

MÁSTER EN HEPATOLOGÍA

UAM
Universidad Autónoma
de Madrid

 Universidad
de Alcalá

Asignatura: Enfermedad Hepática Autoinmune

Tratamiento de la Hepatitis Autoinmune

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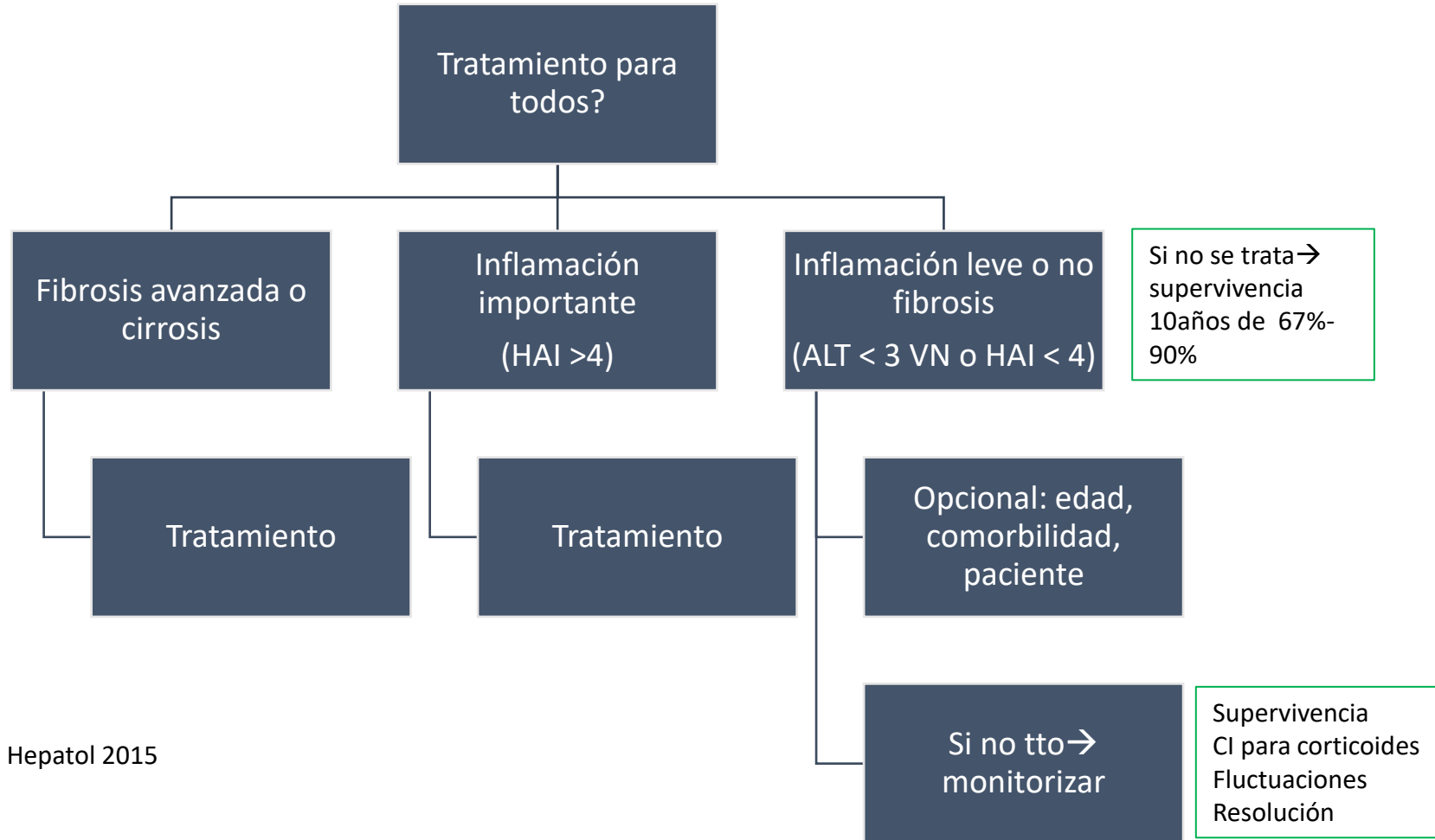
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Tratamiento

Definiciones

- Objetivo: Lograr la remisión de la enfermedad y prevenir la progresión de la fibrosis
- Respuesta bioquímica completa : Normalización transaminasas e IgG
- Remisión: mHAI < 4/18 en la biopsia
- Respuesta insuficiente: NO normalización de transaminasas e IgG a los 6 meses de tratamiento
- No respuesta: Disminución menor del 50% en las transaminasas a las 4 semanas del inicio del tratamiento.

Tratamos a todos los pacientes?

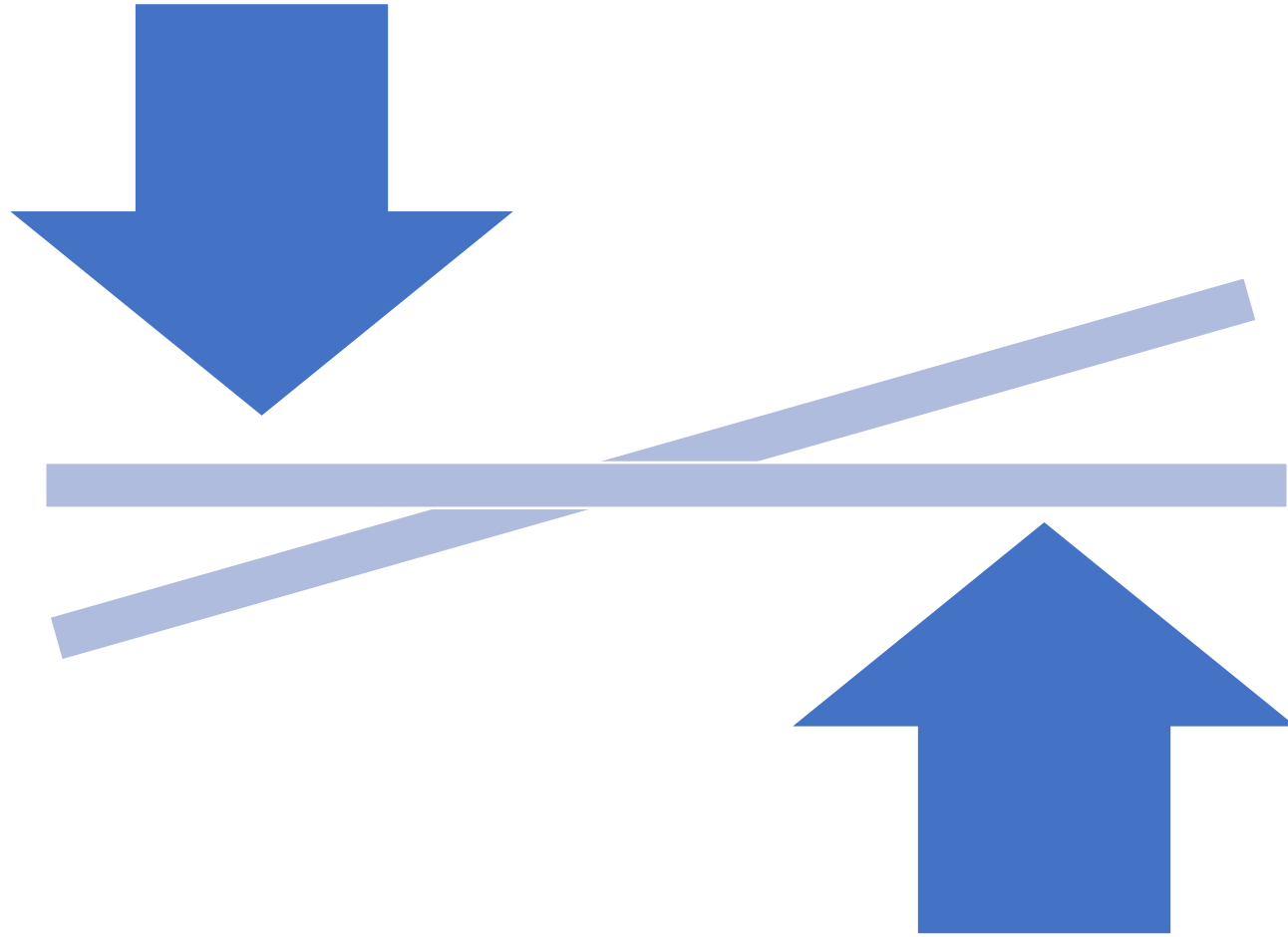


Modificado de EASL guidelines. J Hepatol 2015
Czaja et al. Liver Int 2009
Ferl et al. Hepatology 2005
Kogan et al. J Gastroenterol Hepatol 2002

Antes de Empezar el Tratamiento

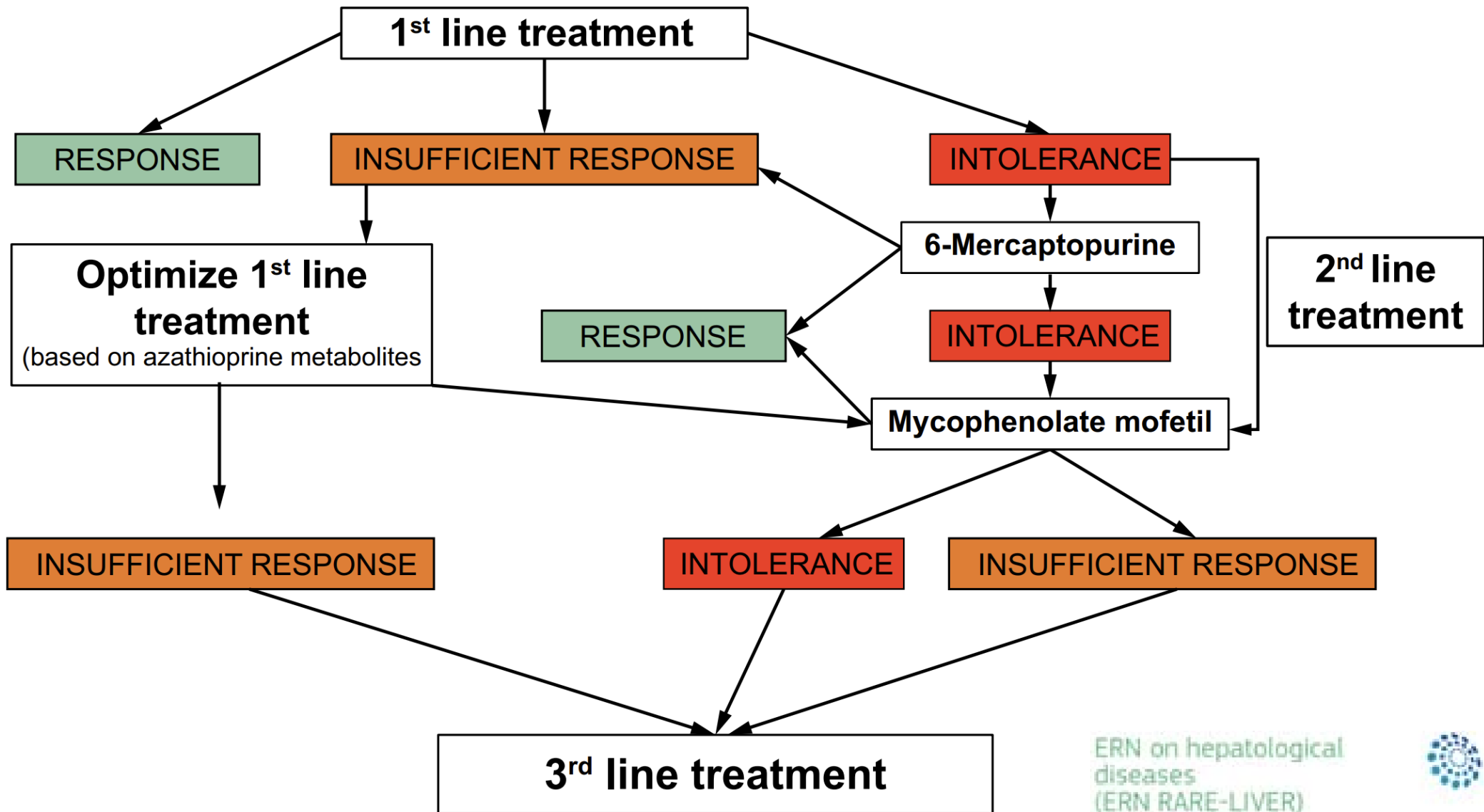
1. Actividad de TPMT
2. Vacunar VHA y VHB
3. Determinar el riesgo de reactivación del VHB
4. DMO y niveles de vitamina D
5. Explicar tratamiento y efectos adversos
6. Planificación familiar

Mecanismos
reguladores

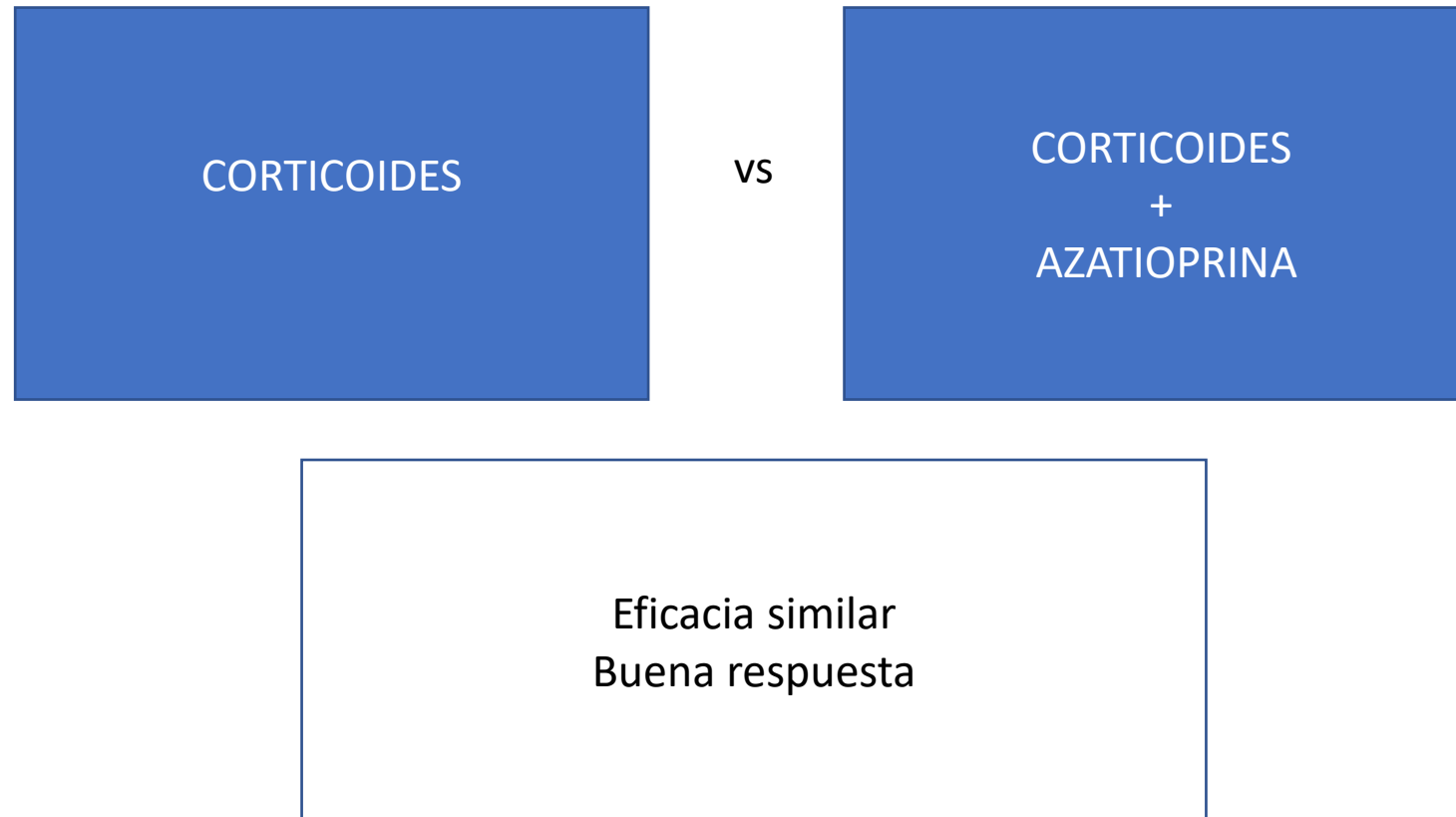


Células
Eectoras

Treatment of Autoimmune Hepatitis

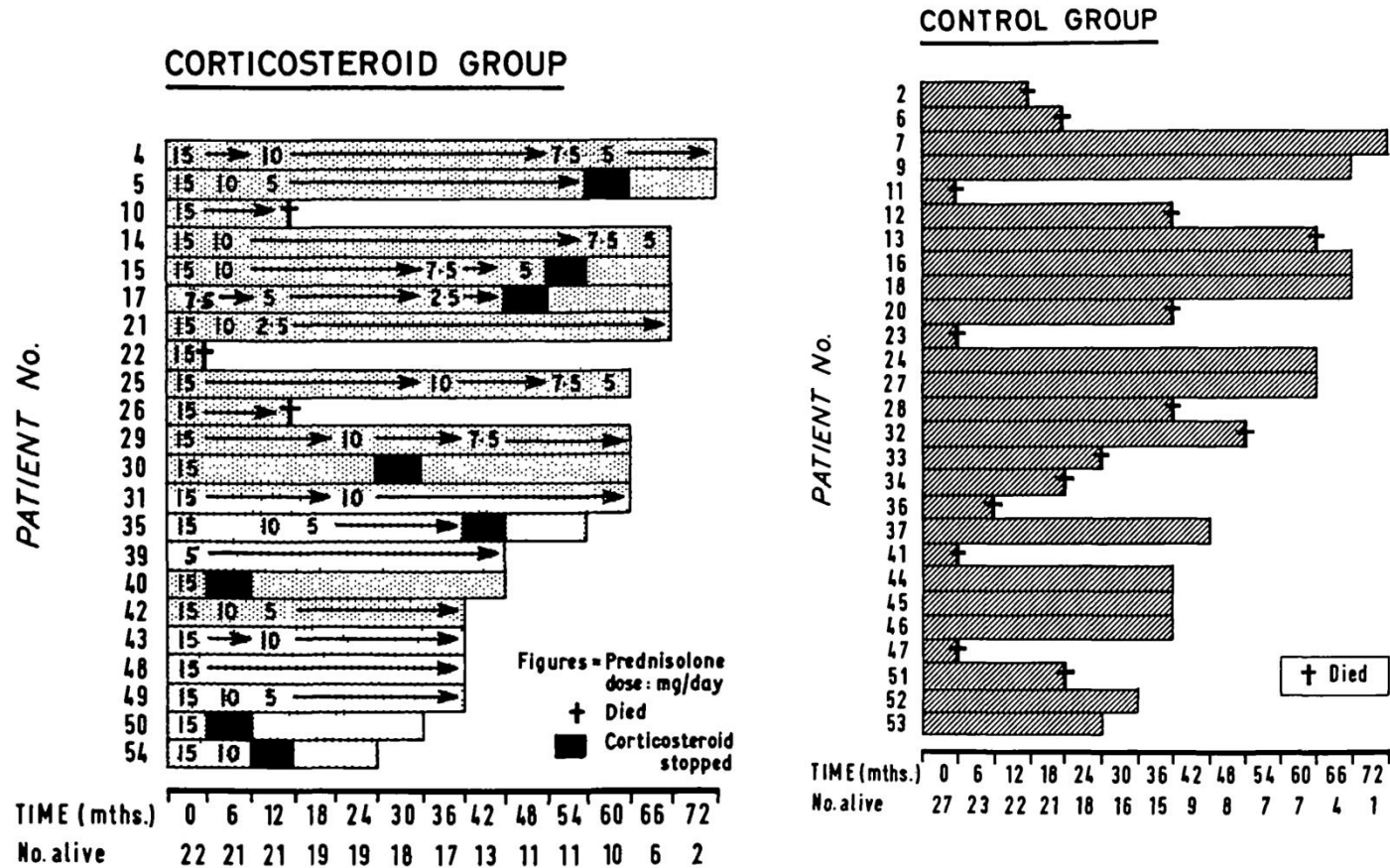


Primera Línea de Tratamiento



Primera Línea de Tratamiento

- 1971 → se demuestra por primera vez el impacto de la prednisona en el pronóstico de la hepatitis autoinmune

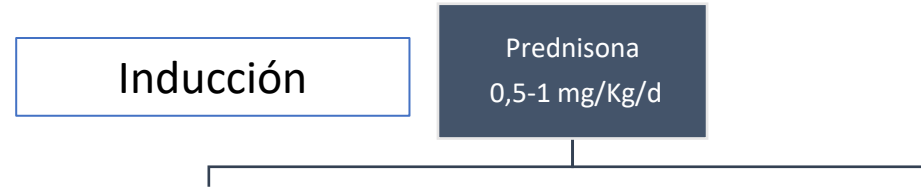


Primera Línea de Tratamiento

- Revisión sistemática de la literature sobre el beneficio de la prednisona en hepatitis autoinmune

Article	Intervención	Duración	Pacientes
Cook, 1971	PDLN 15 mg/d	30 - 72 meses	22
	No intervención		27
Soloway, 1972	PDN 60 mg/d, 40, 30, 20	3 meses - 3,5 años	18
	AZA 100mg/d		14
	PDN 30mg/d, 20, 25, 10		14
	Placebo		17
Murray-Lyon, 1973	PDN 5mg 3dd	2 años	22
	AZA 75mg 1dd		25
Summerskill, 1975	PDN 60mg/d, 40, 30, 20	36 meses	30
	PDN 30mg/d, 20, 15, 10 + AZA 50mg/d		30
	PDN en días alternos		31
	AZA 100mg/d		29
Tage-Jensen, 1982	AZA 10mg/kg/sem, 5	12-83 meses	37
	PDN 10 ó 15 mg/d según peso		47

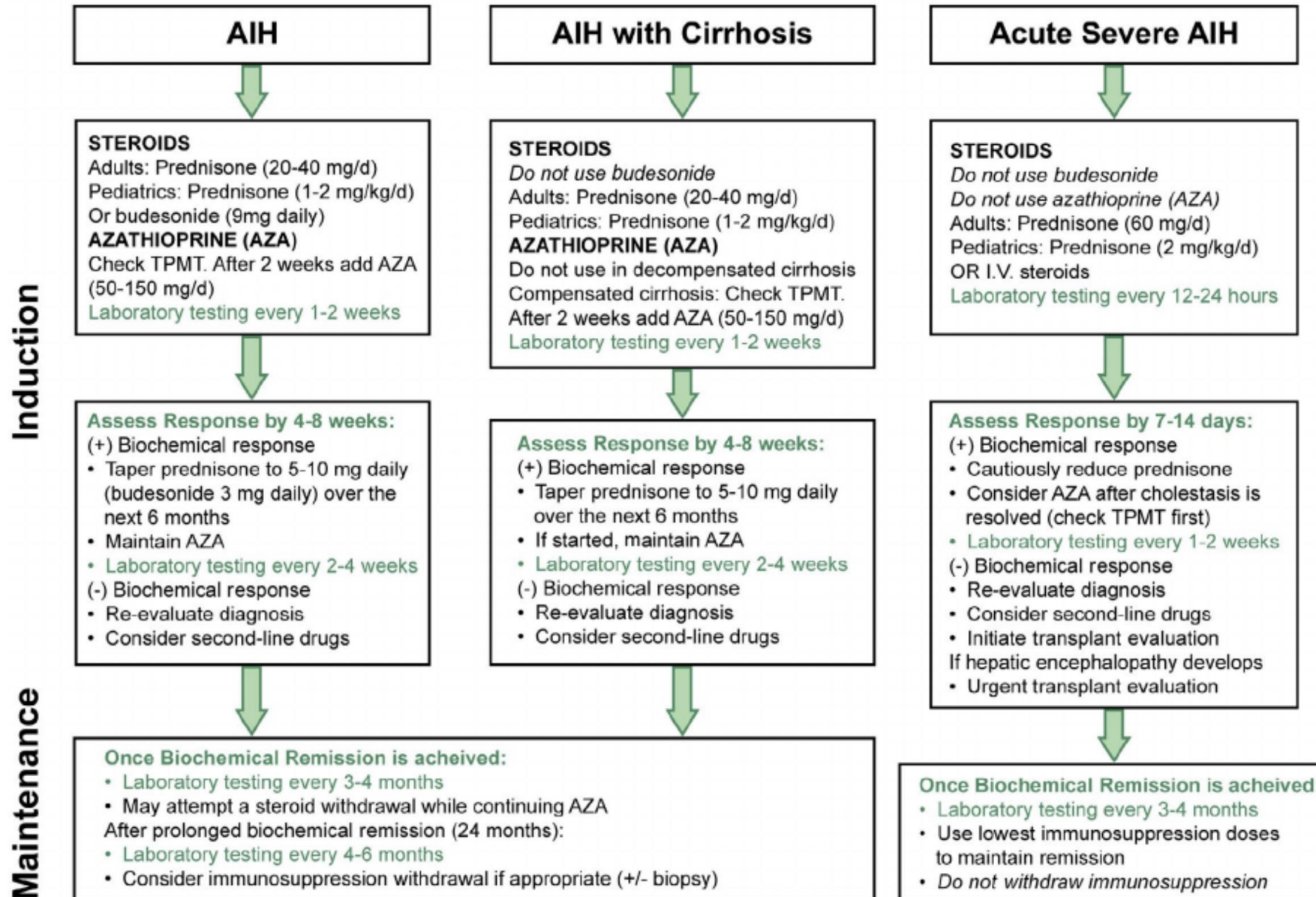
Primera Línea de Tratamiento



Mantenimiento

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*

First-Line Treatment of AIH



Dosis alta o baja de Prednisona?

Diseño: Análisis retrospectivo en 9 centros de 5 países de Europa (n=451).

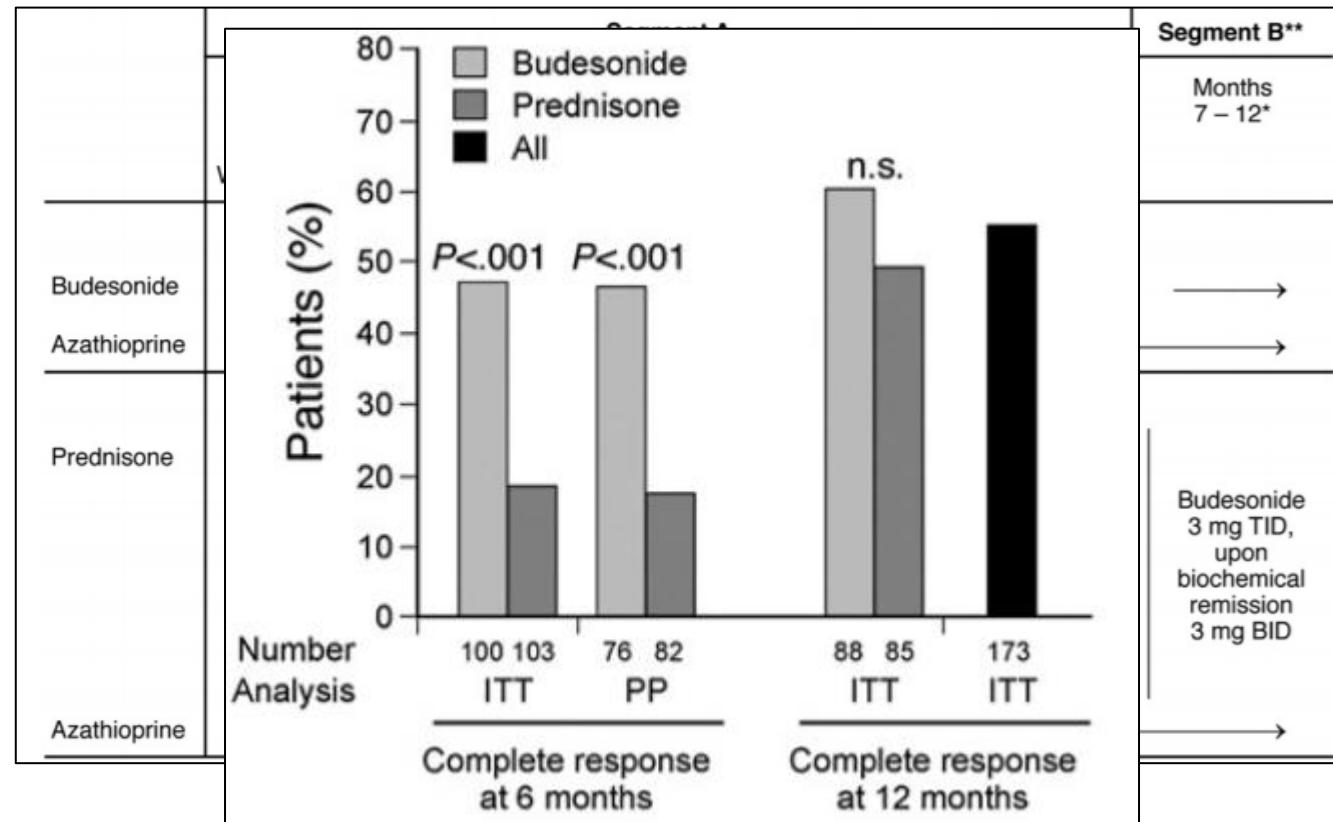
Objetivo: Comparar dosis altas o bajas de prednisona en inducción de remisión (\geq o $<$ 0,5 mg/Kg/d)

End point: 1) Normalización transaminasas a los 6 meses, 2) Remisión a los 6 meses

	<0.50 mg/kg/day (n = 170)	\geq 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 \times ULN, median (IQR) ^a	7.12 (12.69)	13.44 (21.00)	< .01
AST \times ULN, median (IQR) ^b	8.52 (17.40)	13.48 (24.27)	< .01
Bilirubin, μ mol/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

Hay alguna alternativa a la Prednisona?

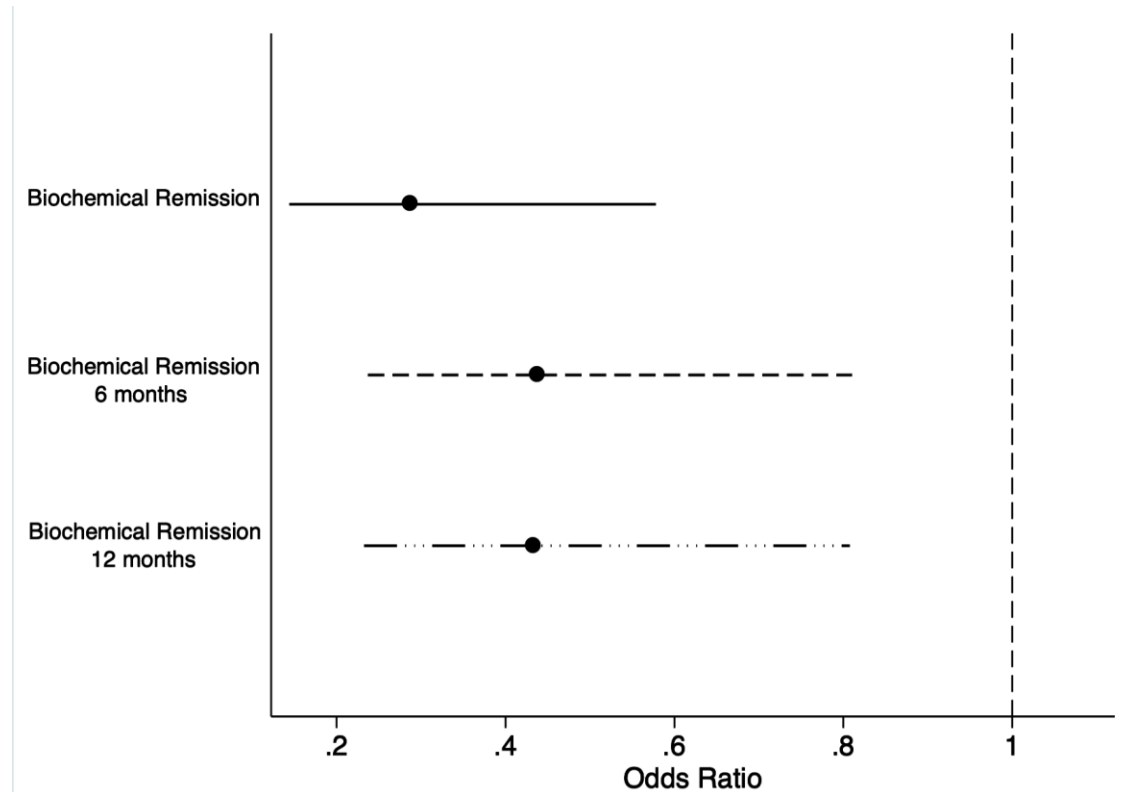
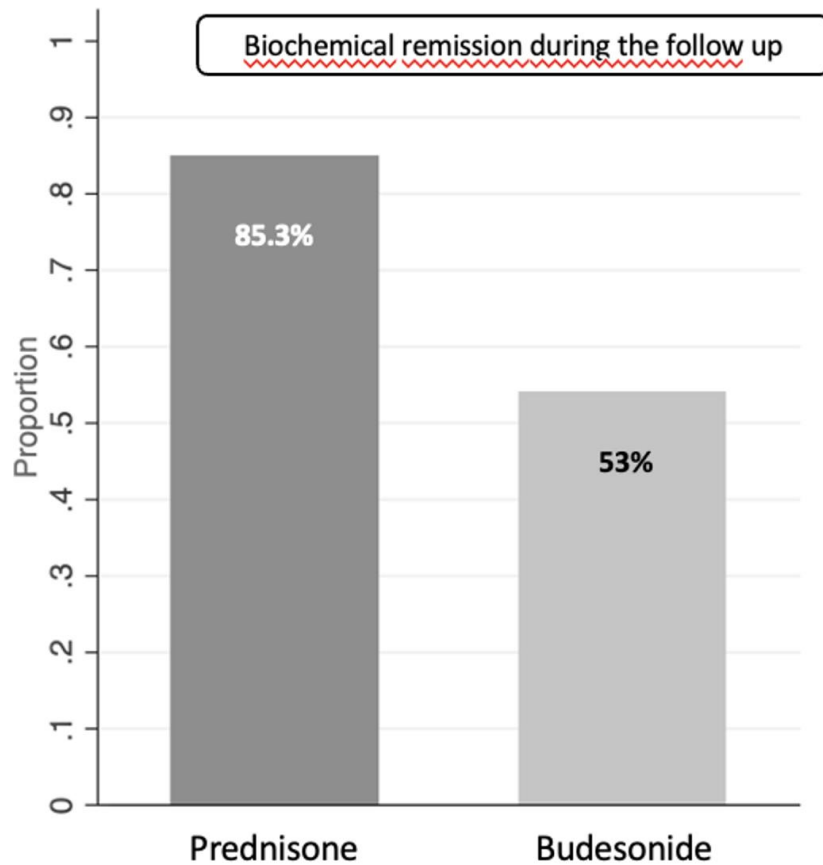
RESULTADOS DEL ESTUDIO



Hay alguna alternativa a la Prednisona?

Estudio multicéntrico Español, COLHAI, 151 pacientes con budesonida

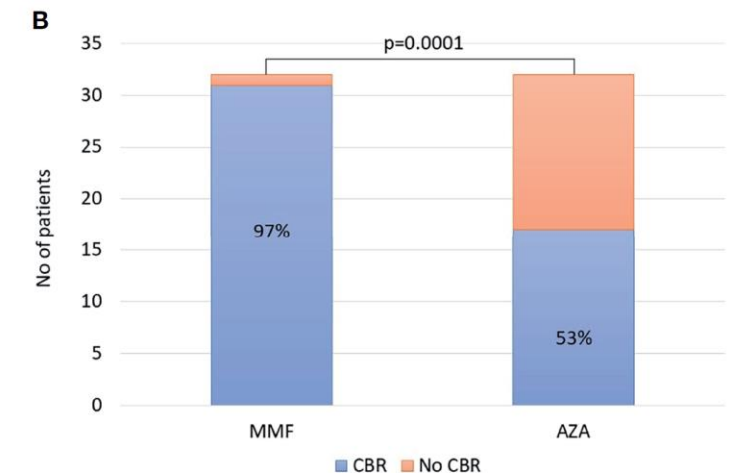
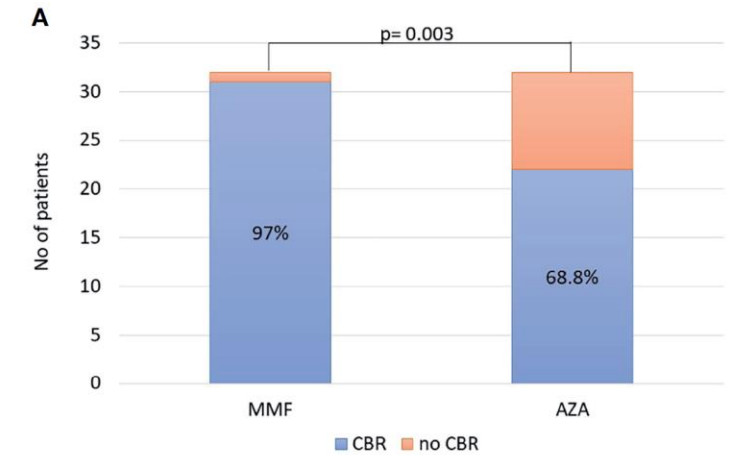
A



Hay alguna alternativa a la Azatioprina?

“Propensity matched study” comparando AZA vs MMF como tratamiento de primera línea

Characteristics	MMF (n = 32)	AZA (n = 32)	p
Sex (female/male)	23/9	23/9	NS
Age at diagnosis (years)	54 (15–80)	55 (15–84)	NS
Time to diagnosis (months)	2.5 (1–402)	3 (1–142)	NS
Acute presentation	16	16	NS
Insidious/asymptomatic presentation	16	16	NS
Follow-up (months)	45 (12–63)	38 (7–70)	NS
Total treatment duration (months)*	39 (11–63)	34 (6–67)	NS
Concurrent autoimmune diseases	18/32	11/32	NS
AIH revised diagnostic score	18 (11–24)	17 (11–22)	NS
AIH simplified diagnostic score	7 (6–8)	7 (6–9)	NS
ALT (IU/ml, ULN: 40)	412 (43–3,716)	425 (8–1,843)	NS
Bilirubin (mg/dl, ULN:1.1)	2 (0.5–13.4)	1.4 (0.3–14.3)	NS
γ-GT (IU/L, ULN: 40)	101 (16–1,136)	159 (14–902)	NS
IgG (mg/dl, ULN: 1,500)	1,844 (782–3,240)	1,760 (870–3,740)	NS
Anti-SLA/LP**	5/32	5/32	NS
Anti-LKM	0/32	0/32	NS
ANA**	17/32	19/32	NS
SMA**	31/32	29/32	NS
Cirrhosis at diagnosis (yes/no)	6/26	6/26	NS
mHAI activity score	8 (3–16)	7 (3–14)	NS
mHAI fibrosis score	2 (2–6)	1 (1–5)	NS



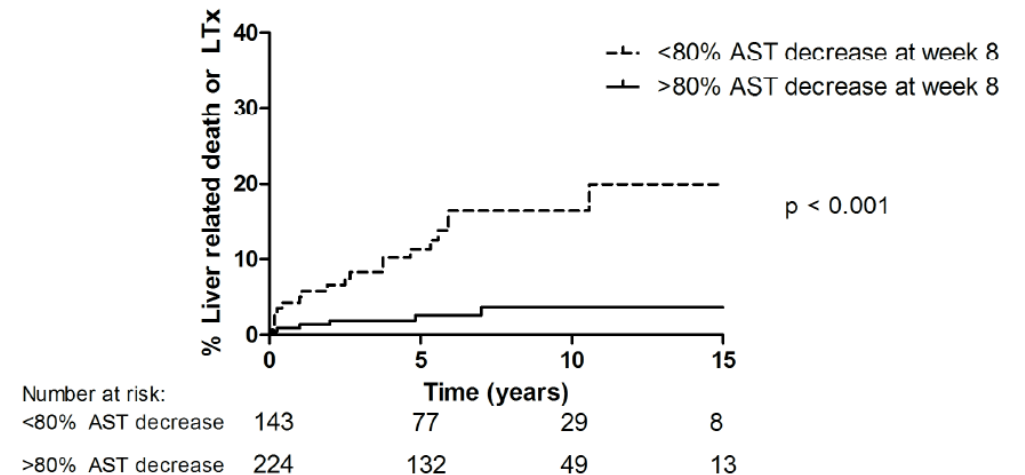
Importancia de la Respuesta Rápida

Estudio retrospectivo multicentrico, n=740 (dividido en 2 cohorts).

Objetivo: Evaluar el pronóstico de los pacientes con respuesta rápida al tratamiento.

Se definió respuesta rápida como descenso de las transaminasas >80% a las 8 semanas.

	<80% AST decrease at week 8 n = 145	≥80% AST decrease at week 8 n = 225	p-value
Normal transaminases at 26 weeks, n (%)	83 (57.2%)	174 (77.3%)	<0.001
Biochemical remission at 26 weeks, n (%)†	46 (52.9%)	108 (77.1%)	<0.001
Predniso(lo)ne dose ≤10 mg at 26 weeks, n (%)	32 (22.1%)	77 (34.2%)	0.01
Normal transaminases at 52 weeks, n (%)	94 (64.8%)	195 (86.7%)	<0.001
Biochemical remission at 52 weeks, n (%)¶	41 (61.2%)	114 (79.7%)	0.004
Predniso(lo)ne dose ≤10 mg at 52 weeks, n (%)	65 (44.8%)	125 (55.6%)	0.04
Liver related death or LTx, n (%)	23 (15.9%)	7 (3.1%)	<0.001
All cause mortality, n (%)	20 (13.9%)	11 (4.9%)	0.002
HCC development, n (%)	4 (2.8%)	0	0.01

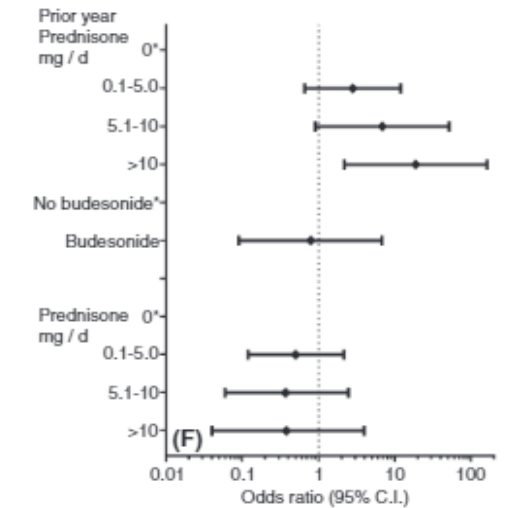
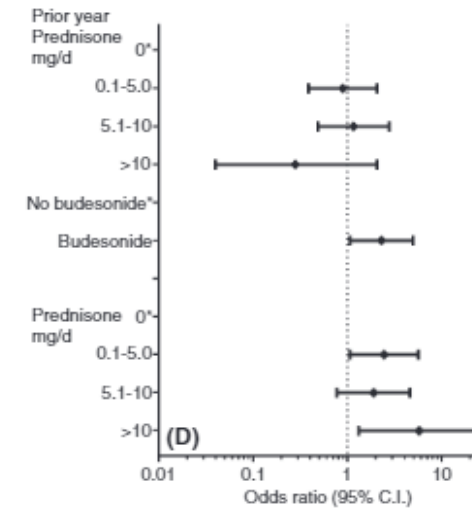
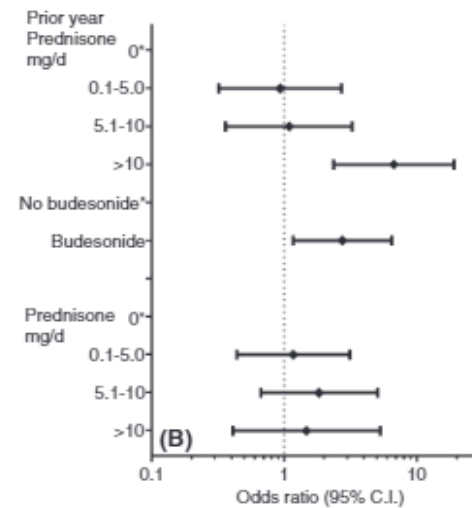
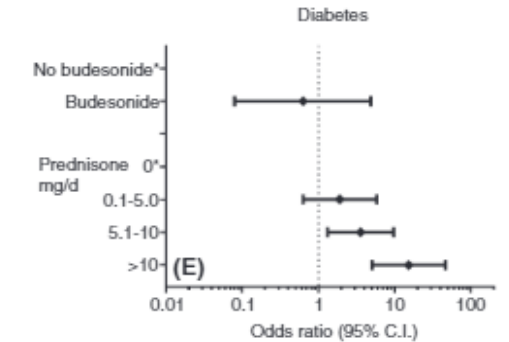
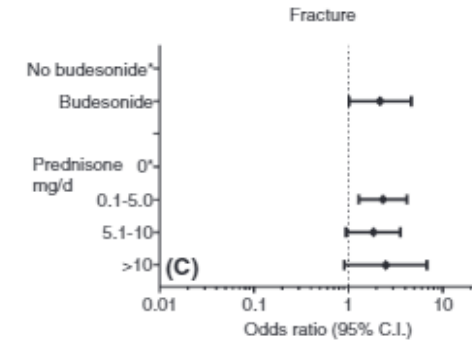
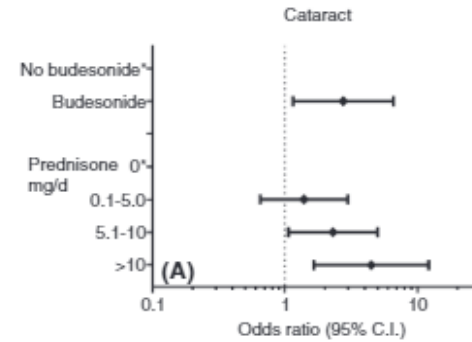


Respuesta al Tratamiento de Primera Línea

44% - 100% de los pacientes responden al tratamiento

30% -40% de los pacientes tienen efectos adversos relacionados con el tratamiento

15-20% de los pacientes son intolerantes o presentan una respuesta insuficiente



Respuesta al Tratamiento de Primera Línea

Respuesta

- Normalización de transaminasas y niveles IgG

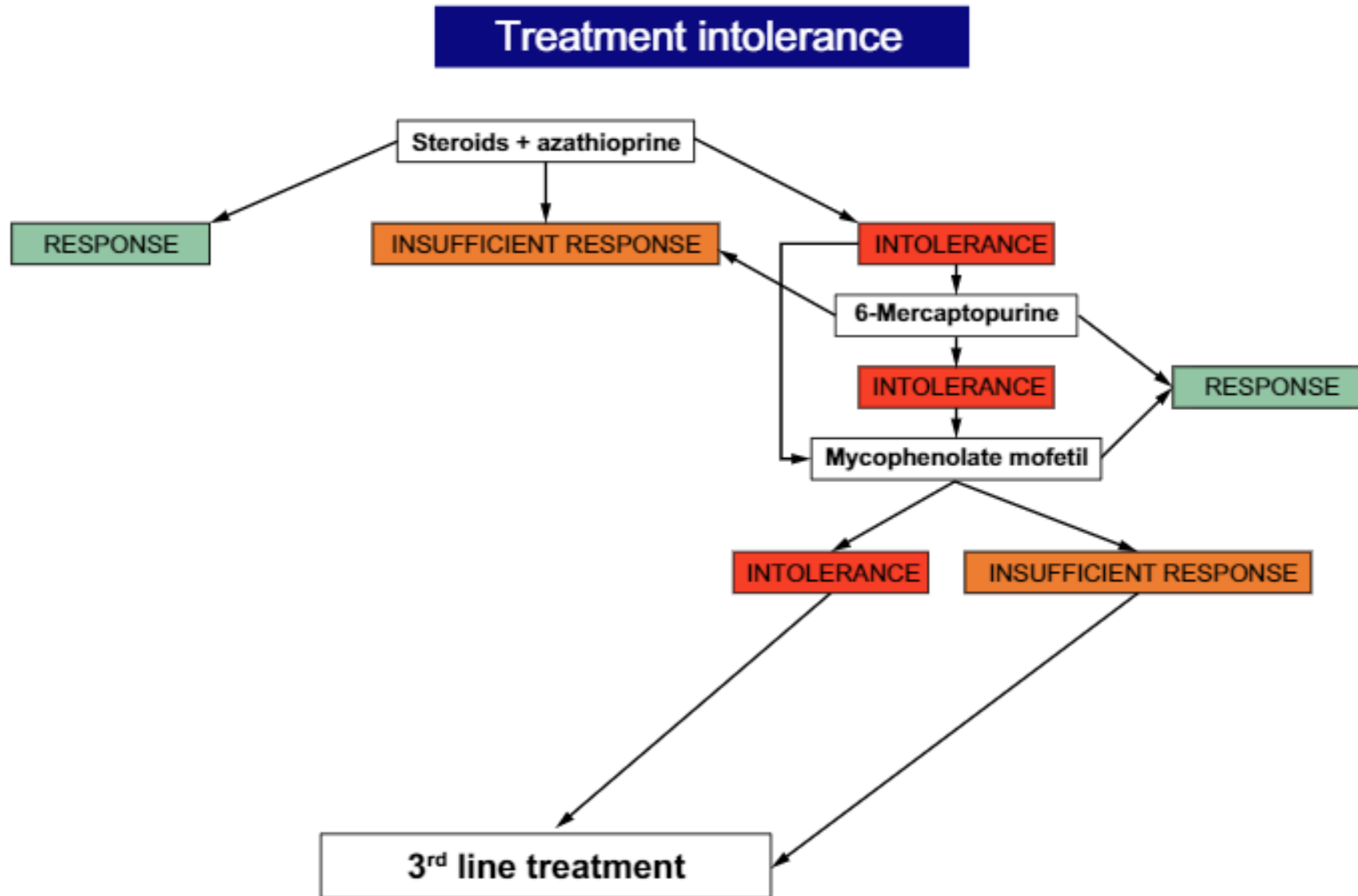
Intolerancia

- Efectos adversos relacionados con AZA y/o corticoides

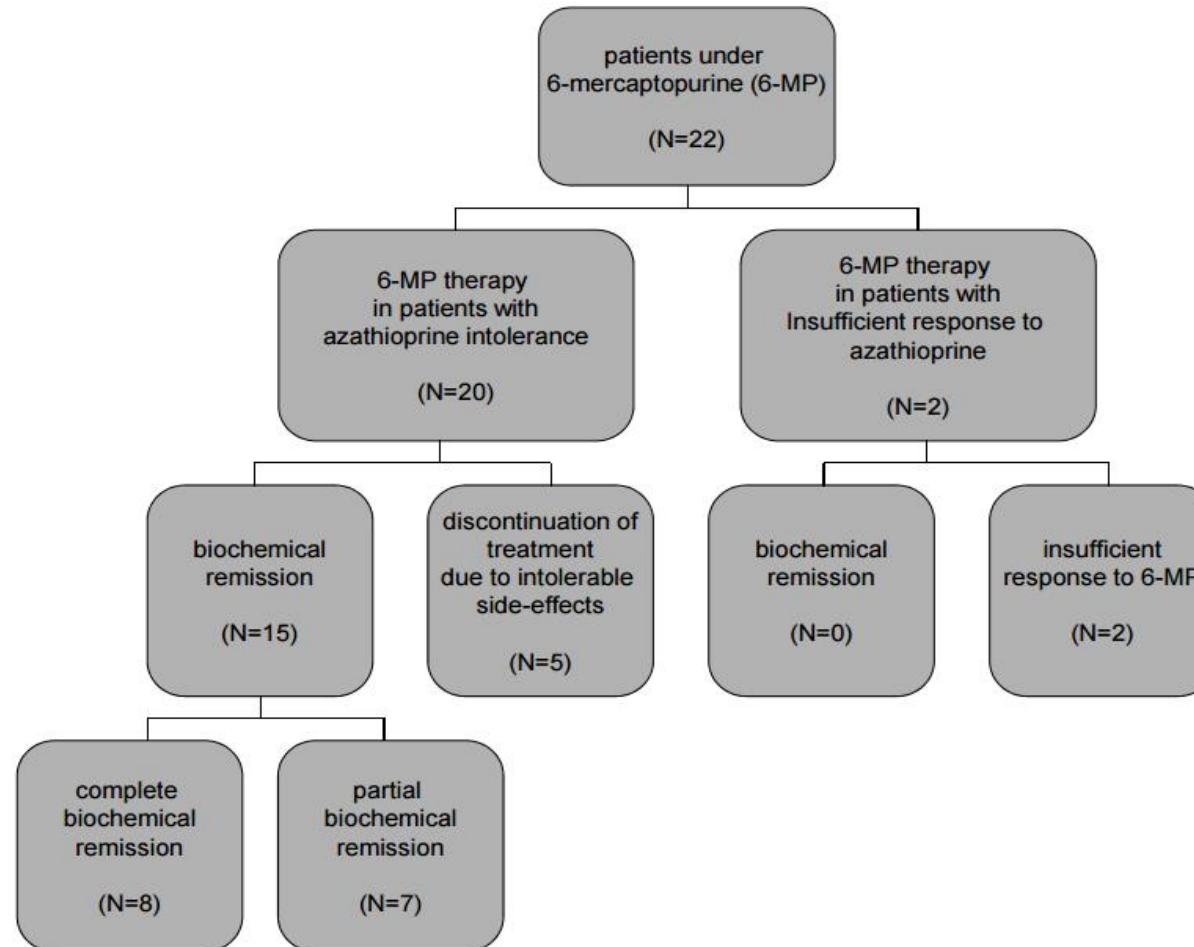
Respuesta insuficiente

- Ausencia de normalización de transaminasas y niveles IgG

Qué hacemos si no responde?



Intolerancia a AZA-Mercaptopurina

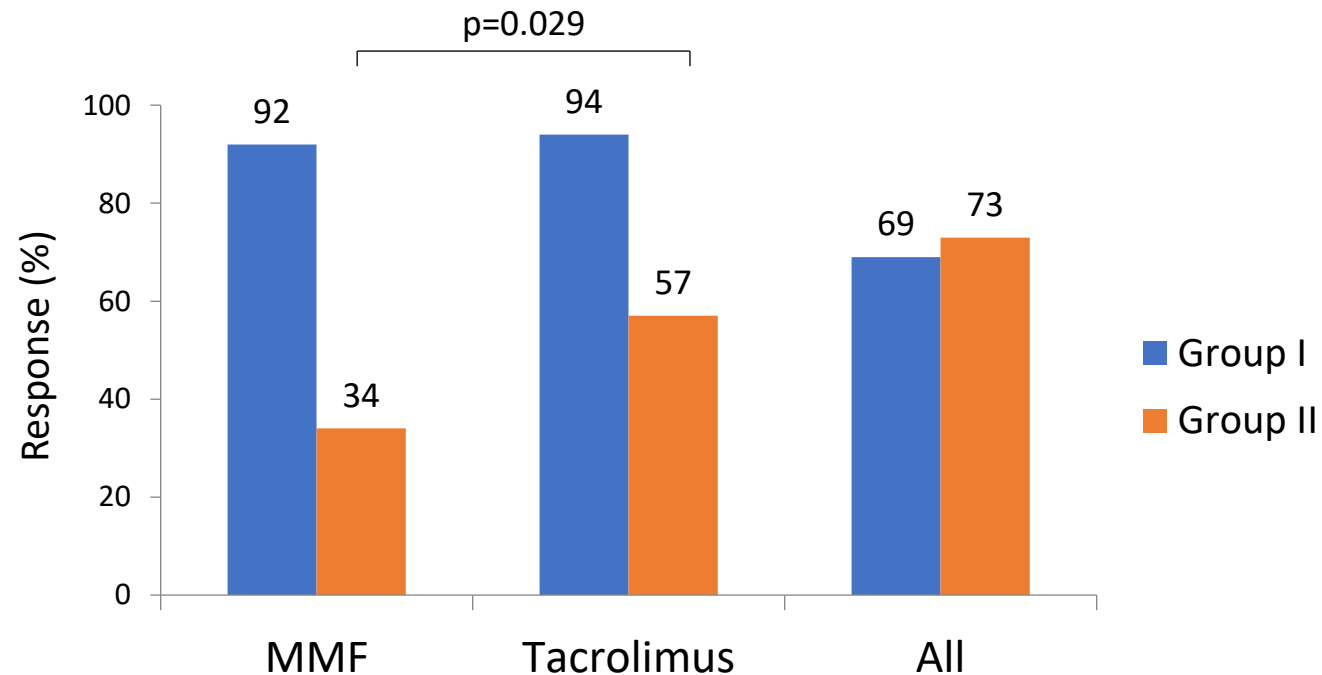


Intolerancia a AZA-Micofenolato

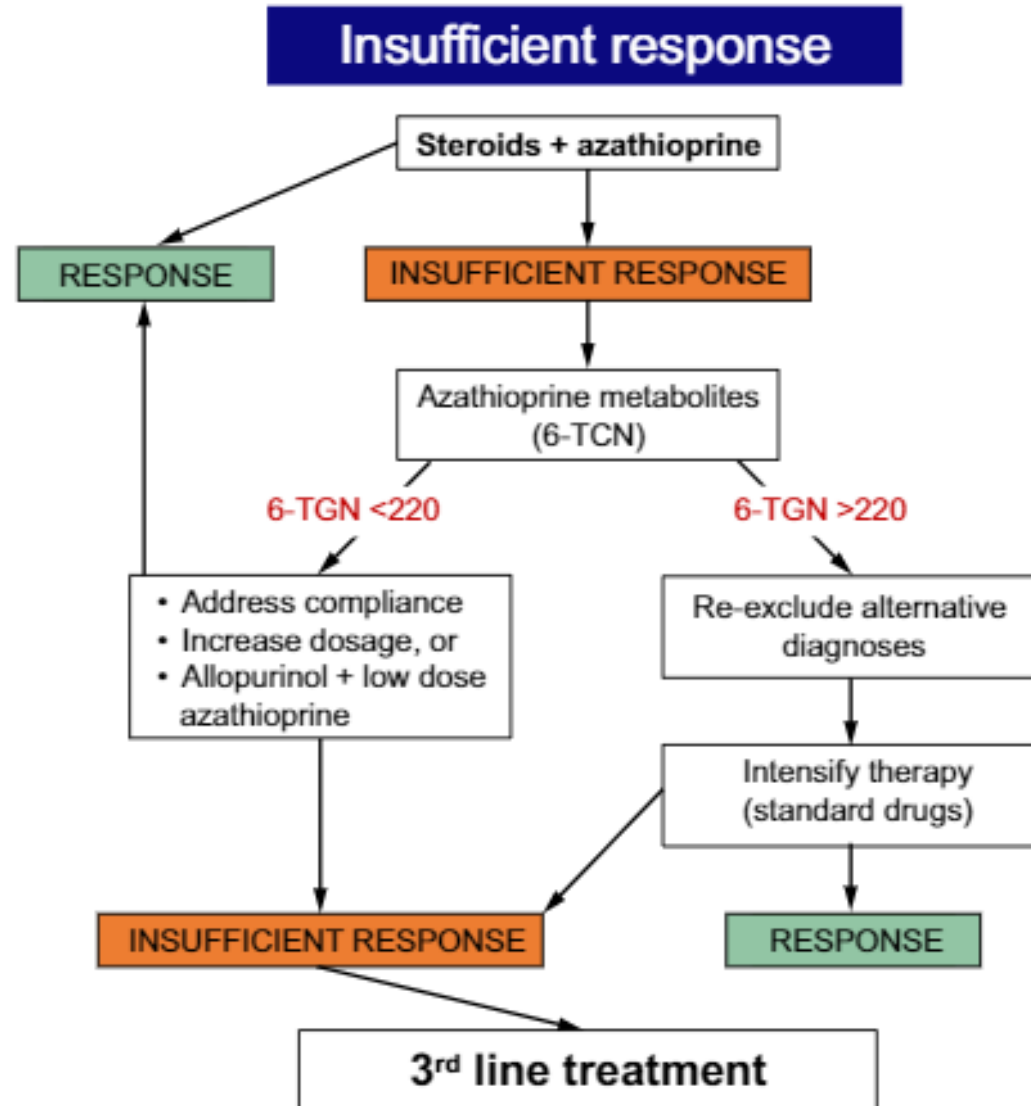
	Overall n=201	MMF n=121	Tacrolimus n=80
AZA intolerance, n (%)	78 (38.8)	56 (46.3)	22 (27.5)
Steroid side effects n (%)	30 (14.9)	18 (14.9)	12 (15.0)
Non response to standard therapy, n (%)	93(46.3)	47(38.8)	46 (57.5)

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

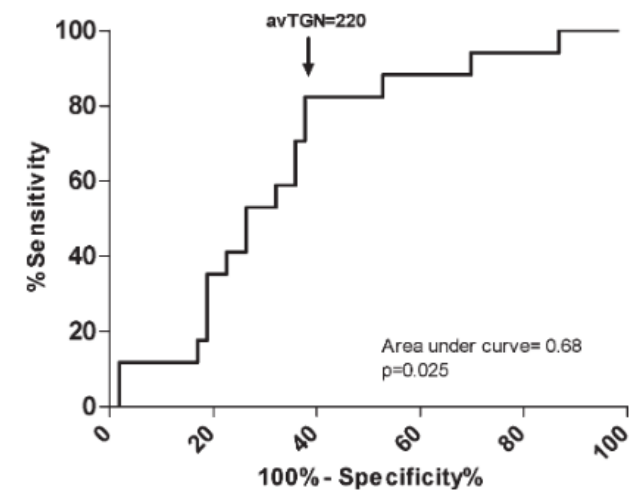
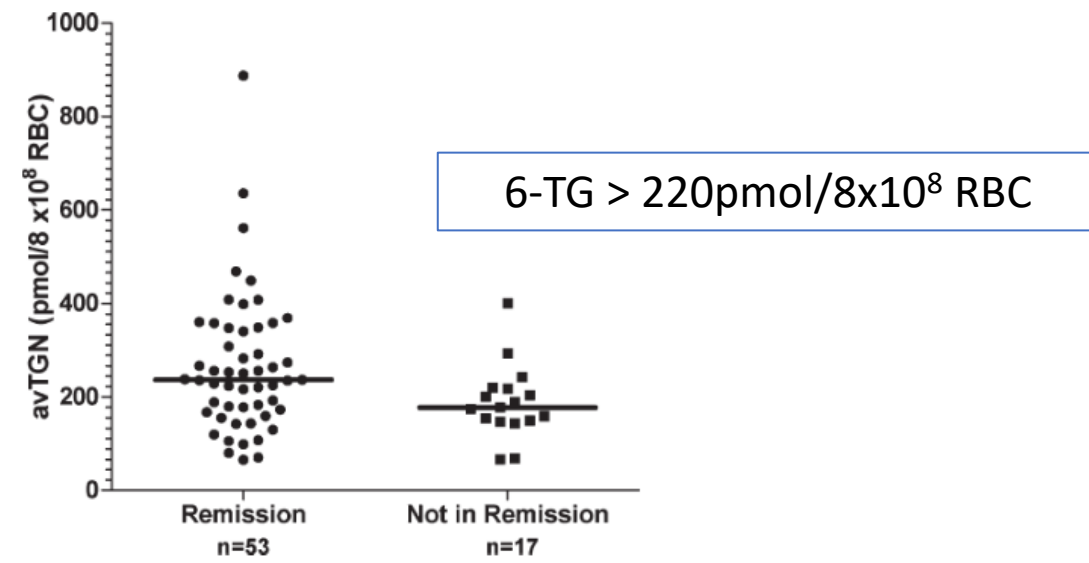
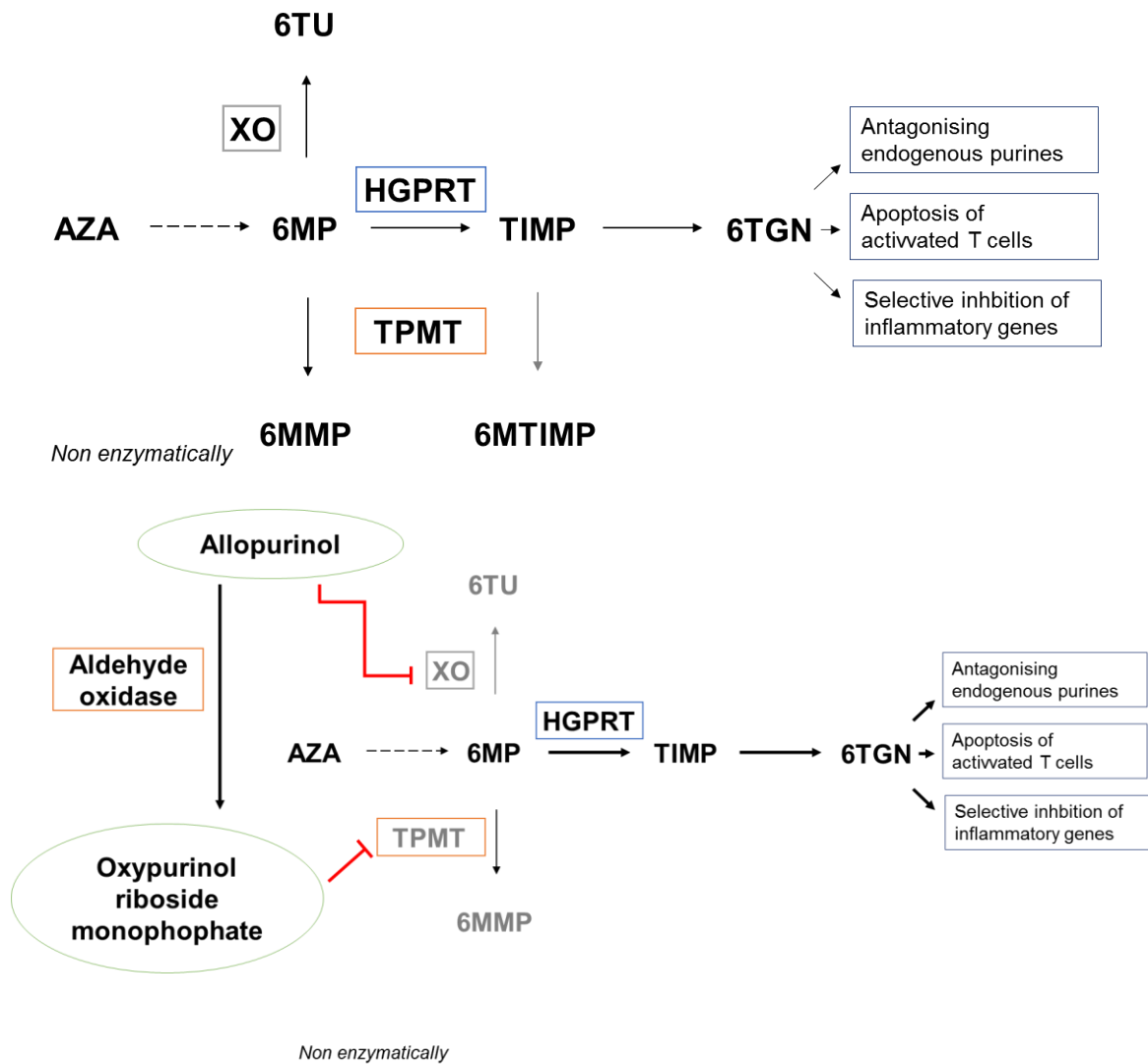
Group II: insufficient response to SOC



Qué hacemos si no responde?



Respuesta Insuficiente



Manejo guiado por metabolitos de AZA

6-TGN	6-MMP	Interpretación	Recomendación
Muy bajo (<50)	Muy bajo (<50)	No adherencia	Educación
Bajo (<220)	Bajo (<220)	Dosis baja	Aumentar dosis
Bajo (<220)	Alto (>5700)	Hipermetilador	Alopurinol
OK (220-450)	Alto o bajo	No respondedor	Tratamiento de 3ra línea

Respuesta Insuficiente



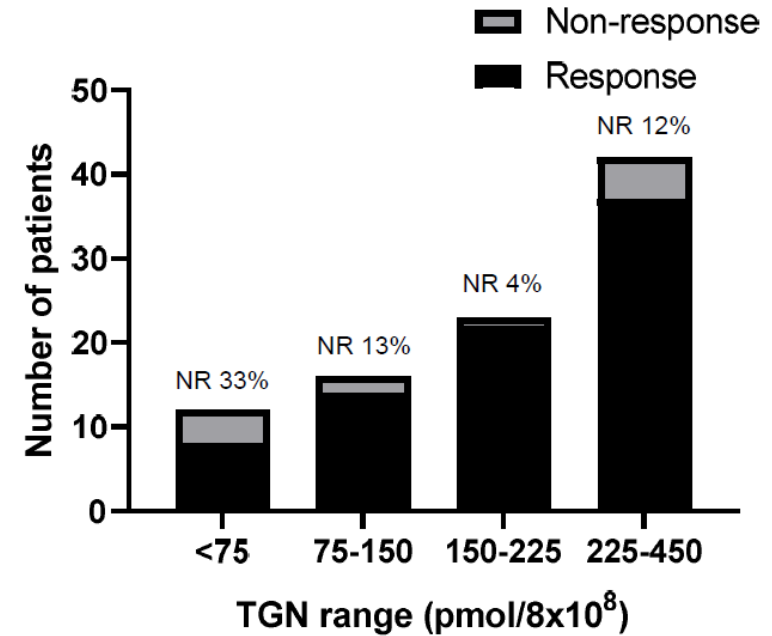
Journal of Hepatology
Available online 16 April 2021
In Press, Journal Pre-proof



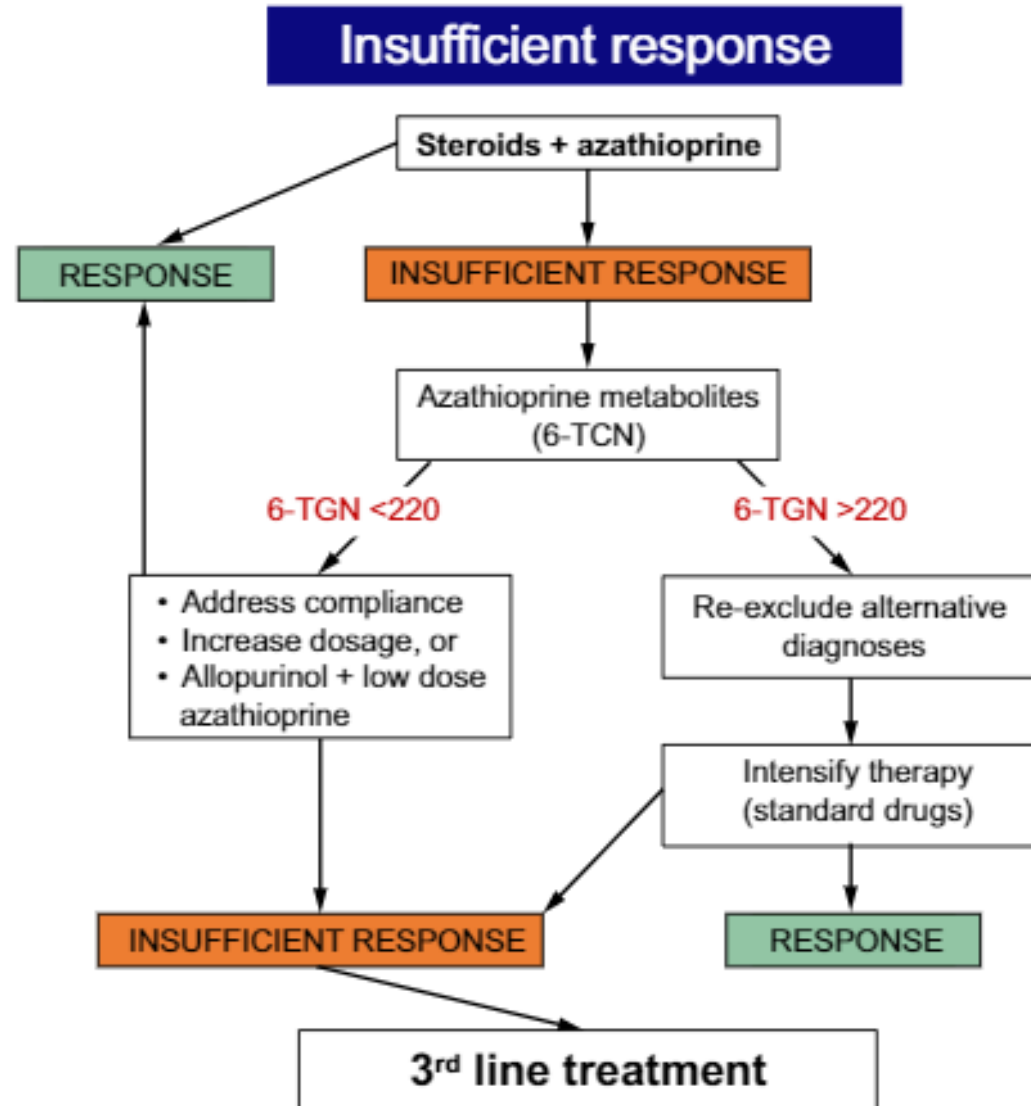
Towards personalised medicine in autoimmune hepatitis: Measurement of thiopurine metabolites results in higher biochemical response rates compared to standard weight-based dosing of thiopurine therapy

Lena S. Candels ^{1,2,3,4}, Mussarat N. Rahim ^{1,3}, Sital Shah ¹, Michael A. Heneghan ^{1,3,4}

Respuesta bioquímica (6 meses)
77% vs. 60% p=0.008



Qué hacemos si no responde?



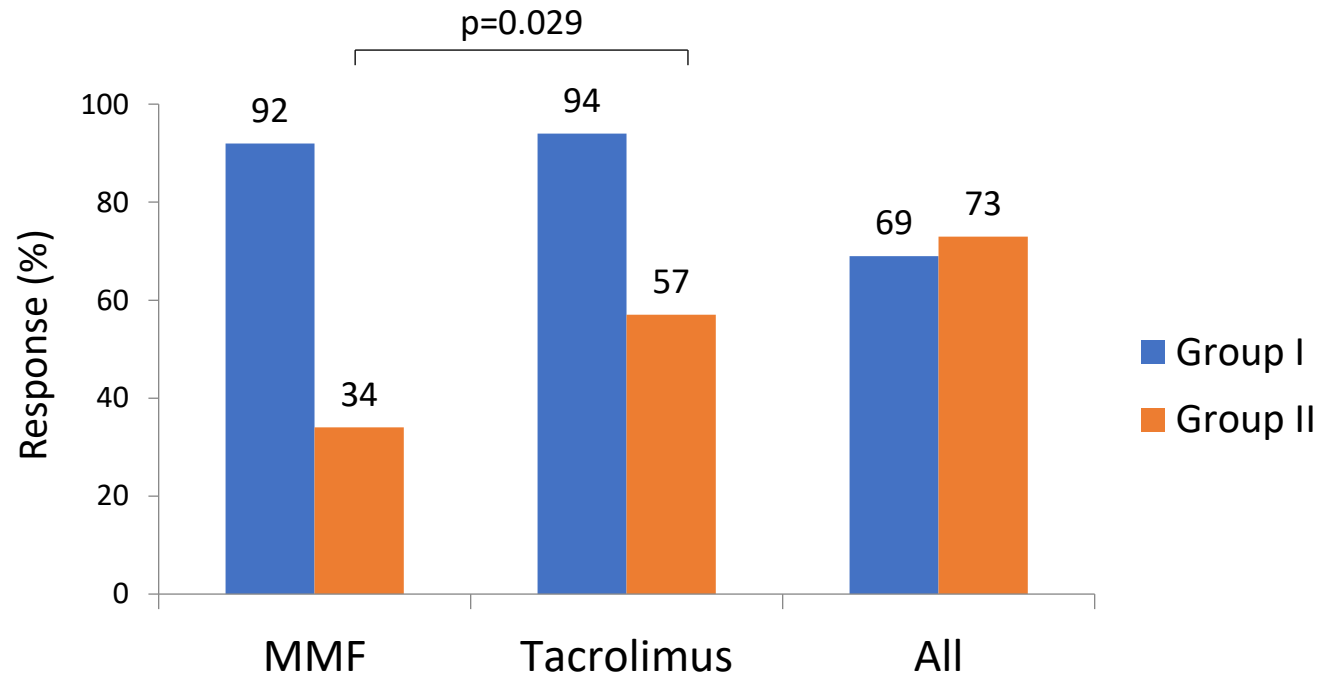
Tratamiento de Tercera Línea

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



Tratamiento de Tercera Línea

Tacrolimus

Concomitant treatments given with tacrolimus

Thiopurines	6 (26%)
Mofetil mycophenolate	6 (26%)
Steroids (including budesonide)	16 (70%)
No co-treatment	2 (9%)

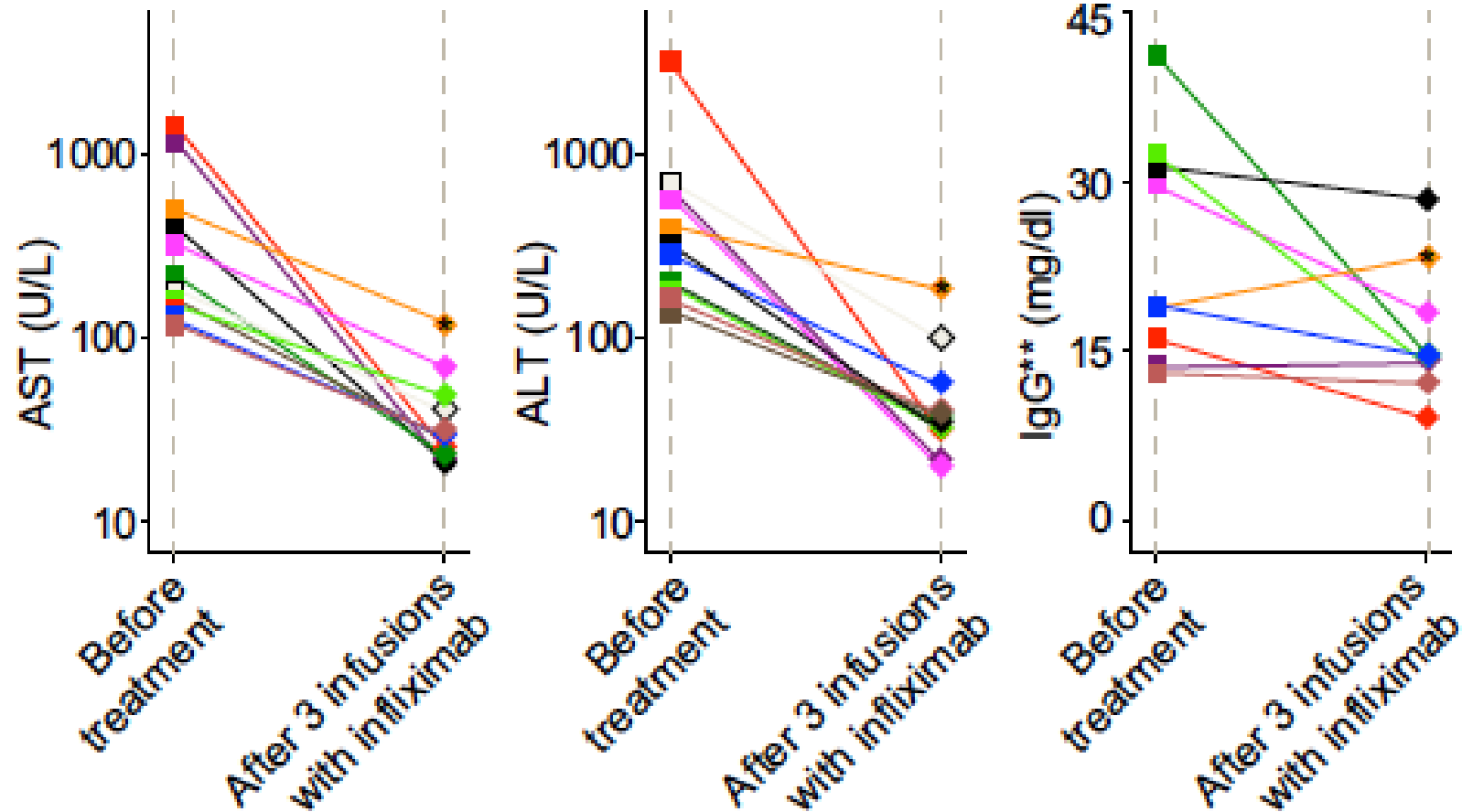
Analytical and elastographic variables during treatment

	Beginning treatment	Last follow-up	<i>p</i> value
AST (IU/L)	81 [175]	43 [29]	0.0002
ALT (IU/L)	139 [152]	47 [73]	0.003
GGT (IU/L)	120 [276]	60 [70]	0.006
AP (IU/L)	113 [139]	92 [87]	0.002
Bilirubin (mg/dL)	1 [2.47]	0.72 [0.6]	0.08
Platelets (/mm ³)	208,913 (95,399)	202,478 (95,613)	0.2
INR	1.05 [0.2]	1.02 [0.16]	0.4
IgG (mg/dL)	1906 (1242)	1501 (1124)	0.02
Creatinine (mg/dL)	0.73 (0.16)	0.79 (0.18)	0.9
Liver stiffness (kPa)	17.8 [16.5]	8.1 [3.7]	0.1

Eficacia
78%

Tratamiento de Tercera Línea

Infliximab



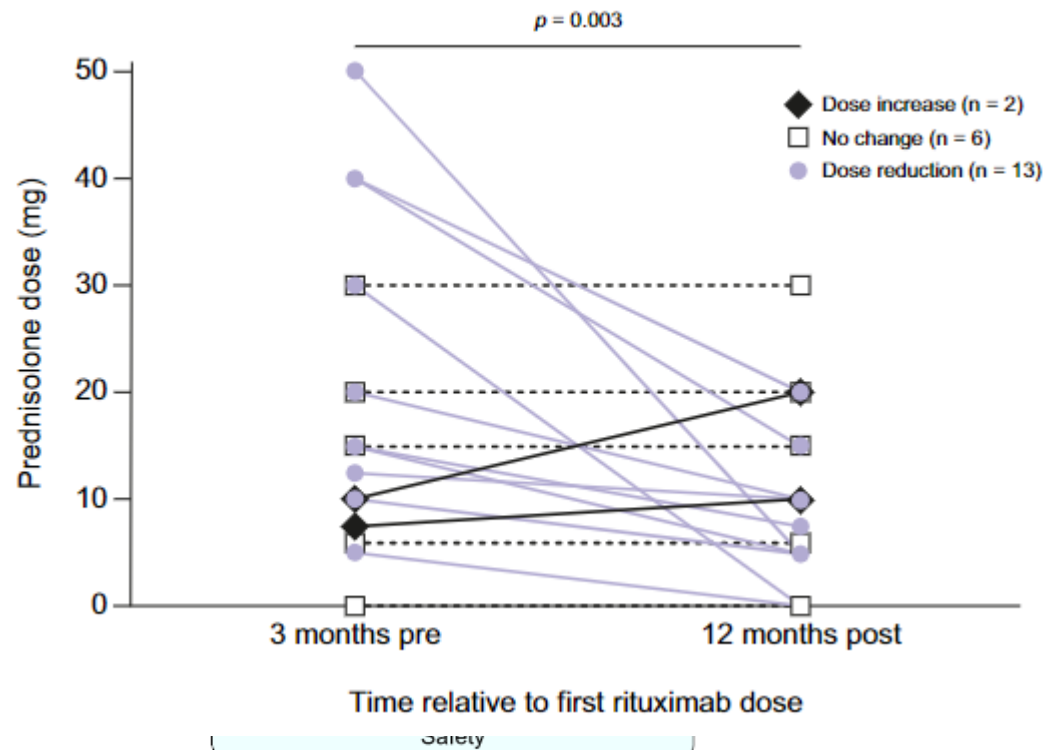
Tratamiento de Tercera Línea

Infliximab

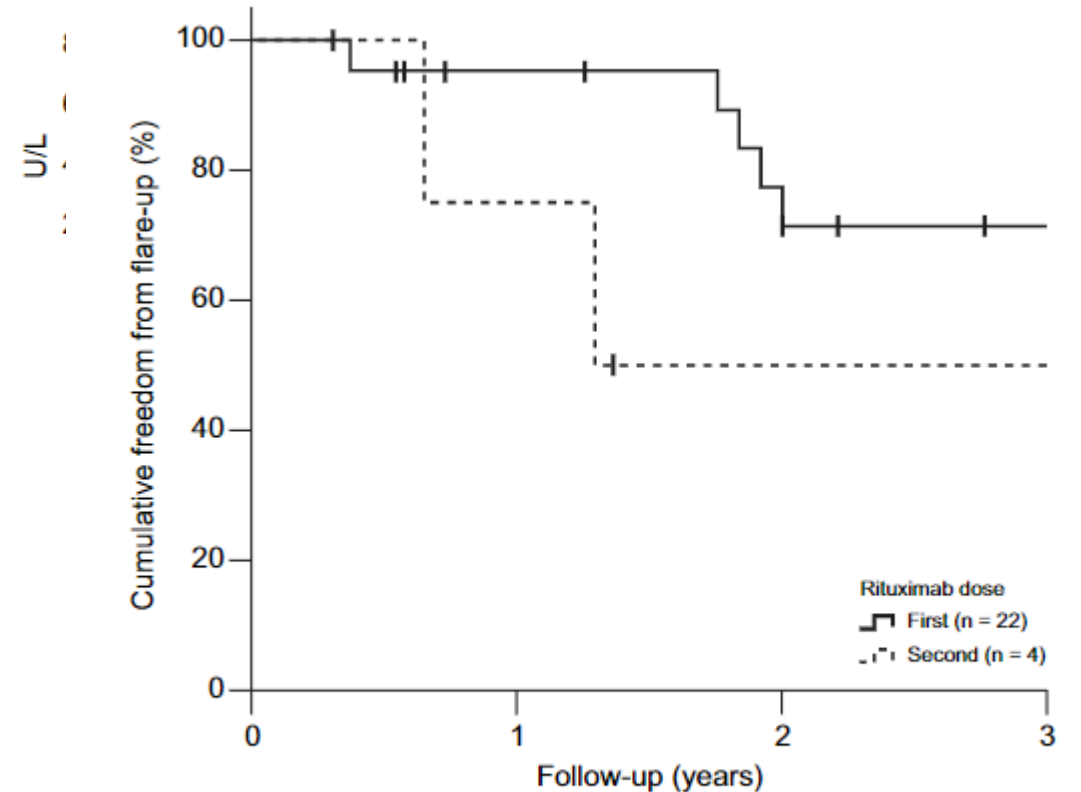
Patient	Cause of infliximab treatment	Complications of treatment	Response to treatment	Duration of treatment	Number of infusions	Prednisolone dose
1*	Cirrhosis, cyclophosphamide hepatitis, flare under ongoing standard treatment	Multiple infectious complications →	Repeated prompt full remission	Treatment ongoing (on/off) since 2001	>>40 infusions	20 mg/d
2	Azathioprine intolerance, MMF intolerance, aggravated depression under steroids	Shingels	Initial remission, flare under ongoing treatment	Treatment stopped after 18 mo due to flare under treatment	14	5 mg/d
3	Azathioprine intolerance, MMF intolerance, cyclophosphamide cumulative dose reached	Pneumonia, recurrent urinary tract infections →	Full remission	Treatment ongoing for 31 mo	22	5 mg/d
4	Steroid-induced diabetes and weight gain, uncontrolled disease with cirrhosis	Pneumonia	Incomplete remission with elevated IgG	Treatment stopped after 8 mo after pneumonia	9	10 mg/d
5	Steroid-aggravated depression, weight gain	Recurrent herpes labialis →	Repeated full remission	Treatment ongoing (on/off) for 24 mo	10	10 mg/d
6	Steroid-refractory flare under treatment	→	Full remission	Stopped after 8 mo due to full remission	6	Steroids tapered out
7	Steroid-induced diabetes, weight gain	→	Full remission	Treatment ongoing for 15 mo	14	10 mg/d
8	Azathioprine intolerance	→	Full remission	Treatment ongoing for 12 mo	7	10 mg/d
9	Azathioprine intolerance	→	Full remission	Treatment ongoing for 15 mo	10	10 mg/d
10	Azathioprine induced pancreatitis	Ocular <i>herpes simplex</i> infection, recurrent urinary tract infections	Partial response	Treatment stopped after 6 mo due to allergic reaction and incomplete response	6	15 mg/d
11	Azathioprine intolerance	→	Full remission	Treatment ongoing for 13 mo	10	10 mg/d

Tratamiento de Tercera Línea

Reduction of corticosteroid dose



Increase the probability of being without flares



N° at risk			
First	17	12	9
Second	3	1	1

Futuro

Proposed:

IL-2

Anti-BAFF

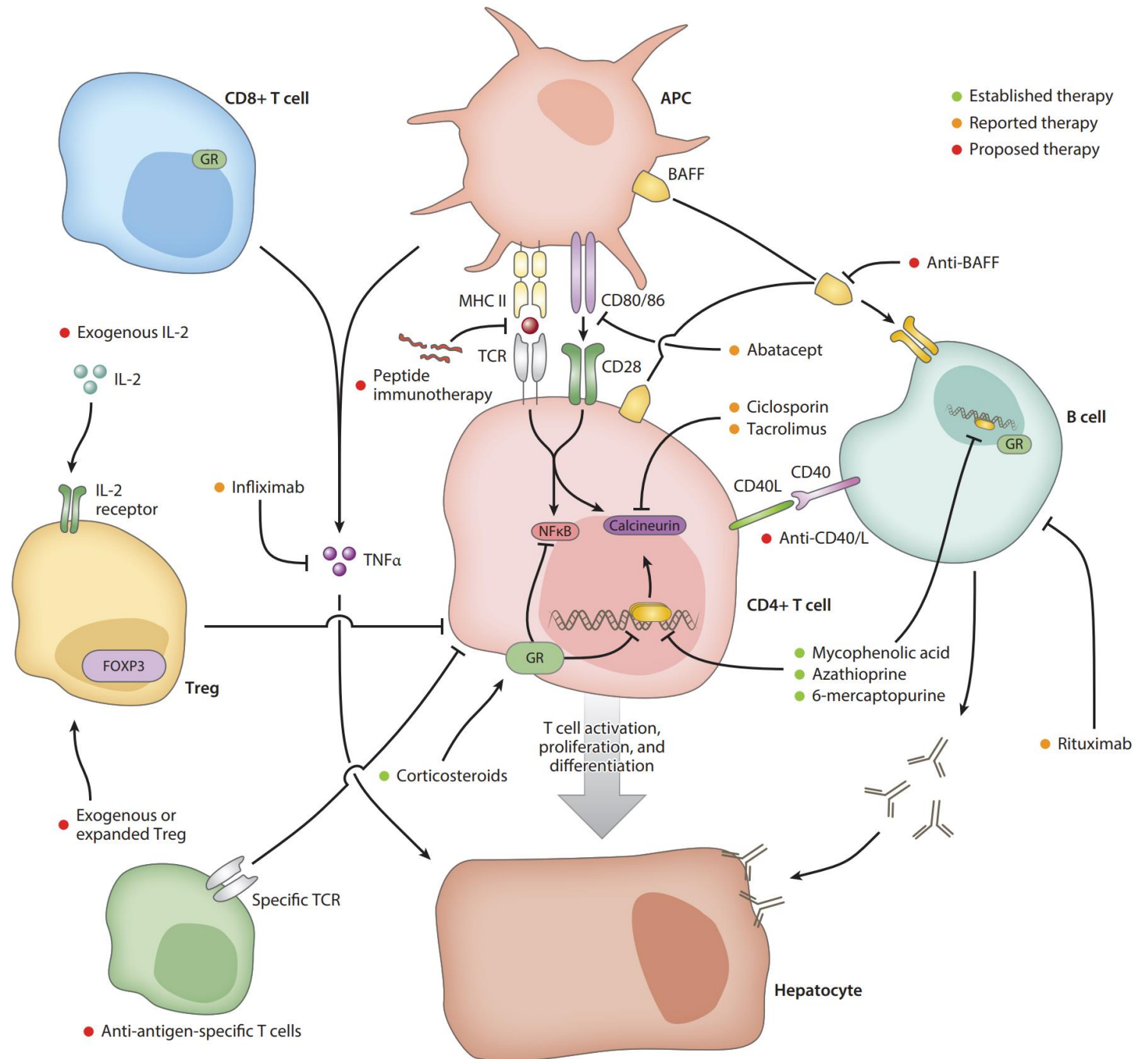
Tregs (polyclonal or antigen-specific)

Anti-CD40

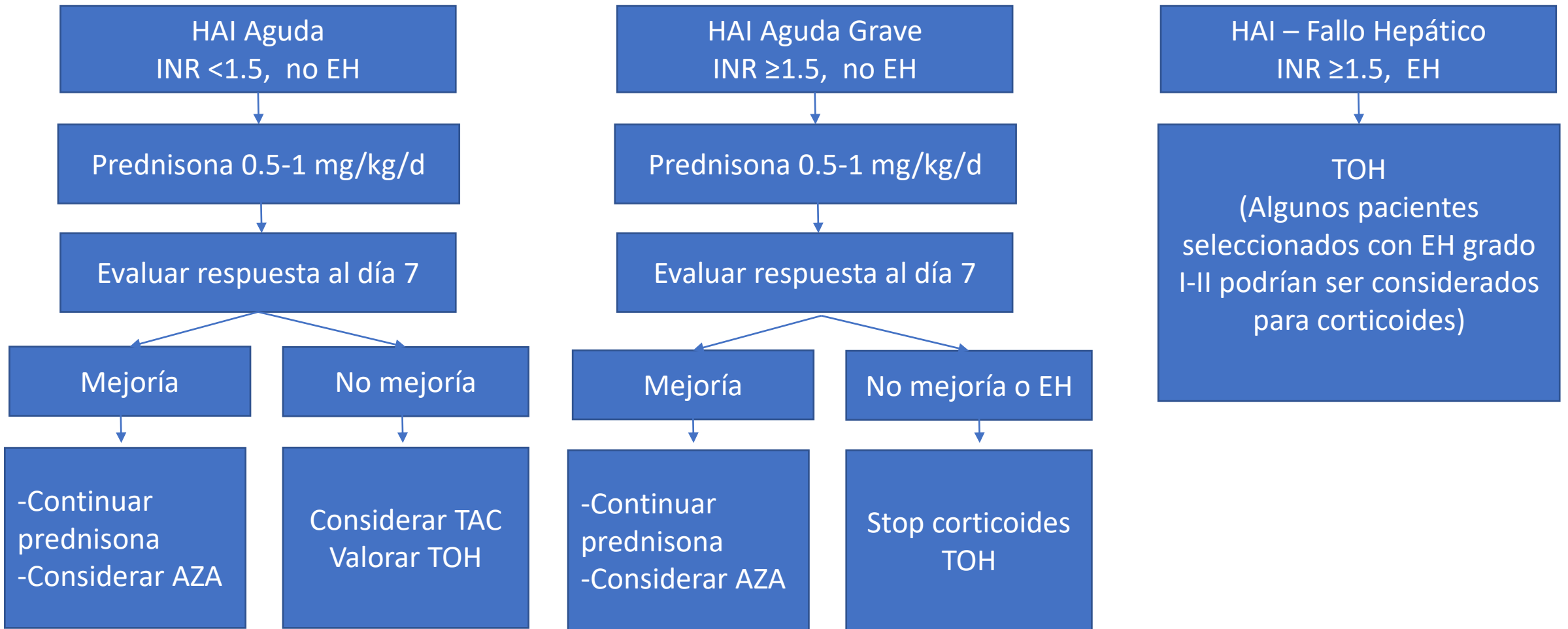
JAK inhibitors

Anti-TLR

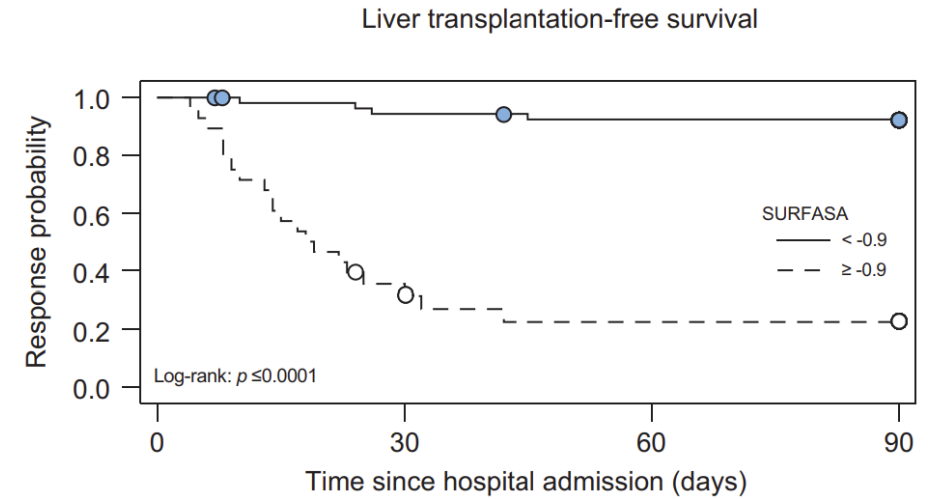
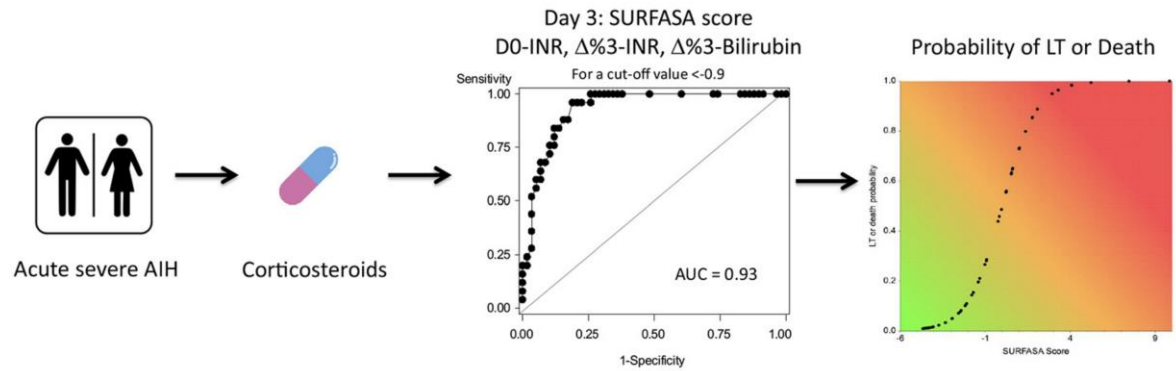
Preimplantation factor



Hepatitis Aguda



Hepatitis Aguda



Patients at risk				
<-0.9	55	50	48	47
≥-0.9	28	8	5	4

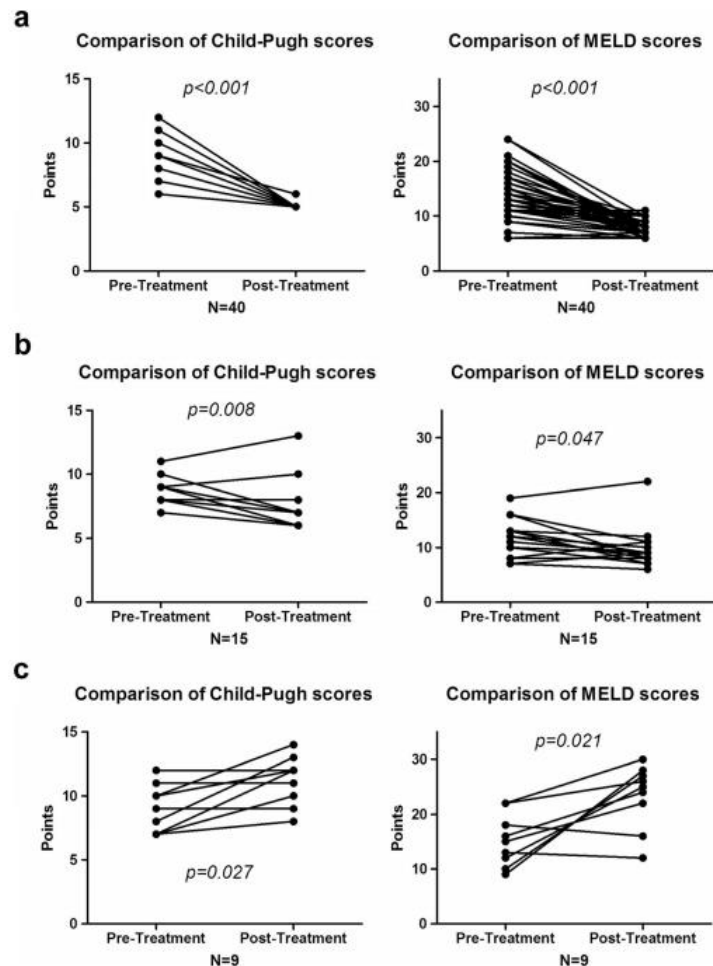
Cirrosis Descompensada

Tratamiento

Variable	Total (n=82)	Tratados (n=64)	No tratados (n=18)	p
82 pacientes con cirrosis descompensada seguidos en un solo centro				
Albumina	31 (20-41)	31 (20-42)	26 (20-36)	0,001
Bilirrubina	2,44 (0,35-25,7)	2,44 (0,58-25,74)	2,35 (0,35-13,6)	0,460
Tratamiento según el médico				
INR	1,26 (0,85-1,9)	1,26 (0,85-1,9)	1,26 (0,89-1,65)	0,788
Plaquetas	78 (4-410)	79 (14-410)	68 (4-144)	0,287
Ascitis				
50 mg	5			
40 mg	3			
30 mg	16	2/26/23/13	1/8/3/6	0,919
20 mg	25			
15 mg	12			
10 mg	3	7 (11%)	5 (28%)	0,124
EH	3 (4%)	2 (3%)	1 (6%)	0,530
Child-Pugh Score	9 (6-12)	9 (6-12)	9 (6-11)	0,224
A/B/C	4/50/28	3/41/20	1/9/8	0,367
MELD score	13 (6-24)	13 (6-24)	13 (8-22)	0,698

Cirrosis Descompensada

Tratamiento



Mejoría (n=40)

Estabilidad (n=15)

Deterioro (n=9)

7 pacientes fallecieron y 2 necesitaron trasplante hepático (TH)

Causa de muerte o TH → infecciones (n=7)

EH (n=5)

ascitis refractaria (n=4)

SHR (n=1)

Cirrosis Descompensada

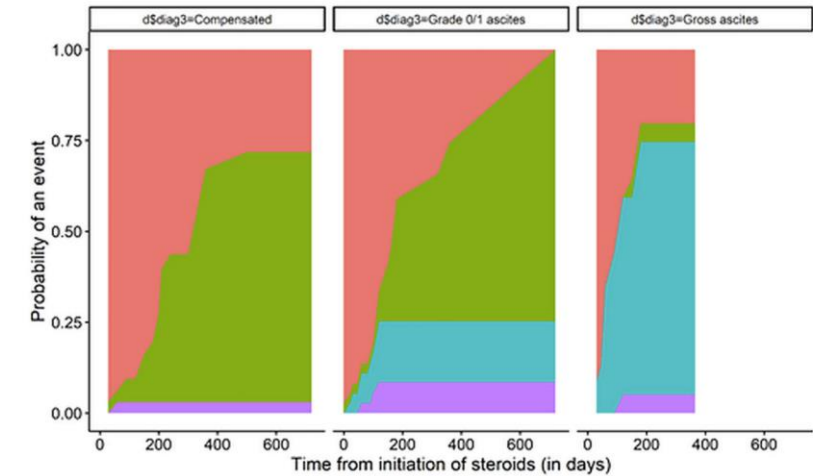
Table 2 Comparison of outcomes among patients with decompensated cirrhosis with gross ascites, mild/no ascites, and compensated cirrhosis

Variable	Compensated cirrhosis (n = 32)	Decompensated cirrhosis with no/mild ascites (n = 38)	Decompensated cirrhosis with moderate/gross ascites (n = 24)	P-value
Immunosuppressants				0.072
Steroids	32 (100)	38 (100)	24 (100)	
Azathioprine	24 (75)	0	0	
MMF	4 (12.5)	0	0	
Tacrolimus	1 (3.1)	0	0	
Dose of prednisolone (mg/day)	40 (30–50)	25 (20–30)	20 (20–25)	0.01
Discontinuation of steroids	1 (3.1)	21 (57.8)	23 (95.8)	0.001
Clinical outcome				<0.001
No change	5 (15.6)	15 (39.5)	9 (37.5)	
New decompensation	2 (6.2)	3 (7.9)	2 (8.3)	
Worsening of ascites	0	3 (7.9)	3 (12.5)	
ACLF	0	2 (5.3)	8 (33.3)	
Adverse effects				
Infection	3 (9.3)	9 (23.7)	12 (50.0)	0.002
Leukopenia	8 (25)	0	0	<0.001
Diabetes	8 (25)	12 (31.5)	6 (25)	0.782
Hypertension	2 (6.2)	0	0	0.139
Rise in IOP	1 (3.1)	0	0	0.381
Duration of follow-up (months)	12 (7–28)	5 (4–9)	3 (2–6)	<0.001
Biochemical remission	17 (53.1)	12 (31.6)	1 (4.2)	0.001
Deaths	0	6 (15.8)	16 (66.7)	<0.001
Liver transplant	1 (3.1)	3 (7.9)	1 (4.2)	0.41

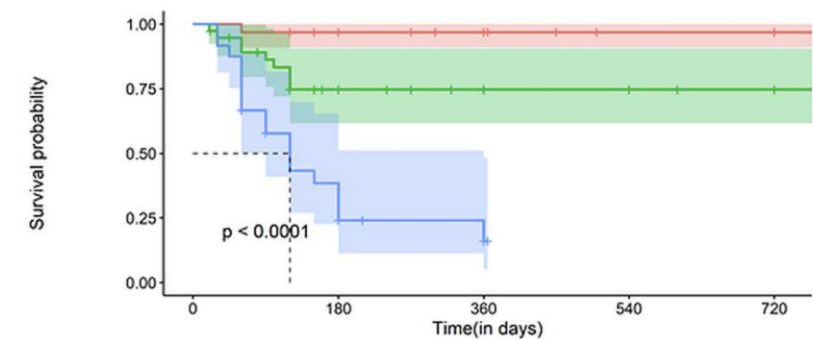
Data are presented as mean ± standard deviation or median (interquartile range) for quantitative variables and n (%) for qualitative variables unless otherwise specified.

ACLF, acute-on-chronic liver failure; IOP, intraocular pressure; MMF, mycophenolate mofetil.

a Cumulative incidence functions



b Transplant free survival after initiating steroids



Transplant free survival after initiating steroids

Strata	Compensated	No/mild ascites	Gross ascites
0	32	38	24
180	27	15	8
360	20	8	3
540	13	5	0
720	13	3	0

Conclusiones

- La hepatitis autoinmune es cada vez más frecuente.
- La respuesta al tratamiento es buena en la mayoría de los casos pero generalmente debe mantenerse de por vida.
- Existe poca evidencia para el tratamiento de segunda línea.
- Los nuevos fármacos en investigación podrían tener un papel en los pacientes sin respuesta al tratamiento habitual



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