Manejo Actual de la Hepatitis Autoinmune

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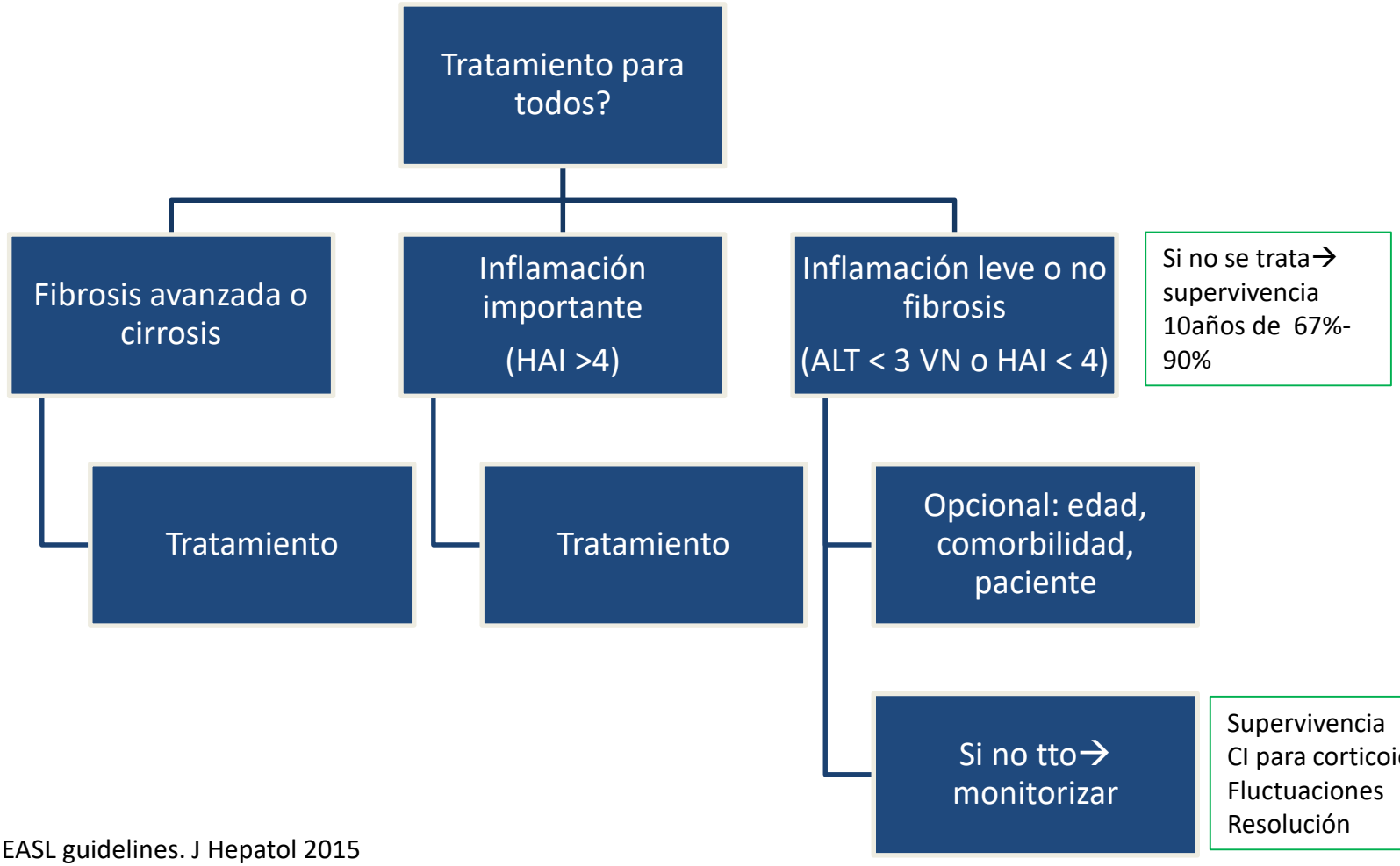
Tratamiento

- Objetivo: Lograr la remisión de la enfermedad y prevenir la progresión de la fibrosis
- Remisión: Normalización bioquímica e histológica
- Controles de por vida.
- Tratamiento prolongado al menos 3 años después de lograr la remisión

EASL guidelines. J Hepatol 2015

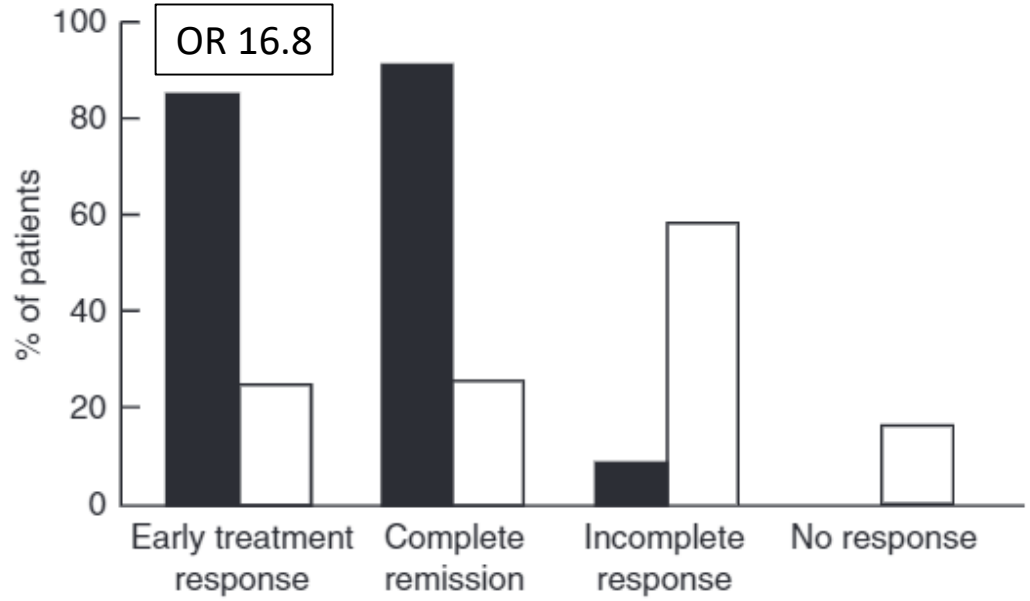
Tratamos a todos los pacientes?



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

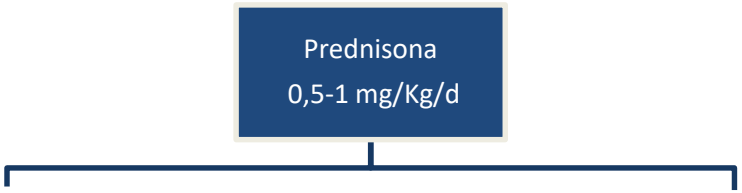
Con qué los tratamos?

Independiente del tratamiento es fundamental garantizar una buena respuesta inicial ya que se asocia con mejor supervivencia



EASL guidelines. J Hepatol 2015
Lamers et al. J Hepatol 2010
Tam et al. Liver Int 2005

Con qué los tratamos?



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*

EASL guidelines. J Hepatol 2015

Dosis alta o baja de Prednisona?

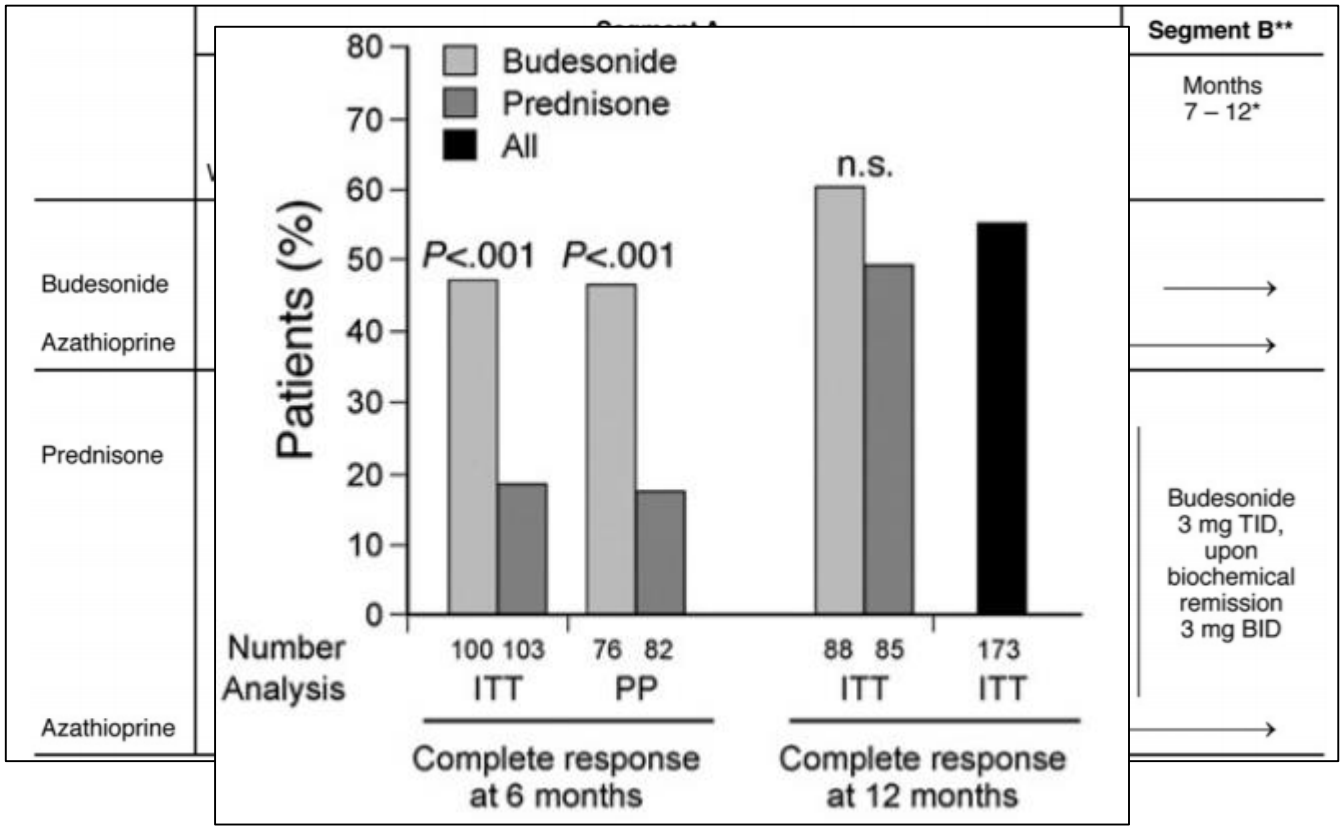
Diseño: Análisis retrospectivo en 9 centros de 5 países de Europa (n=451).
Objetivo: Comparar dosis altas o bajas de prednisona en inducción de remisión (≥ o < 0,5 mg/Kg/d)
End point: 1) Normalización transaminasas a los 6 meses, 2) Remisión a los 6 meses

	<0.50 mg/kg/day (n = 170)	≥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

Pape et al. Clin Gastroenterol Hepatol 2019

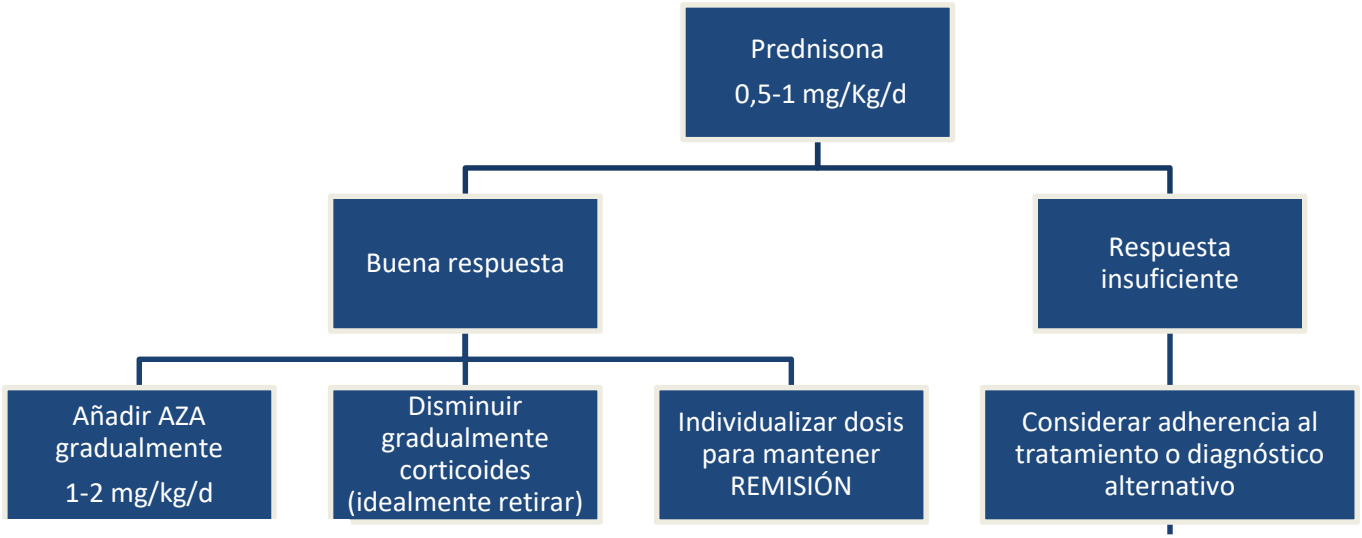
Hay alguna alternativa a la Prednisona?

RESPUESTA AL TRATAMIENTO



Manns et al. Gastroenterology 2010

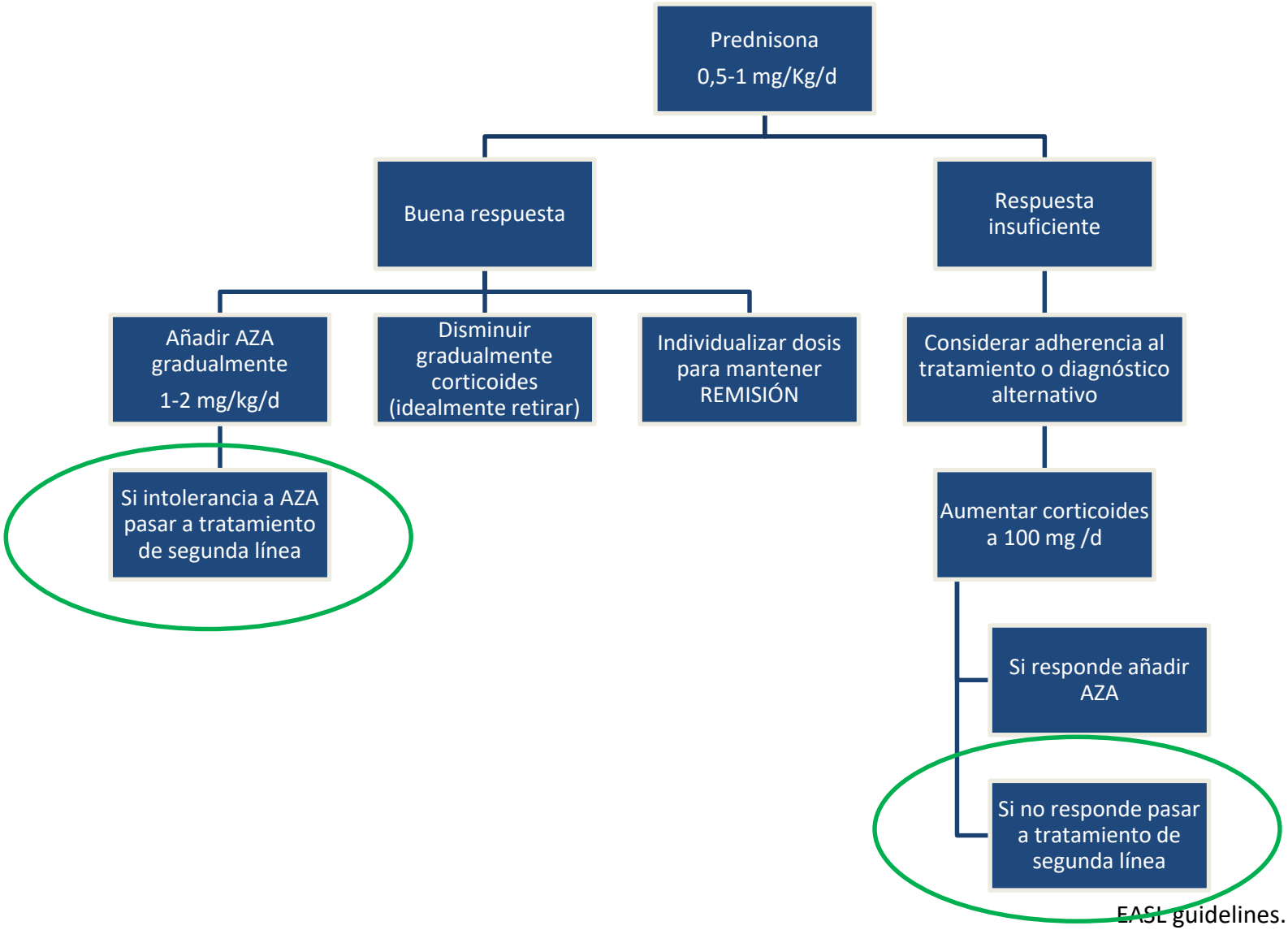
Y si no responde?



Prednisona 60 mg/d y mantener por 1 mes solo o con AZA

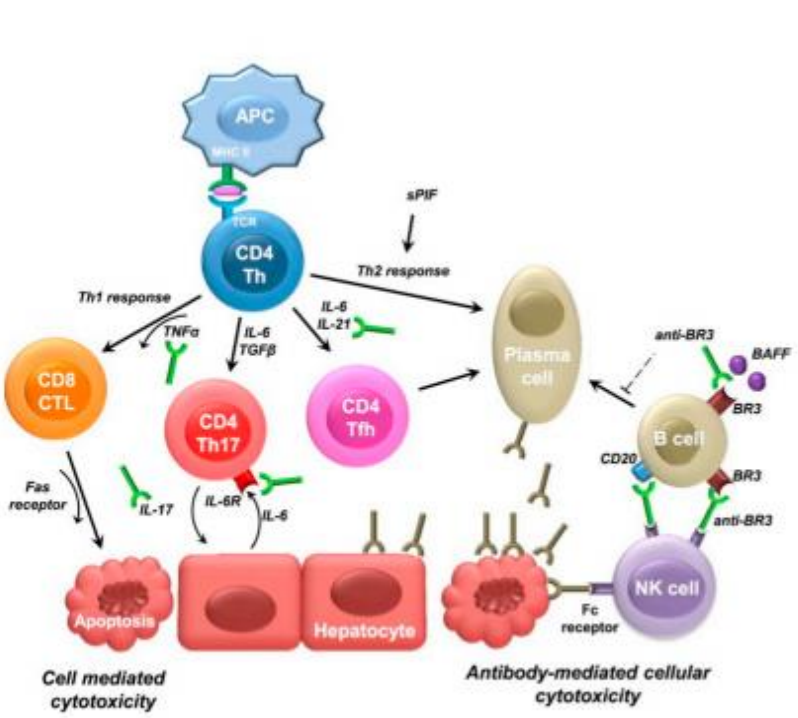
EASL guidelines. J Hepatol 2015
AASLD guidelines. Hepatology 2010

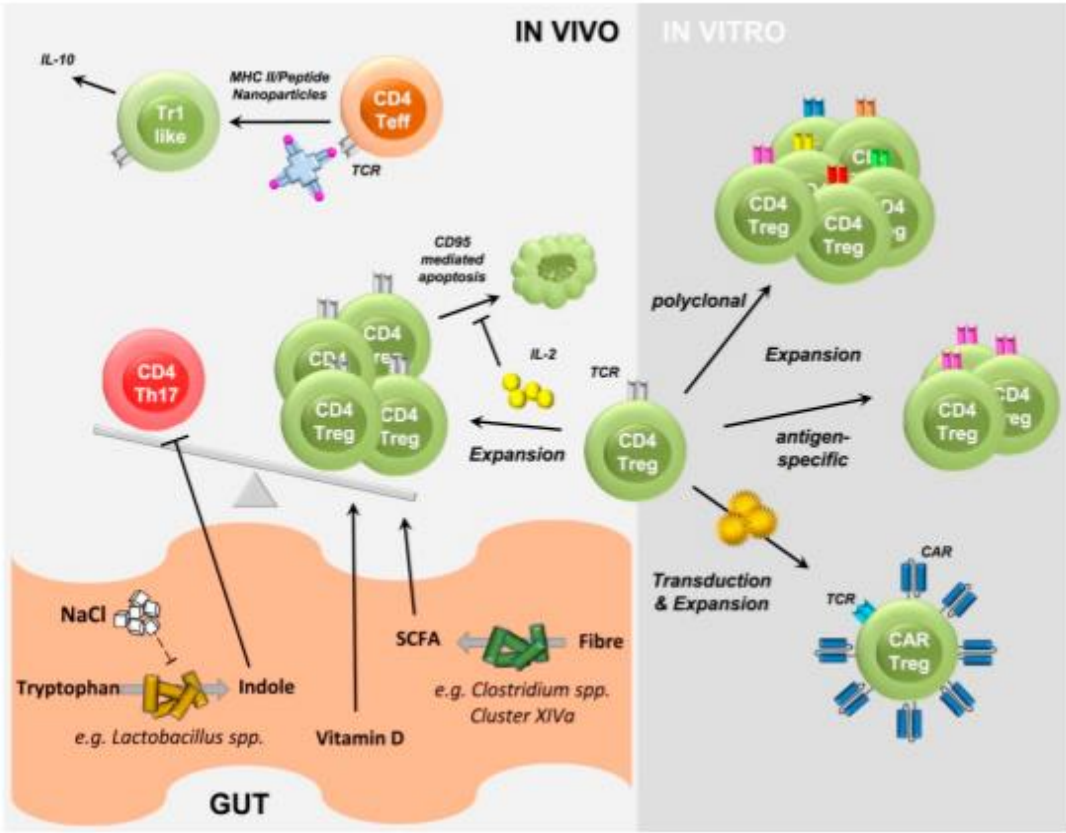
Y si no responde?



EASL guidelines. J Hepatol 2015

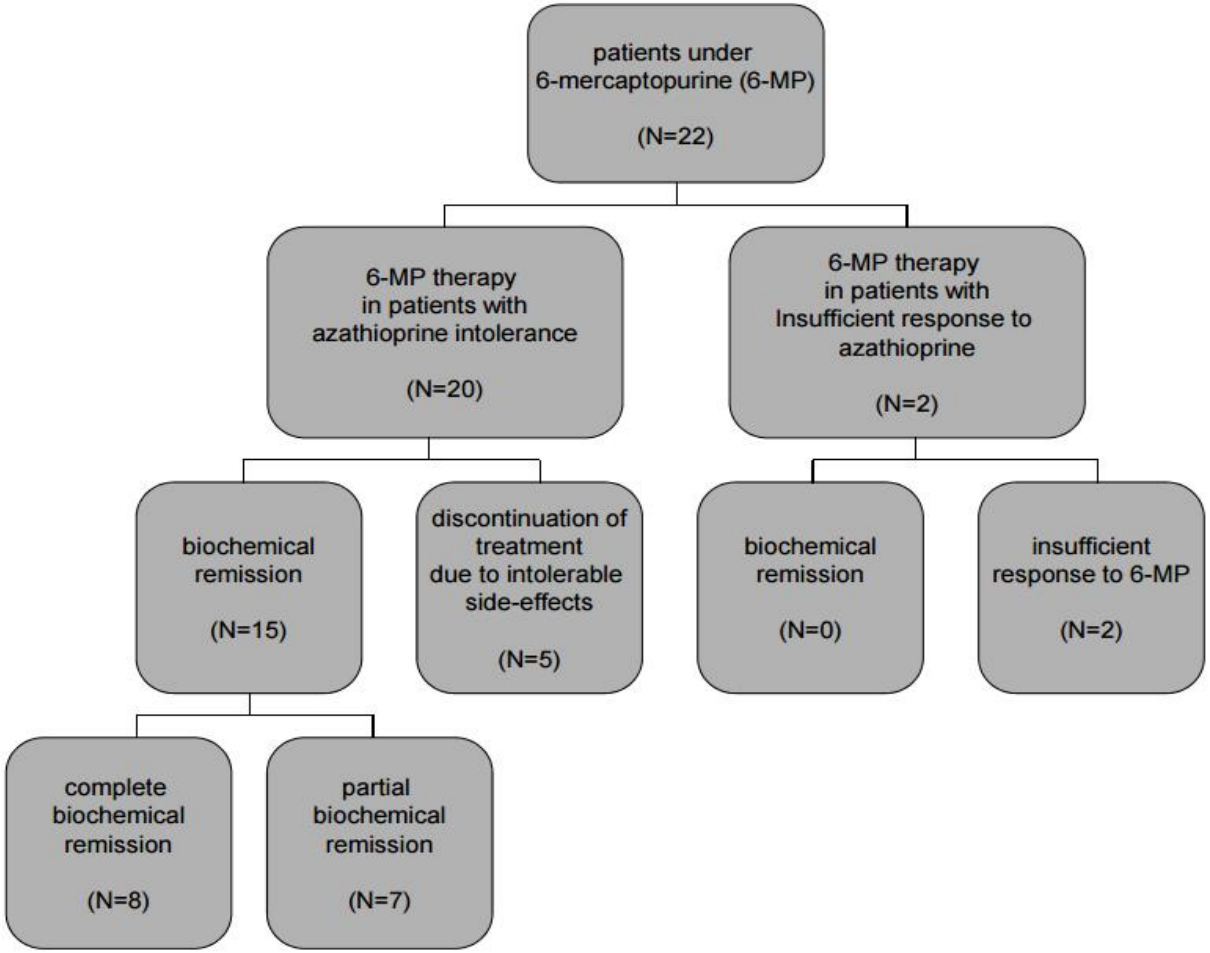
Tratamiento de Segunda Línea





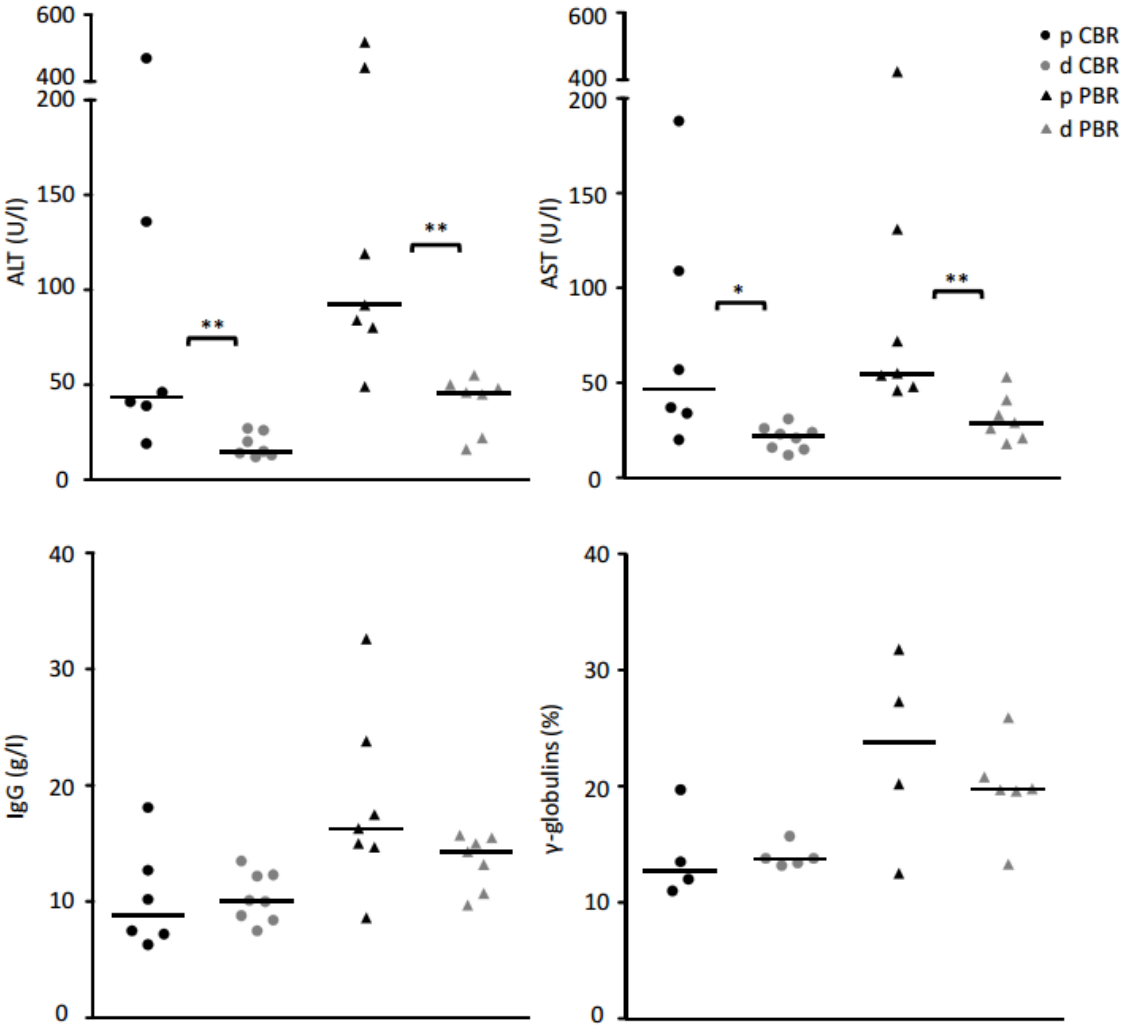
Taubert et al. J Autoimmunity 2018

Tratamiento de Segunda Línea



Hübener et al. Clin Gastroenterol Hepatol 2017

Tratamiento de Segunda Línea

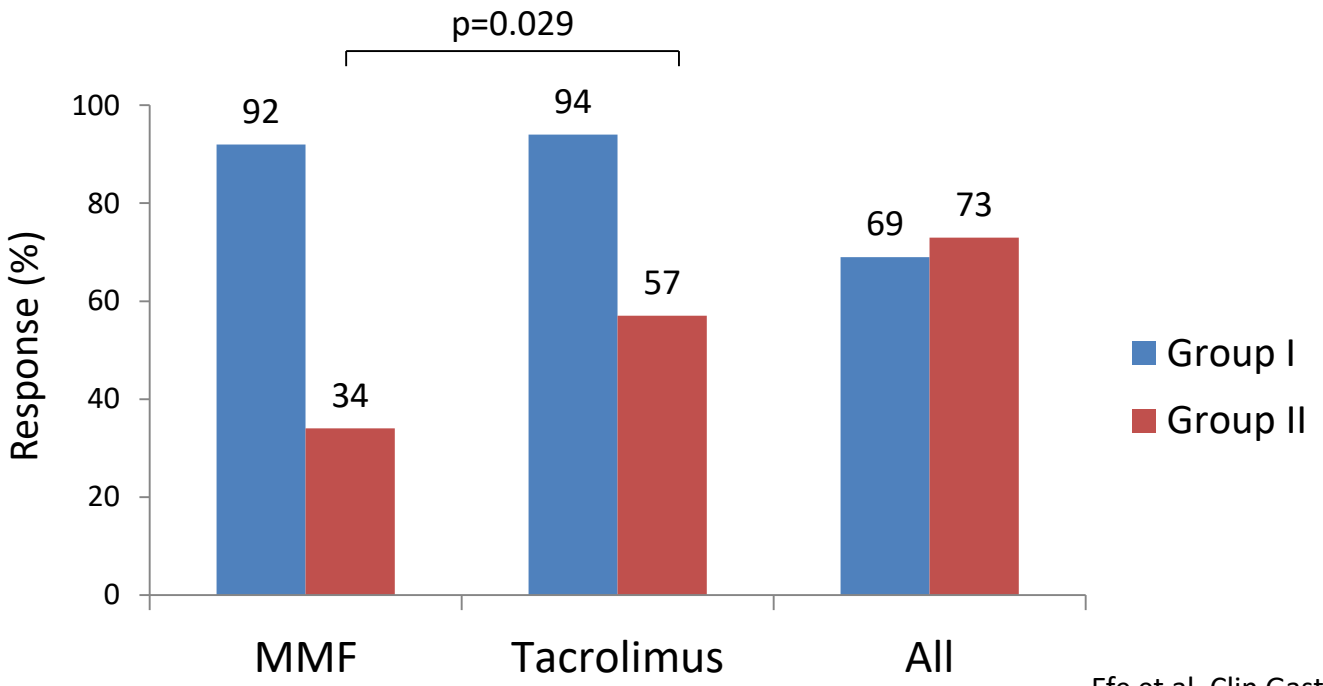


Hübener et al. Clin Gastroenterol Hepatol 2017

Tratamiento de Segunda Línea

	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)

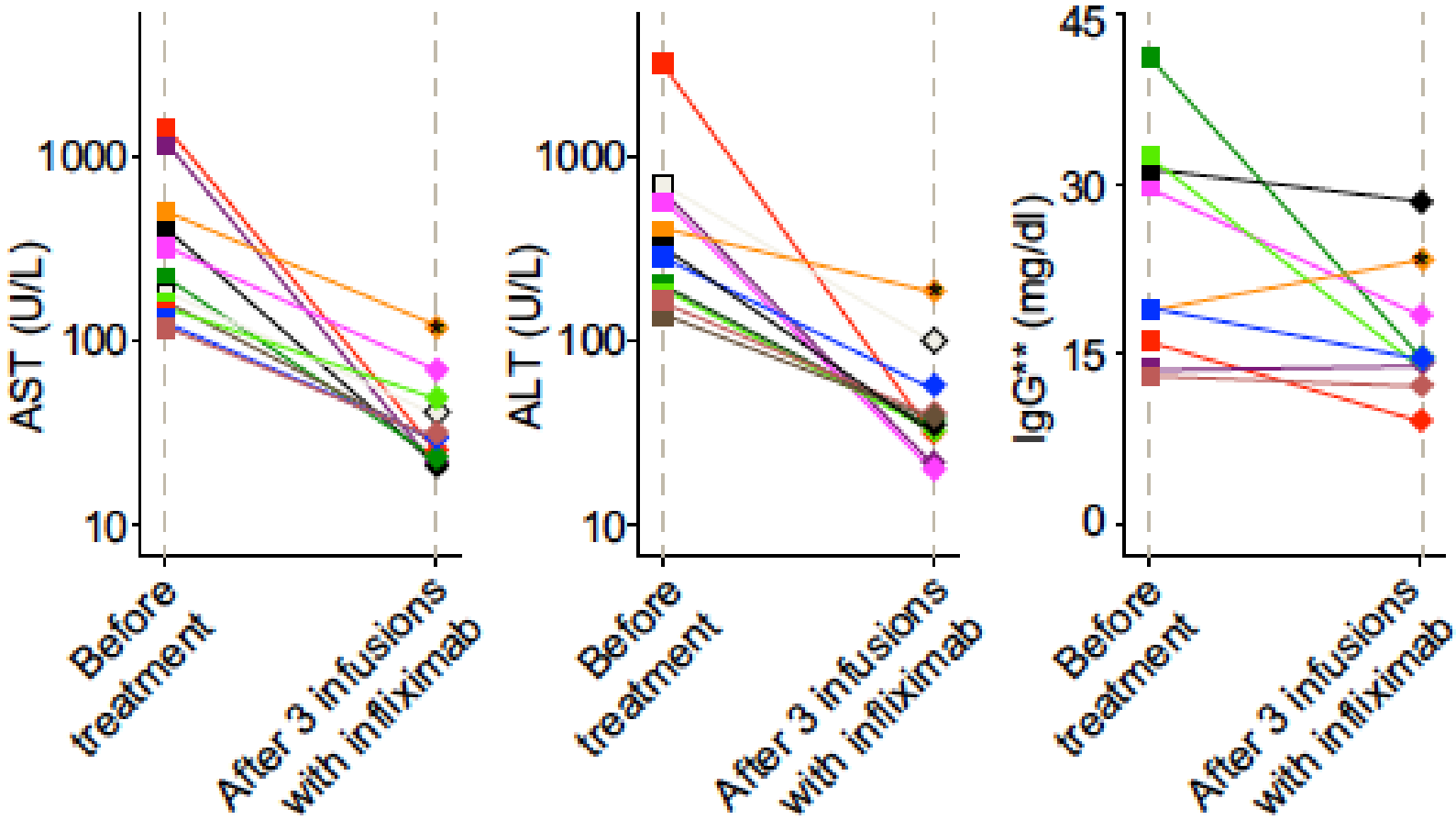
Group I: responded to SOC, switched due to side effects
Group II: insufficient response to SOC



Efe et al. Clin Gastroenterol Hepatol 2017

Tratamiento de Segunda Línea

Infliximab



Weiler-Normann C et al. J. Hepatol. 2013; 58: 529

Tratamiento de Segunda 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 on-going 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 *herpes simplex* 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

Weiler-Normann C et al. J. Hepatol. 2013; 58: 529

Tratamiento de Segunda Línea

22 pacientes de Inglaterra, Alemania y Canadá
Retrospectivo
Tratamiento con Rituximab
Respuesta bioquímica a las 24 semanas post-tratamiento
Reducción de prednisona

Mejoría de transaminasas y albúmina
No impacto en bilirrubina o INR

Figure 1: Changes in Prednisolone dose post therapy

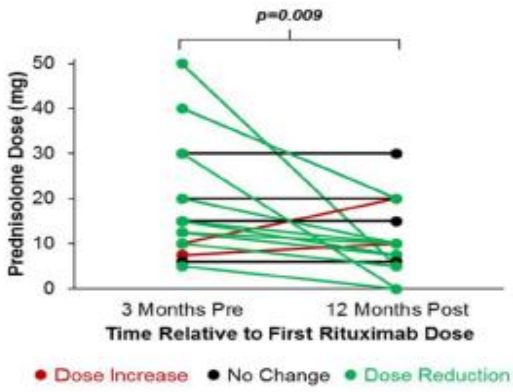
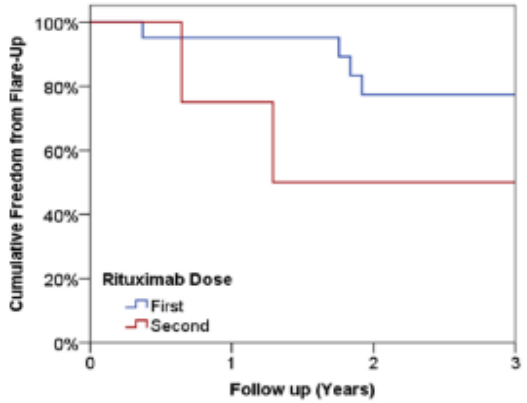


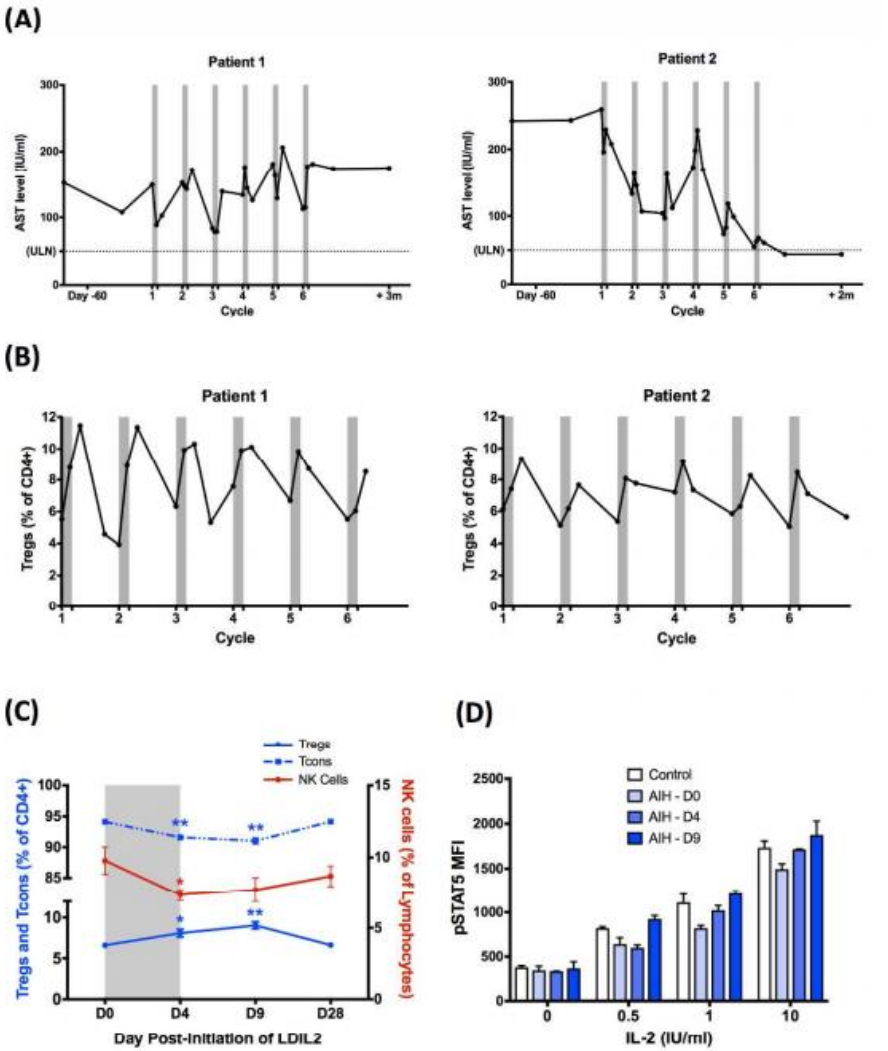
Figure 2: Freedom from flare up following Rituximab therapy



Than et al. EASL 2018

Tratamiento de Segunda Línea

Patient Characteristics	Patient 1
Age (years)	20
Sex	Female
Age at diagnosis (years)	13
Duration of disease (years)	7
Serology	SMA^{+} (1/160)
IAIHG score	8
Immunosuppression at baseline	Tacrolimus 1 mg q.d. MMF 1 g b.i.d. Prednisolone 15 mg q.d.
Liver histology	Severe AIH with cirrhosis
Baseline serum tests (normal range)	
AST (10-50 IU/mL)	149
Globulin (25-35 g/L)	53
IgG (6.3-18.1 g/L)	29.4
Albumin (35-50 g/L)	42
Bilirubin (3-20 μmol/L)	40
Platelet (150-450 × 10^9/L)	152
INR (0.90-1.20)	1.17
Serum tests at end of treatment	
AST (10-50 IU/mL)	174
Globulin (25-35 g/L)	49
IgG (6.3-18.1 g/L)	30.2
Albumin (35-50 g/L)	37
Bilirubin (3-20 μmol/L)	33
Platelet (150-450 × 10^9/L)	132
INR (0.90-1.20)	1.07



Lim et al. Hepatology 2018

Tratamiento de Segunda Línea

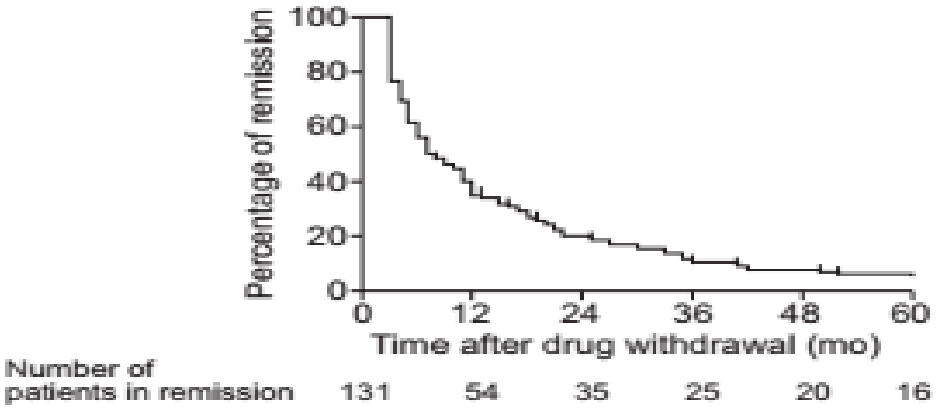
- Ianalumab→ Inhibidor de BAFF
- Inhbidores de TLR4
- Otras: dieta, probioticos, suplementos de vitamin D
- CAR-Treg cells

Clinicaltrials.gov

Tratamiento para siempre?

Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission

Nicole M.F. van Gerven[1,†], Bart J. Verwer[1,†], Birgit I. Witte[2,†], Bart van Hoek[3,†], Minneke J. Coenraad[3,†], Karel J. van Erpecum[4,†], Ulrich Beuers[5,†], Henk R. van Buuren[6,†], Rob A. de Man[6,†], Joost P.H. Drenth[7,†], Jannie W. den Ouden[8,†], Robert C. Verdonk[9,†], Ger H. Koek[10,†], Johannes T. Brouwer[11,†], Maureen M.J. Guichelaar[12,†], Chris J.J. Mulder[1,†], Karin M.J. van Nieuwkerk[1,†], Gerd Bouma[1,*,†]



137 patients
- 47% relapsed
- 42% loose biochemical remission

van Gerven et al. J Hepatol 2013

Tratamiento para siempre?

Patient selection based on treatment duration and liver biochemistry increases success rates after treatment withdrawal in autoimmune hepatitis

Johannes Hartl[1], Hanno Ehlken[1], Christina Weiler-Normann[1], Marcial Sebode[1], Benno Kreuels[1,2], Nadine Pannicke[1], Roman Zenouzi[1], Claudia Glaubke[1], Ansgar W. Lohse[1], Christoph Schramm[1,*]

Variable	Relapse group (n=13)	Remission group (n=15)
Age	41 (20-64)	39 (18-73)
Gammaglobulins (%)	16.9%	12.9%
IgG levels (g/L)	12.7 (9.6-17)	10.3 (5.2-12)
ALT (IU/mL)	20 (14-24)	14.7 (8-17)
Time to achieve remission (months)	5.3 (2-13)	2.7 (1-5)
Cirrhosis, n(%)	2 (15%)	0

Hartl J et al. J Hepatol 2015

Tratamiento para siempre?

PREDICTIVE FACTORS

Favorable	Unfavorable
▪ Age > 40 ▪ No cirrhosis ▪ Time to remission < 5 months ▪ Adherence to treatment ▪ Normal liver tests ▪ Absence of plasma cells in the liver biopsy	▪ Concomitant autoimmune diseases ▪ Cirrhosis ▪ Disease progression during treatment

Czaja, A. J. APT 2014

Seguimiento

- Monitorizar la progresión de la fibrosis
- Estudio de VE en pacientes con cirrosis
- Ecografía semestral para detección de carcinoma hepatocelular en pacientes con cirrosis

Janmohamed & Hischfield. Frontline Gastroenterol 2019

Seguimiento

Elastografía en Hepatitis Autoinmune

	Histological fibrosis stage		
	F ≥2 (≥5.8 kPa)	F ≥3 (≥10.5 kPa)	F = 4 (≥16.0 kPa)
<3 months (n = 34) Group 1			
AUROC	0.68	0.80	0.71
Sensitivity	0.71	0.60	0.60
Specificity	0.66	0.88	0.93
Positive predictive value	0.65	0.75	0.60
Negative predictive value	0.58	0.85	0.93
6-12 months (n = 25) Group 2			
AUROC	0.97	1.00	1.00
Sensitivity	0.94	1.00	1.00
Specificity	0.88	1.00	1.00
Positive predictive value	0.94	1.00	1.00
Negative predictive value	0.88	1.00	1.00
>4 years (n = 27) Group 3			
AUROC	0.94	0.96	1.00
Sensitivity	1.00	0.95	1.00
Specificity	0.77	0.94	1.00
Positive predictive value	0.80	0.80	1.00
Negative predictive value	0.88	0.94	1.00

Hartl et al. J Hepatol 2016

Seguimiento

Elastografía en Hepatitis Autoinmune

- 112 pacientes con cirrosis
- El **59% y 51%** de los pacientes presentaron un **FS inferior** a los puntos de corte habituales para el **diagnóstico de cirrosis**, 14kPa i 12,5kPa, respectivamente
- Los pacientes con HTP presentaban un FS más elevado (9,4 vs 12, 5 kPa)
- Criterios de Baveno útiles para descartar VE. VPN 100% y ahorro de 51% de endoscopias.

Llovet et al. AEEH 2019
EASL 2019

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