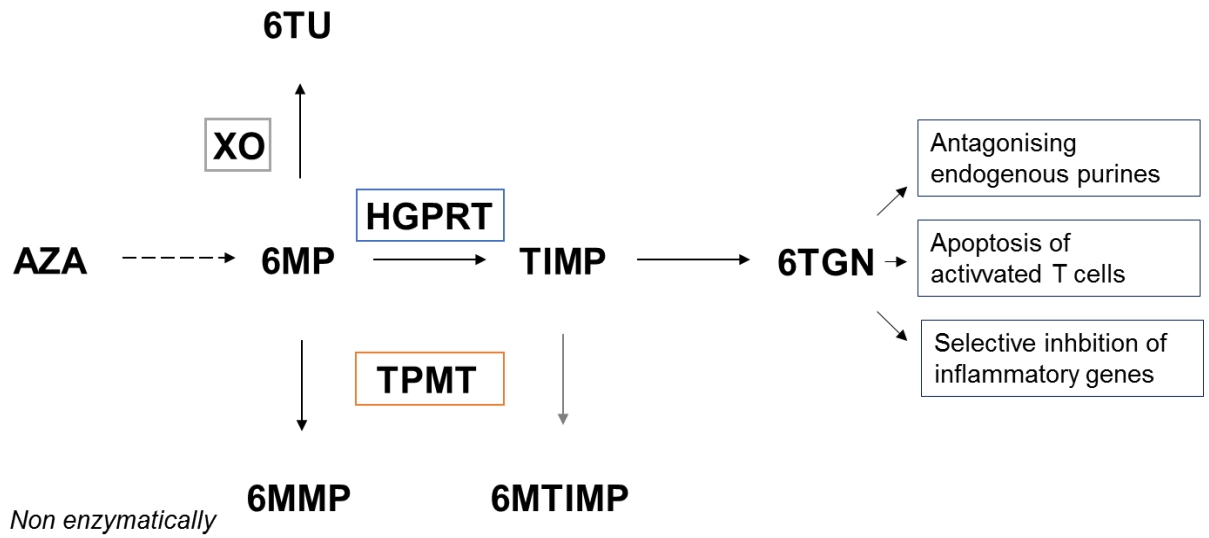
15-20% of patients are intolerant to first line treatment of have insufficient response



EASL guidelines. J Hepatol 2015; 63 (4):971-1004; Mack et al. Hepatology 2020; 72: 671-722; Halliday et al. Aliment Pharmacol Ther 2020; 52: 1134-149

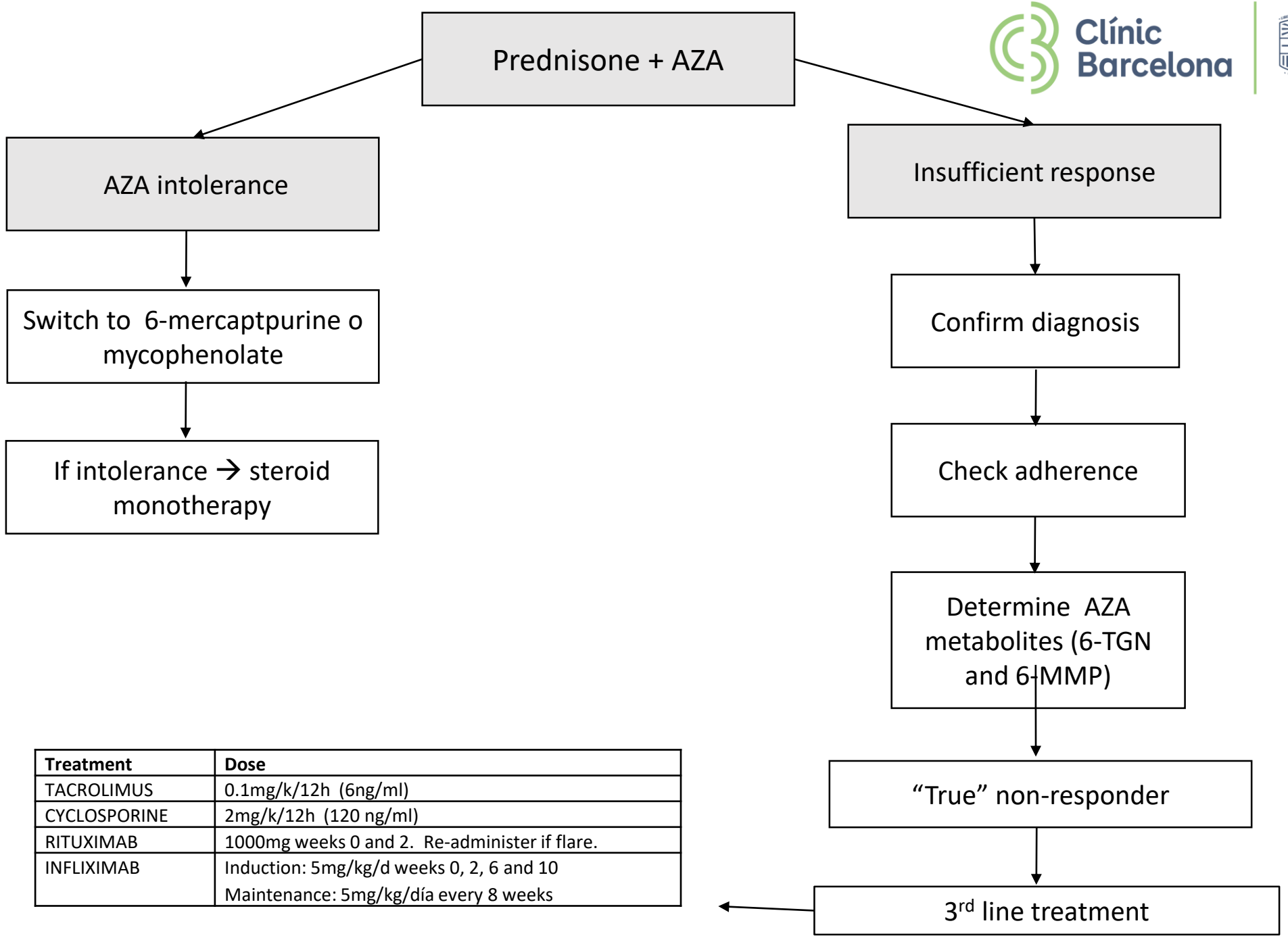


Modified from Lohse A. J Hepatol 2020



6-TGN	6-MMP	Significance	Recommendation
Very low (<50)	Very low (<50)	Non-adherent	Education
Low (<220)	Low (<220)	Low AZA dose	↑ AZA dose
Low (<220)	High (>5700)	Hypermethilator	Allopurinol
OK (220-450)	High or low	No-responderr	3rd line treatment

Modified from Lohse A. J Hepatol 2020



Treatment	Dose
TACROLIMUS	0.1mg/k/12h (6ng/ml)
CYCLOSPORINE	2mg/k/12h (120 ng/ml)
RITUXIMAB	1000mg weeks 0 and 2. Re-administer if flare.
INFLIXIMAB	Induction: 5mg/kg/d weeks 0, 2, 6 and 10 Maintenance: 5mg/kg/día every 8 weeks

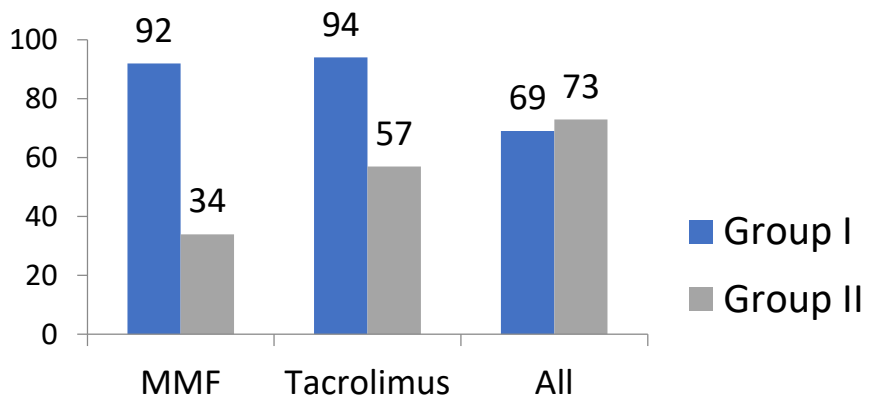
Modified from Lohse A. J Hepatol 2020

Tacrolimus

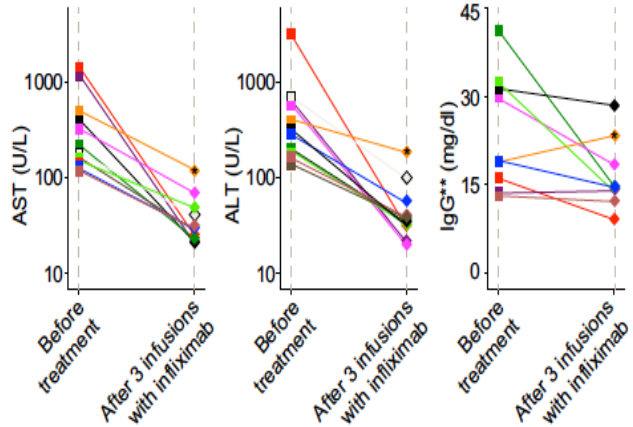
	Overall n=201	MMF n=121	Tacrolimus n=80
AZA intolerance, n (%)	78 (38.8)	56 (46.3)	22 (27.5)
Steroid side effects n (%)	30 (14.9)	18 (14.9)	12 (15.0)
Non response to standard therapy, n (%)	93(46.3)	47(38.8)	46 (57.5)

Group I: responded to SOC, switched due to side effects

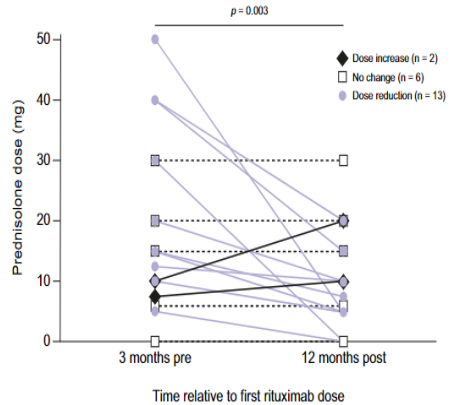
Group II: insufficient response to SOC



Infliximab



Rituximab



Efe et al. Clin Gastroenterol Hepatol 2017, Lohse et al. J Hepatol 2013, Than et al J HEP Rep 2019

Treatment Withdrawal

EASL™
The Home of Hepatology

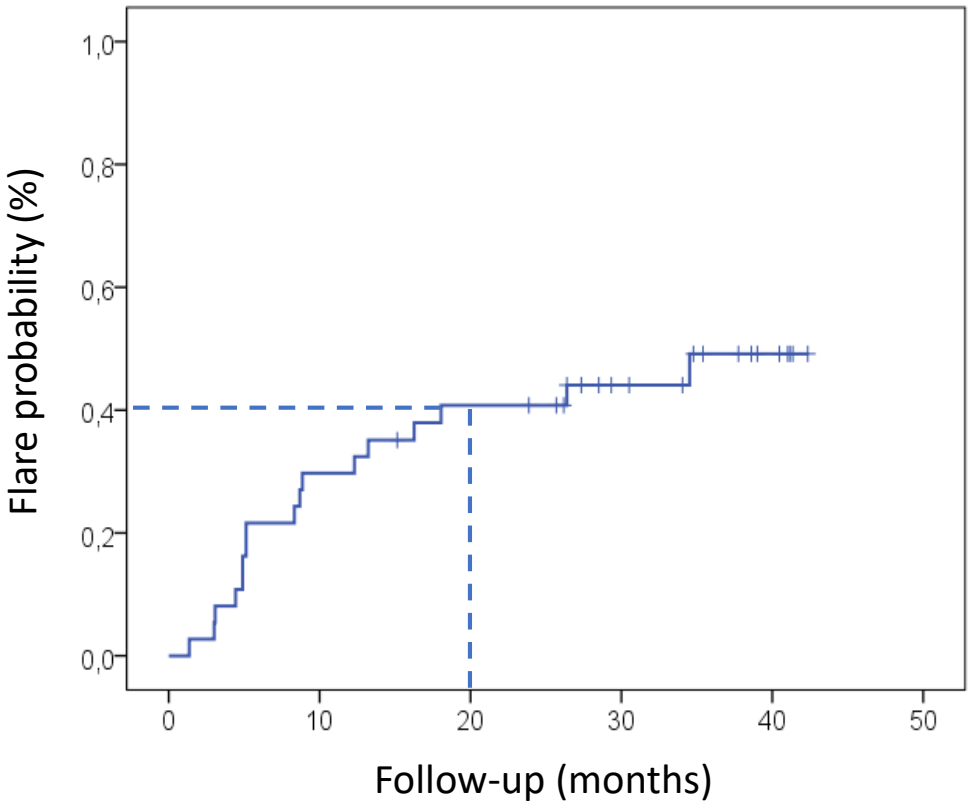
- 3 years of treatment (2y on biochemical remission)
- Liver biopsy without histological activity

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

- Biochemical remission for 2 years
- Liver biopsy is not mandatory.

Hennes et al. Hepatology 2008, Pape et al. J Hepatol 2022

Treatment Withdrawal



	Flare (n=17)	Remission (n=21)	p
Age (years)	53 (42-75)	65 (22-80)	0.165
Female sex (n,%)	8 (50%)	11 (52%	0.886
ALT (U/L)	**20 (5-34)**	**14 (6-23)**	**0.021**
IgG (g/L)	10 (8-14)	10 (6-14)	0.403
Taime on remission (years)	4 (3-10)	3.5 (3-11)	0.728
mHAI	1 (0-3)	1 (0-2)	0.423
Transient elastography (kPa)	4.9 (3.6-8.5)	4.6 (3.9-9.1)	0.773
Inmunosuppression(n,%) AZA Corticoids AZA + Corticoids	 12 (75%) 1 (6%) 3 (19%)	 15 (72%) 4 (19%) 2 (9%)	0.430
Presentation (n,%) Chronic Acute Acute-severe	 10 (59%) 5 (29%) 2 (12%)	 13 (65%) 7 (35%) 0	0.287

Llovet et al. EASL 2021

Summary

- ✓ Autoimmune hepatitis is a very heterogeneous disease, and this impacts diagnosis and treatment.
- ✓ Autoimmune hepatitis is an exclusion diagnosis but needs to be suspected.
- ✓ Liver biopsy is mandatory for the diagnosis.
- ✓ Treatment should be individualized according the patients' characteristics.
- ✓ Always aim for biochemical response but be aware that some patients are slow responders.
- ✓ In case of insufficient response, re-evaluate the diagnosis and check adherence to avoid over-immunosuppression.
- ✓ Treatment withdrawal is possible in a small proportion of patients but should be attempted.