LA INCOMPATIBILIDAD DONANTE / RECEPTOR PARA LOS ALELOS DE LA GLUTATION S-TRANSFERASA T1 CONSTITUYE UN FACTOR DE RIESGO PARA EL RECHAZO CRÓNICO DEL INJERTO HEPÁTICO.

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HEPATITIS AUTOINMUNE “DE NOVO” POSTRASPLANTE HEPÁTICO

- La hepatitis autoinmune “de novo” postrasplante hepático fue descrita por primera vez en niños en 1996 y en adultos en 1997.

  Kerkar, Abstr Hepatology 1996; Hernandez Albujar, abstr J. Hepatology 1997

- No descripciones de CBP ni CEP “de novo” en Trasplante hepático, ni HAI “de novo” en otros trasplantes de órganos sólidos.

- En el año 2001 describimos la presencia de anticuerpos Anti-GSTT1 en la hepatitis inmune “de novo”.

Antibodies against glutathione S-transferase T1 (GSTT1) in patients with *de novo* immune hepatitis following liver transplantation

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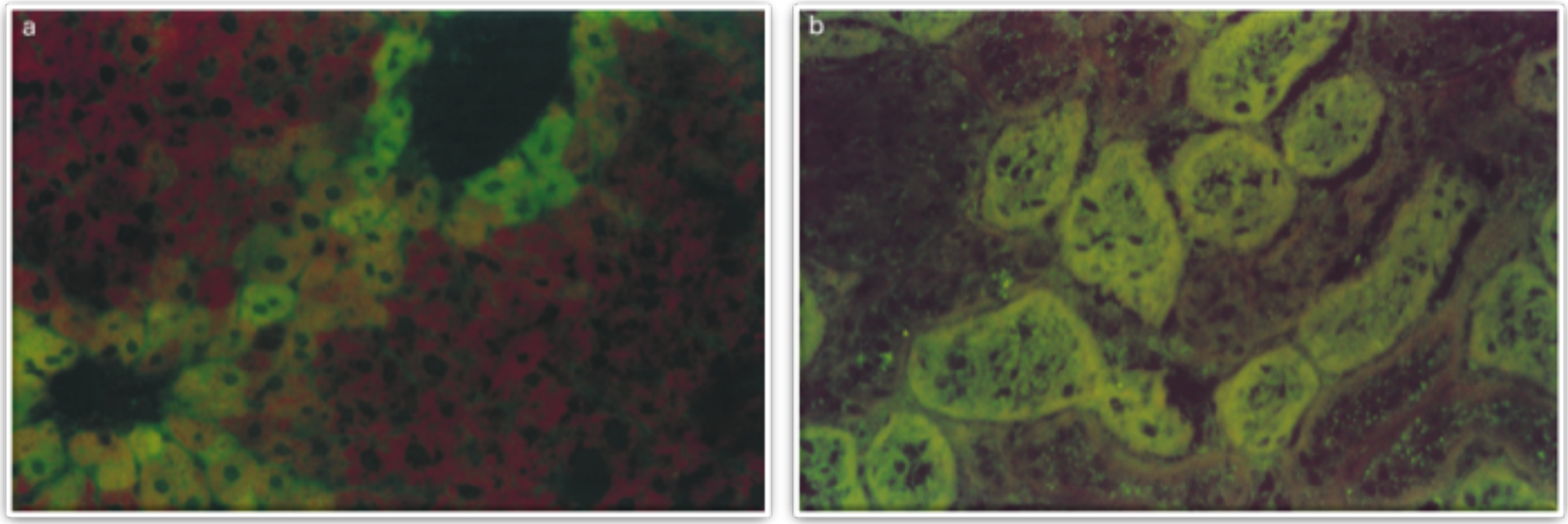


Clin Exp Immunol 2001;126: 535-539

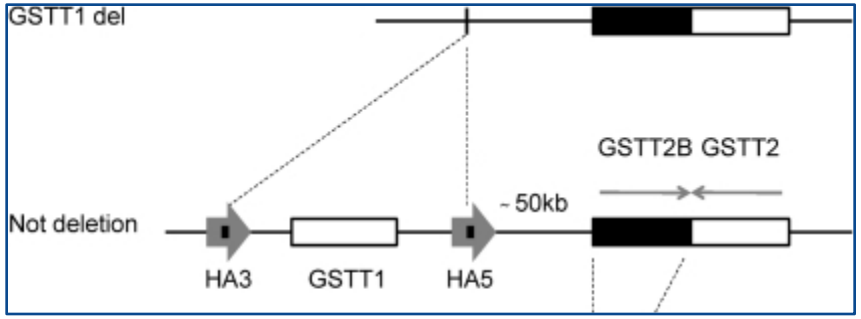
POLIMORFISMOS GLUTATION S-TRASFERASAS

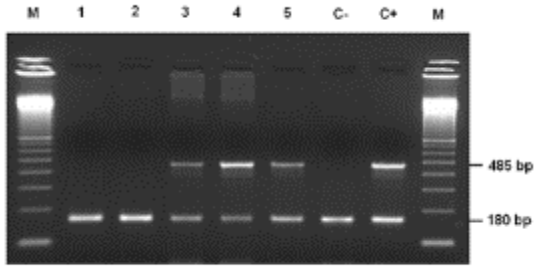
Class or superfamily	Gene	Allele	Alterations in gene or in nucleotides	Protein or amino acids affected
Alpha	*GSTA2*	*GSTA2*A* *GSTA2*B*	C335, A629 G335, C629	Thr^{112}, Glu^{210} Ser^{112}, Ala^{210}
Mu	*GSTM1*	*GSTM1*A* *GSTM1*B* *GSTM1*0* *GSTM1*1×2*	G519 C519 Gene deletion Gene duplication	Lys^{173} Asn^{173} No protein Overexpression
	GSTM3	*GSTM3*A* *GSTM3*B*	Wildtype 3 bp deletion in intron 6	Wildtype protein Primary structure unaltered
	GSTM4	*GSTM4*A* *GSTM4*B*	Wildtype Changes in introns	Wildtype Unchanged
Pi	*GSTP1*	*GSTP1*A* *GSTP1*B* *GSTP1*C* *GSTP1*D*	A313, C341, C555 G313, C341, T555 G313, T341, T555 A313, T341	Ile^{105}, Ala^{114}, Ser^{185} Val^{105}, Ala^{114}, Ser^{185} Val^{105}, Val^{114}, Ser^{185} Ile^{105}, Val^{114}
Theta	*GSTT1*	*GSTT1*A* *GSTT1*0*	Unique gene Gene deletion	Unique protein No protein
	GSTT2	*GSTT2*A* *GSTT2*B*	A415 G415	Met^{139} Ile^{139}
Zeta	*GSTZ1*	*GSTZ1*A* *GSTZ1*B* *GSTZ1*C* *GSTZ1*D*	A94; A124; C245 A94; G124; C245 G94; G124; C245 G94; G124; T245	Lys^{32}; Arg^{42}; Thr^{82} Lys^{32}; Gly^{42}; Thr^{82} Glu^{32}; Gly^{42}; Thr^{82} Glu^{32}; Gly^{42}; Met^{82}

Sherratt, Enzyme systems that metabolise drugs and other xenobiotics, 2001

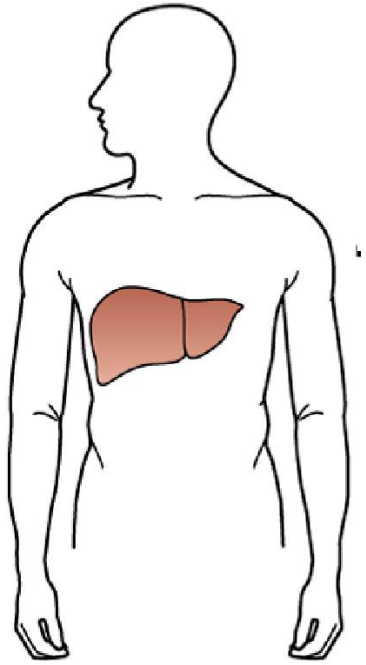
GLUTATION S-TRANSFERASA T1

20% de la población caucásica no tiene el gen GSTT1
GSTT1*A/A, GSTT1*A/0, GSTT1*0/0





GSTT1



Rec-/Don+

La enzima GSTT1 se expresa altamente en las células del endotelio vascular y de los conductos biliares

Pemble et al., 1994

Glutathione S-Transferase T1 Mismatch Constitutes a Risk Factor for *De Novo* Immune Hepatitis After Liver Transplantation

Isabel Aguilera,[1] Jose M. Sousa,[2] Francisco Gavilán,[3] Angel Bernardos,[2] Ingeborg Wichmann,[1] and Antonio Nuñez-Roldán[1]

Table 3. Distribution of the 4 Possible GSTT1 Combinations Between Donor and Recipient of a LT

Post transplant Immune Hepatitis Status (N-110)	Recipient/Donor Phenotype			
	+/−	+/+	−/−	−/+
No response	23	66	6	3
With *de novo* IH	0	0	0	6
With anti-GSTT1 ab*	0	0	0	12

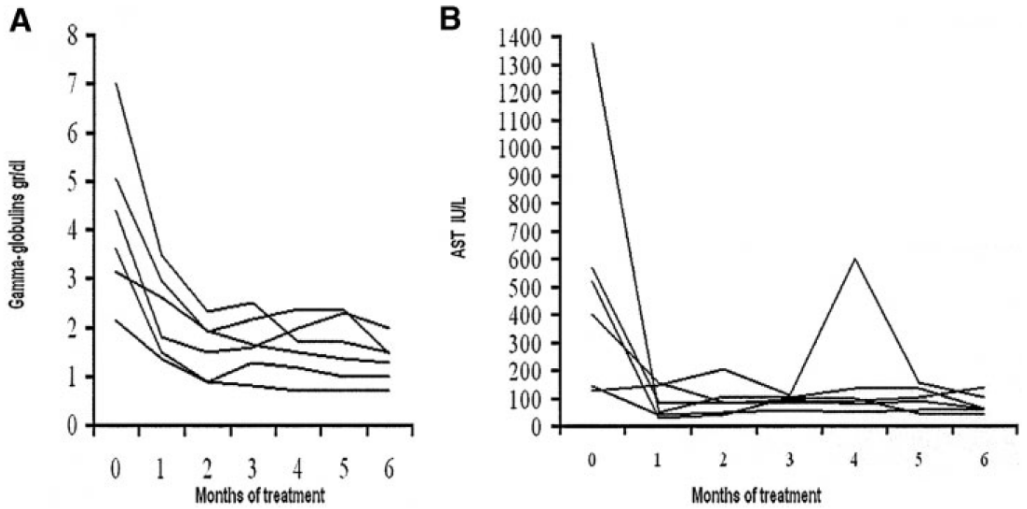


Figure 1. Evolution of (A) gammaglobulin levels and (B) AST levels in the 6 patients with *de novo* IH after 6 months of steroid treatment. Patient 5 suffered a relapse in the context of a transient suppression of steroids 3 months after LT.

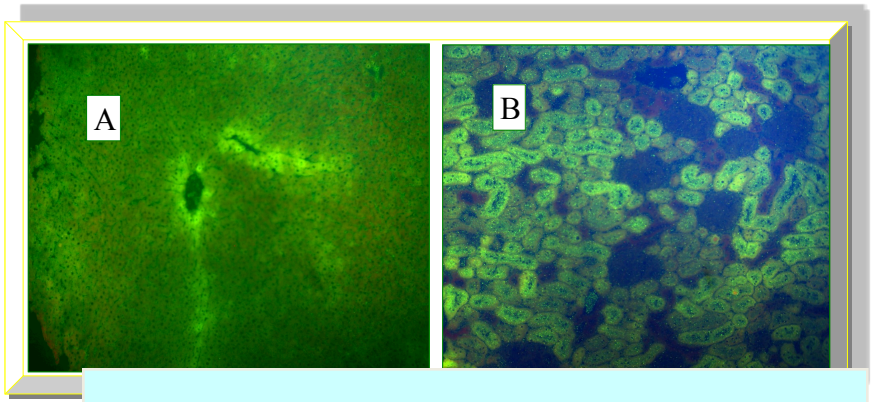
Liver Transpl 2004;10: 1166–1172

Antibodies Against Glutathione S-Transferase T1 (GSTT1) in Patients With GSTT1 Null Genotype as Prognostic Marker: Long-Term Follow-Up After Liver Transplantation

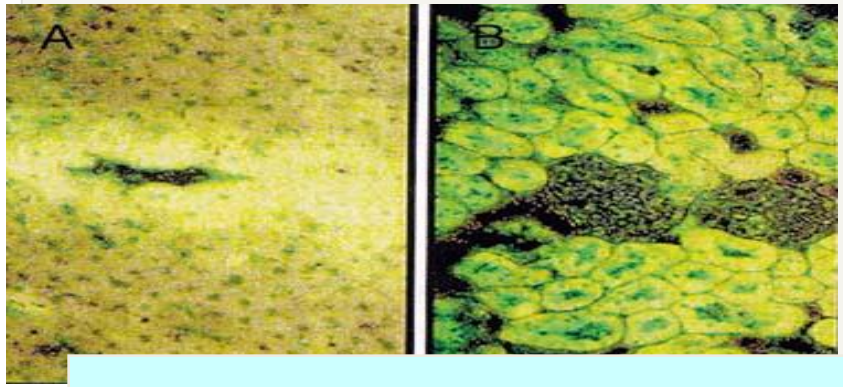
TABLE 1. Baseline characteristics of the LTX patients with atypical autoantibodies and their immunological, genotypical, and clinical features

Patient	Age at LTX (years)	Recipient/ donor sex	Indication for TX (type of transplantation)	Maximal titer of atypical autoantibodies	Interval between LTX and diagnosis of de novo immune hepatitis (months)	Patient GSTT1 genotype	Donor GSTT1 genotype	Diagnosis of de novo immune hepatitis with graft dysfunction
1LTX	20	M/M	Biliary atresia	>1:640	14	Null	Positive	Yes
2LTX	57	M/M	HCV cirrhosis	>1:640	20	Null	Positive	Yes
3LTX	43	M/M	OH cirrhosis	1:640	26	Null	Positive	Yes
4LTX	57	M/F	HCV/HBV cirrhosis	1:640	20	Null	Positive	Yes
5LTX	62	F/M	HCV cirrhosis	>1:640	12	Null	Positive	Yes
6LTX	38	M/M	HBV cirrhosis	1:640	6	Null	Positive	Yes
7LTX	50	F/M	HBV cirrhosis	1:320	14	Null	Positive	Yes
8LTX	58	M/M	OH cirrhosis	1:640	24	Null	Positive	Yes
9LTX	55	M/F	HCV cirrhosis	1:640	31	Null	Positive	Yes
10LTX	56	M/F	OH cirrhosis	1:640	16	Null	Positive	Yes
11LTX	28	F/F	Cryptogenic cirrhosis	1:80	97	Null	Positive	Yes
12LTX	64	F/M	HCV cirrhosis	>1:640	7	Null	Positive	Yes
13LTX	56	M/M	Primary sclerosing cholangitis	>1:640	16	Null	Positive	Yes
14LTX	46	M/M	HCV cirrhosis	1:160	19	Null	Positive	Yes
15LTX	41	M/M	OH cirrhosis	1:640	47	ND	ND	Yes
16LTX	50	M/F	OH cirrhosis	1:80	22	ND	ND	Yes
17LTX	37	M/F	OH cirrhosis	>1:640	25	ND	ND	Yes
18LTX	29	M/M	Autoimmune cirrhosis	1:160	63	Null	Positive	Yes
19LTX	60	F/F	HCV cirrhosis	1:160	28	Null	Positive	Yes
20LTX	51	M/M	OH cirrhosis	>1:640	42	Null	Positive	Yes
21LTX	46	F/M	OH cirrhosis	1:320	NA	Null	Positive	No
22LTX	58	M/F	OH cirrhosis	1:80	NA	Null	Positive	No
23LTX	37	M/F	OH cirrhosis	1:80	NA	Null	Positive	No
24LTX	58	M/F	HCV cirrhosis	>1:640	NA	Null	Positive	No
25LTX	30	M/M	OH cirrhosis	1:640	NA	Null	Positive	No
26LTX	43	M/F	OH cirrhosis	1:80	NA	ND	ND	No
27LTX	63	M/F	OH cirrhosis	1:640	NA	ND	ND	No
28LTX	53	F/F	HCV cirrhosis	>1:640	NA	Null	Positive	Uncertain
29LTX	60	M/M	OH cirrhosis	1:640	NA	Null	Positive	Uncertain

LTX, orthotopic liver transplantation; M, male; F, female; HBV, hepatitis B virus; HCV, hepatitis C virus; OH, alcoholic hepatitis; ND, genotype not analyzed; NA, not applicable.



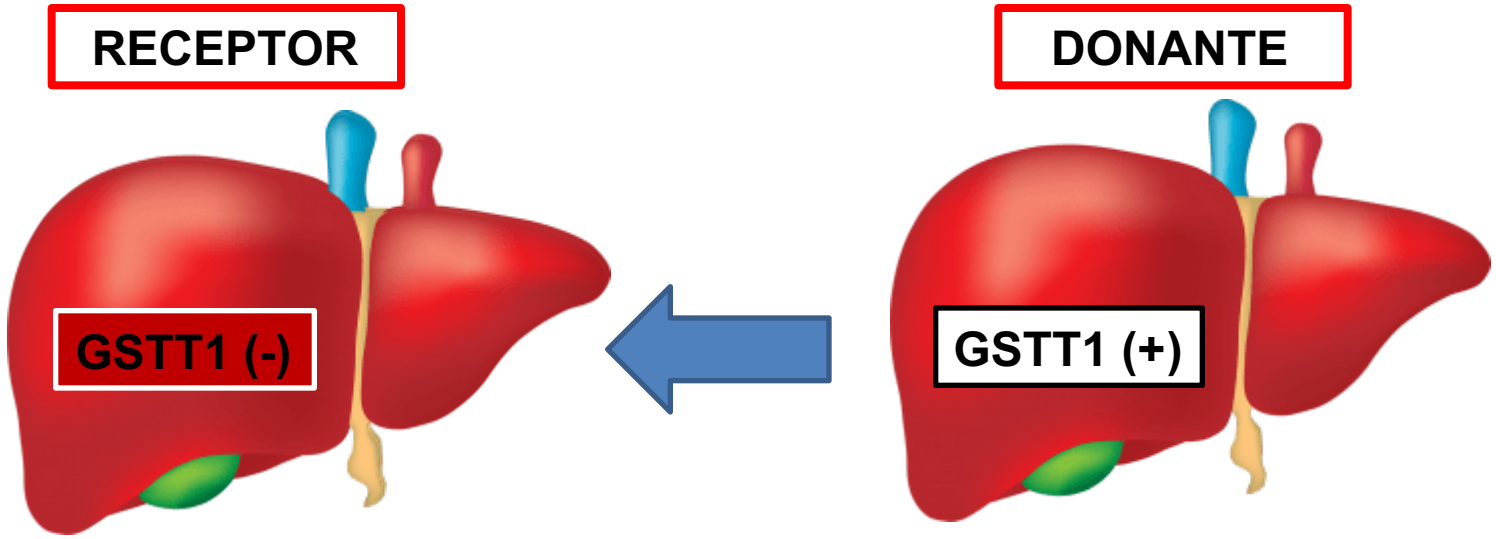
Aguilera, Clin Exp Inmunol Dic 2001

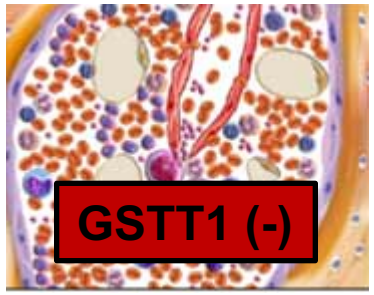


Salcedo, Hepatology Feb 2002

Rodríguez-Mahou, Transplantation 2007

TRASPLANTE HEPÁTICO
DONANTE GSTT1 (+) / RECEPTOR GSTT1 (-)

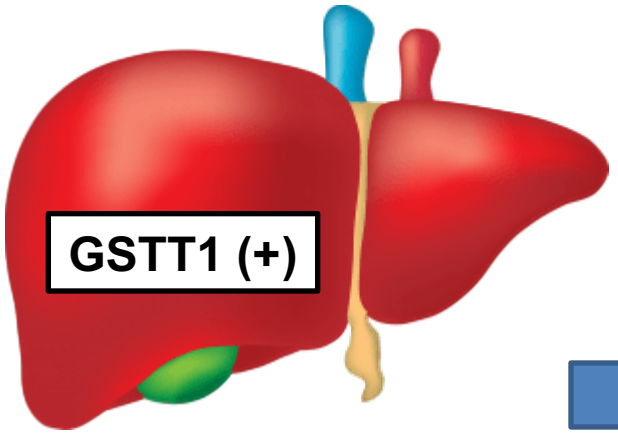


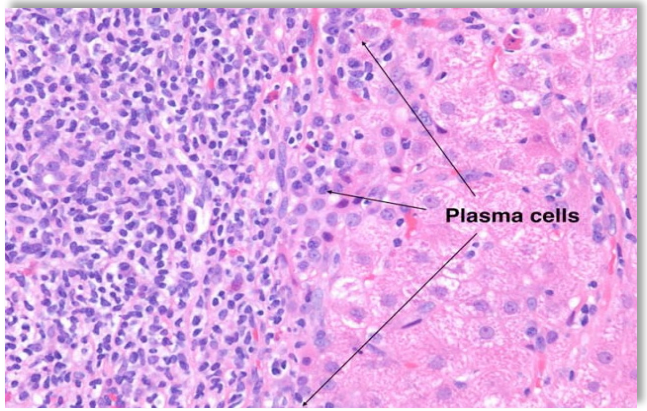


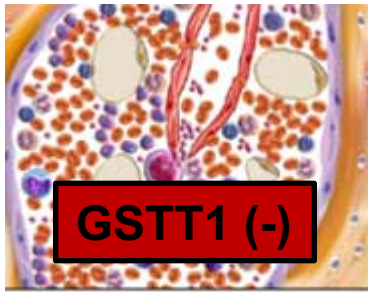
INMUNOLOGICAMENTE

TRASPLANTE HEPÁTICO
DONANTE GSTT1 (+) / RECEPTOR GSTT1 (-)

RECEPTOR





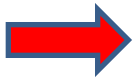


INMUNOLOGICAMENTE

HEPATITIS INMUNE "DE NOVO"
HEPATITIS DE CÉLULAS PLASMÁTICAS
RECHAZO RICO EN CELULAS PLASMÁTICAS

2016 Comprehensive Update of the Banff Working Group on Liver Allograft Pathology: Introduction of Antibody-Mediated Rejection

Older (discouraged) terminology	Newer (preferred) terminology
Humoral rejection	Antibody-mediated rejection (AMR)
(Acute) cellular rejection	T cell–mediated rejection (TCMR)
De novo auto-immune hepatitis	Plasma cell rich–rejection
Plasma cell hepatitis	



Demetris AJ, Am J Transpl. 2016;16:2816–2835

OBJETIVOS Y CRITERIOS DE INCLUSIÓN

PAPEL DE LA INCOMPATIBILIDAD GSTT1 EN EL RECHAZO CRÓNICO.

ESTUDIO RETROSPECTIVO

CRITERIOS DE INCLUSIÓN:

- Disponibilidad de ADN del donante y del receptor. n= 611 pacientes (2003-2016)
- Seguimiento >6 meses
- Exclusión retrasplantante

DEFINICIÓN DE “MISMATCH” O INCOMPATIBILIDAD PARA GSTT1

MISTMACH

- Receptor nulo (-) /donante positivo (+)

MATCH

- Receptor nulo (-) / donante nulo (-)
- Receptor positivo (+) / donante nulo (-)
- Receptor positivo (+) /donante positivo (+)

DIAGNÓSTICO DE RECHAZO CRÓNICO

Parameter	Early CR *(at least 2 findings should be present)*	Late CR *(at least 2 findings should be present)*
Small bile ducts (<60 μm)	Senescence-related changes involving a majority of ducts; bile duct loss	Degenerative changes in remaining bile ducts, loss in ≥50% of portal tracts
Terminal hepatic venules and zone 3 hepatocytes	*Perivenular mononuclear inflammation* Lytic zone 3 necrosis and inflammation Mild perivenular fibrosis	Focal obliteration Variable inflammation Moderate to severe (bridging) fibrosis
Portal tract hepatic arterioles	Occasional loss involving <25% of portal tracts	Loss involving >25% of portal tracts
Large perihilar hepatic artery branches	Intimal inflammation, focal foam cell deposition without lumenal compromise	Lumenal narrowing by subintimal foam cells Fibrointimal proliferation
Large perihilar bile ducts	Inflammation damage and focal foam cell deposition	Mural fibrosis
Other	So-called "transition" hepatitis with spotty necrosis of hepatocytes	Sinusoidal foam cell accumulation; marked cholestasis

"El diagnóstico final de RC debe basarse en una combinación de hallazgos clínicos / radiológicos / de laboratorio e histopatológicos"

*- Demetris A, Update of the **International Banff Schema for Liver Allograft Rejection**: working recommenda-tions for the histopathologic staging and reporting of chronic rejection. An international panel. **Hepatology. 2000**;31:792–799*
*- Demetris AJ, 2016 comprehen-sive update of the Banff Working Group on Liver Allograft Pathology: introduction of antibody-mediated rejection. **Am J Transpl. 2016**;16:2816–2835*
- Tabla: Modificación: Choudhary, J Clic Exp Hepatology 2017

CARACTERÍSTICAS DE LOS PACIENTES

Patients characteristics n=611	
Recipient age (mean)	53.1 +-9.4 (16-70)
Donor age (mean)	53.3 +-17.7 (8-86)
Gender	
Female	146 (23.9 %)
Male	465 (76.1 %)
Primary liver disease	
Alcohol	**246 (40.3 %)**
Virus-induced	**229 (37.5 %)**
Autoimmune etiology*	35 (5.7 %)
NASH	22 (3.6 %)
FLF	12 (2%)
Criptogenetic	17 (2.8 %)
Others	50 (8.2 %)
Induction therapy	
Cyclosporine	99 (16.2%)
Tacrolimus	**512 (83.8 %)**

*Autoimmune etiology includes: Primary biliary cholangitis (PBC), primary sclerosing cholangitis (PEC) and autoimmune hepatitis (AIH). NASH: non-alcoholic steatohepatitis; FLF: fulminant liver failure

COMPARACIÓN MITMACHCH vs MATCH GSTT1

Patients n=611	GSTT1 mismatched n=85 (14%)	GSTT1 matched n=526 (86%)	P-value
Recipient age at transplant (mean +- standard deviation)	53.7 ± 8.7	53+-9.6	NS
Donor age (mean +- standard deviation)	52.4 ± 16.9	53.4 +-17.8	NS
Recipient sex			0.035
Female	28 (32.9 %)	118 (22.4 %)	
Male	57 (67.1 %)	408 (77.6 %)	
Primary liver disease			NS
Alcohol	27 (31.8 %)	219 (41.6 %)	
Virus induced	32 (37.6 %)	197 (37.5 %)	
Autoimmune etiology *	6 (7.1 %)	29 (5.5 %)	
NASH	6 (7.1 %)	16 (3 %)	
FLF	2 (2.4 %)	10 (1.9 %)	
Criptogenetic	3 (3.5 %)	14 (2.7 %)	
Others	9 (10.6 %)	41 (7.8 %)	
Induction therapy			NS
Cyclosporine	16 (18.8 %)	83 (15.8 %)	
Tacrolimus	69 (81.2 %)	443 (84.2 %)	
Exitus	18 (21.2 %)	84 (16 %)	NS

*Autoimmune etiology includes: Primary biliary cholangitis (PBC), primary sclerosing cholangitis (PEC) and autoimmune hepatitis (AIH). NASH: non-alcoholic steatohepatitis; FLF: fulminant liver failure

RECHAZO CRÓNICO: ANÁLISIS UNIVARIANTE

RC 71/611 (11.6 %)

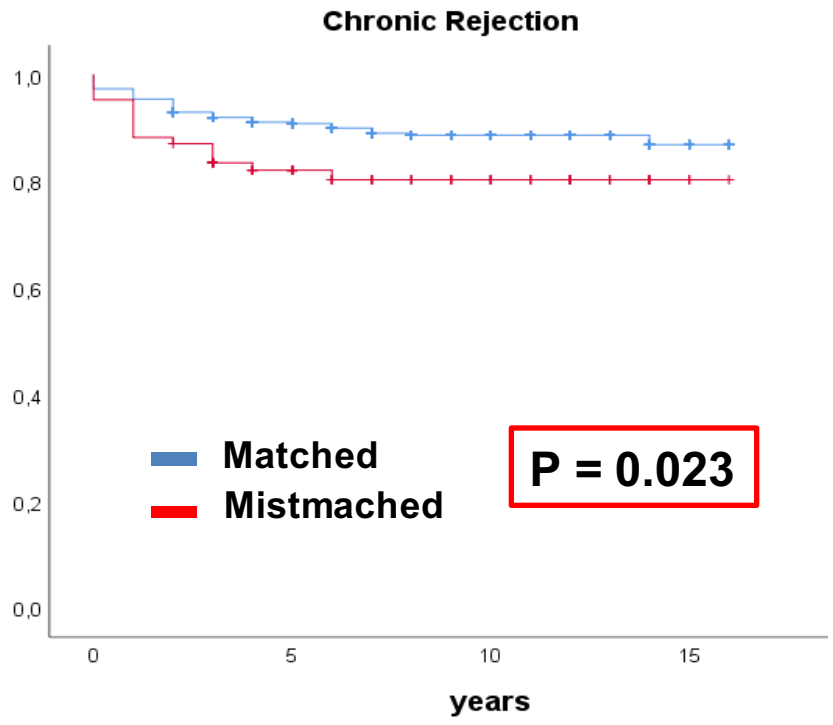
	With CR n=71	Without CR n=540	HR (95% CI)	P Value
Donor/recipient GSTT1				
Matched	55 (77.5 %)	471 (87.2 %)	**1.99 (1.08-3.66)**	**0.026**
Mismatched	16 (22.5 %)	69 (12.8 %)		
Primary liver disease				
Alcohol	26 (36.6 %)	220 (40.7 %)		0.50
Virus-induced	32 (45.1 %)	197 (36.5 %)		0.16
Autoimmune etiology*	3 (4.2 %)	32 (5.9 %)		0.56
NASH	1 (1.4 %)	21 (3.9 %)		0.29
FLF	1 (1.4 %)	11 (2 %)		0.72
Criptogenetic	4 (5.6 %)	13 (2.4 %)		0.12
Others	4 (5.6 %)	46 (8.5 %)		0.40
Recipient sex				
Female	15 (21.1 %)	131 (24.3 %)		0.56
Male	56 (78.9 %)	409 (75.7 %)		
Recipient age	52+-10	53.2+-9.4		0.29
Donor age <40 >40	49.9+-18.1 21 (29.6 %) 50 (70.4 %)	53.7+-17.6 124 (23 %) 416 (77 %)		NS 0.22
Immunosuppression				
Tacrolimus	45 (8.8 %)	467 (91.2%)		**<0.001**
Cyclosporine	26 (26 %)	73 (74 %)		

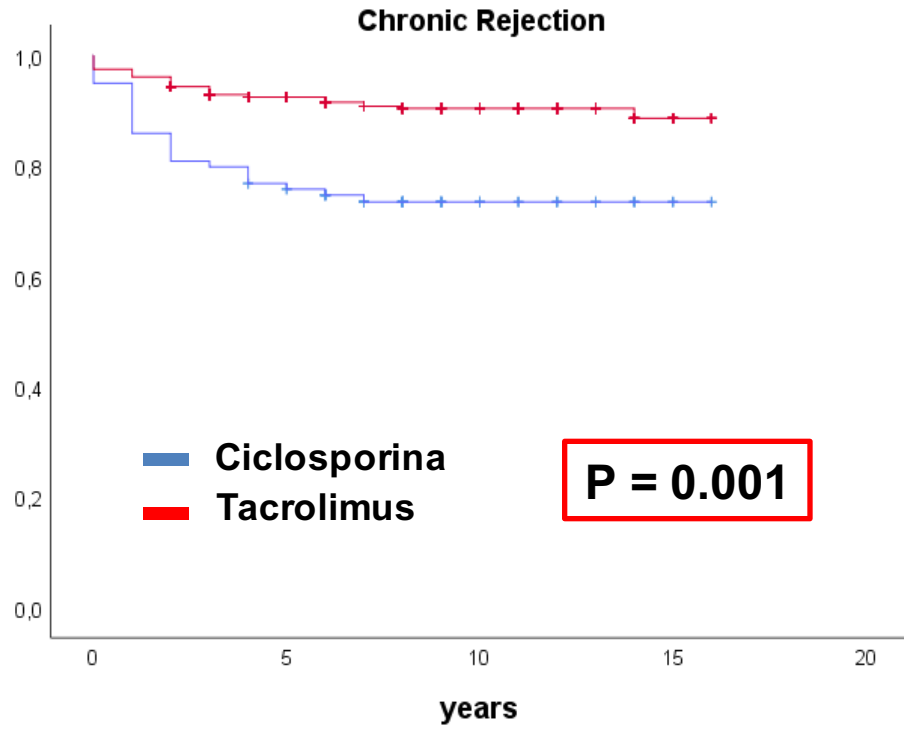
RECHAZO CRÓNICO: ANÁLISIS MULTIVARIANTE

Table 4. Multivariate predictors associated with chronic rejection. Cox regression analysis for chronic rejection

	Hazard ratio	95% confidence interval	P value
GSTT1 mismatch	2.053	1.163-3.623	0.013
Immunosuppression	0.295	0.180-0.483	<0.001

RECHAZO CRÓNICO: GSTT1 E INMUNOSUPRESIÓN





CONCLUSIONES

1. La incompatibilidad para la GTT1 D (+) / R (-) duplica la posibilidad de desarrollar rechazo crónico postrasplante hepático.

2. Es la primera vez que se identifica un antígeno especifico del donante asociado a RC en el trasplante de hígado: GSTT1.

3. El RC en estos pacientes no está asociado a anticuerpos anti-GSTT1 contrariamente al rechazo rico en células plasmáticas.

MUCHAS GRACIAS POR SU ATENCIÓN