

1^a REUNIÓN
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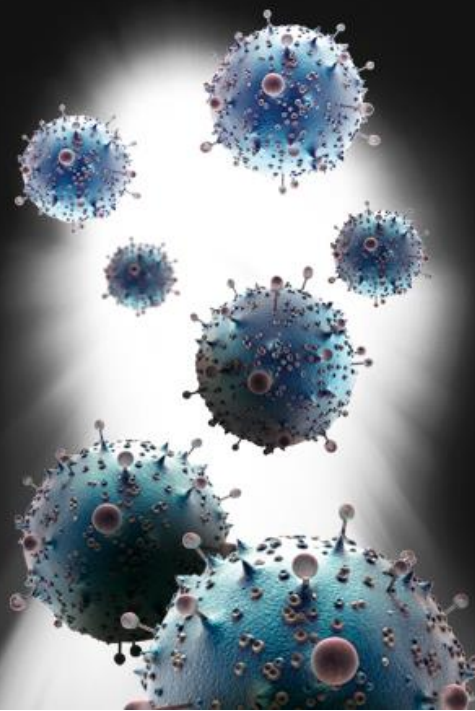
GRUPO DE ESTUDIO
DE HEPATITIS VÍRICAS
DE LA SEIMC

23/24
MAYO
2014
MADRID

HOTEL
NH NACIONAL



"Construyendo las bases para la erradicación del VHC"



Clinical Case. Pablo Barreiro

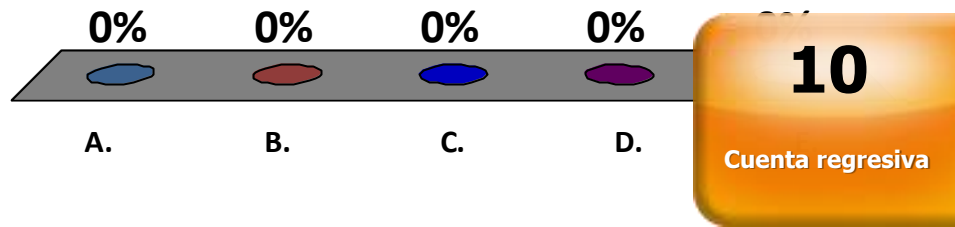
Visit in September 2012

- 35 y-o male, dentist, HIV diagnosis in June 2012 after diagnosis of secondary syphilis (RPR 1/32)
- CD4 count: 350 cells/uL, HIV-RNA 86,870 copies/mL
- HCV-Ab+, HBc+, HBsAg-, HBsAb-, HAV-Ab-

Q&A 1

What is next in your evaluation?:

- A. HCV-RNA
- B. HBV-DNA
- C. RPR
- D. All of above
- E. None of above



Q&A 1

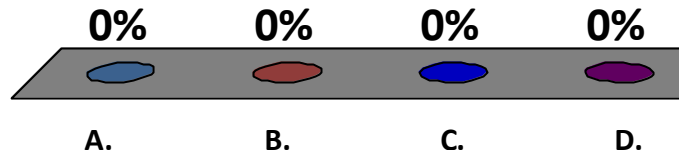
What is next in your evaluation?:

- | | |
|------------------|--------------|
| A- HCV-RNA | Undetectable |
| B- HBV-DNA | Undetectable |
| C- RPR | 1/2 |
| D- All of above | |
| E- None of above | |

Q&A 2

What is not true in this patient?:

- A. HCV recovery
- B. Hepatitis B vaccine not needed
- C. Occult hepatitis B discarded
- D. Needs hepatitis A vaccine
- E. Correct response to therapy for syphilis



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Cuenta regresiva

Q&A 2

What is not true in this patient?:

- A- HCV recovery
- B- Hepatitis B vaccine not needed
- C- Occult hepatitis B discarded
- D- Needs hepatitis A vaccine
- E- Correct response to therapy for syphilis

Anticore Alone Pattern

- Resolving acute hepatitis B
- Past hepatitis B with lack or loss of HBsAb
 - full vaccination
- Occult hepatitis B
 - detectable HBV-DNA
- False positive

Therefore...

Recovered hepatitis B and C

Hepatitis A and B vaccination!!

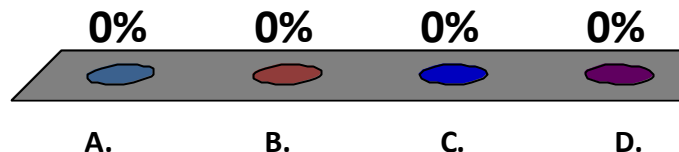
Clinical Case

- October 2012: TDF-FTC-DRV/r started
- June 2013: CD4 count 653 cells/uL and undetectable HIV-RNA
- September 2013: Simplification to TDF-RLP
- October 2013: Consults for jaundice and malaise.
ALT: 354 IU/L, AST: 178 IU/L, BLR: 3.4 mg/dL

Q&A 3

What is more valid in this case?:

- A. Change HAART
- B. Consider HBV vaccine escape mutants
- C. Check HCV serology
- D. Discard syphilis
- E. Discard hepatitis E



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Cuenta regresiva

Q&A 3

What is more valid in this case?:

A- Change HAART

B- Consider HBV vaccine escape mutants

C- Check HCV serology

D- Discard syphilis

RPR: 1/2

E- Discard hepatitis E

HEV IgM negative

Clinical Case

October 2013:

- HBsAb+, HVAb+, HVEAb-, HCV-Ab+
- HCV-RNA: 89,650 IU/mL, Genotype 1b, IL28B CC

Therefore...

Acute hepatitis C

Acute Hepatitis C in HIV+ Persons

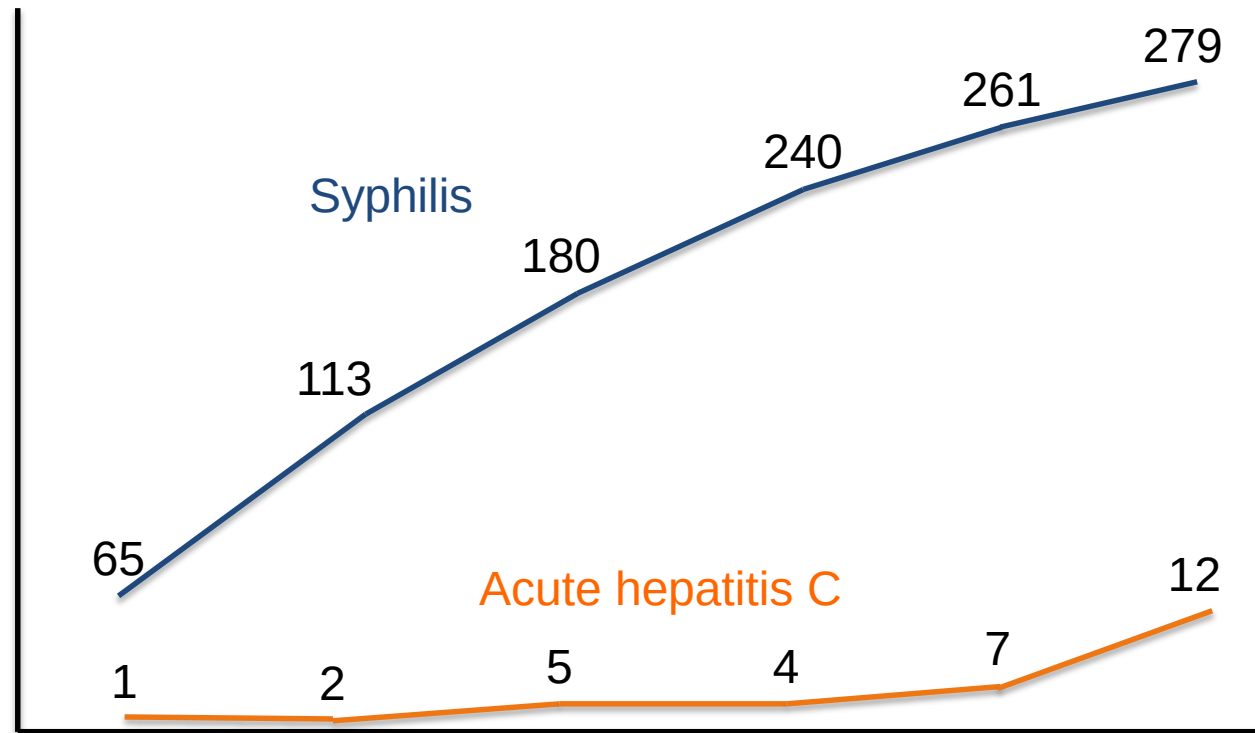
(n=31; period 2008-2013; HCIII, Madrid)

Variables	Values
Median age (years)	38 (27-55)
Male gender	31 (100%)
Country of origin – Spain	22 (70.6%)
South America	8 (21.1%)
Romania	1 (5.2%)
Risk group - MSM	31 (100%)
Symptoms (fever, asthenia...)	12 (36.8%)
Prior HBsAg+	2 (10.5%)
Concomitant syphilis	12 (36.8%)
Antiretroviral therapy	28 (88.2%)
Median CD4 count (cells/mm ³)	541 (417-797)
Undetectable plasma HIV-RNA	27 (84.2%)
IL28B polymorphism CC	14 (42.1%)
HCV genotype 1a	12 (36.8%)
1b	3 (9.8%)
4	14 (47.4%)
Median AST/ALT (IU/mL)	80 (54-199) / 215 (88-435)
Median baseline serum HCV-RNA log IU/mL)	6.1 (4.5-6.7)
Median liver elastometry (Kpa)	6.5 (4.5-8.0)

Acute Hepatitis C in HIV+ Individuals

HCIII, Madrid

No. episodes



2008

2009

2010

2011

2012

2013

No. patients

2094

2130

2245

2357

2512

2872

MSM

804

871

989

1075

1243

1564

(38.4%)

(40.9%)

(44.1%)

(45.6%)

(49.5%)

(54.6%)

Yearly rate syphilis

3.1%

5.3%

8.0%

10.2%

10.4%

10.3%

Yearly rate acute hepatitis C

0.05%

0.1%

0.2%

0.2%

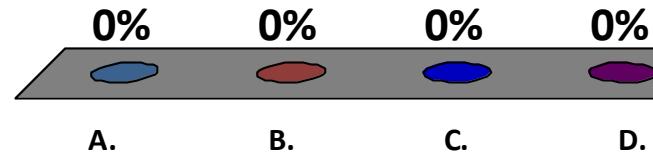
0.3%

0.5%

Q&A 4

What is the best attitude now?:

- A. Hold therapy, good chances for spontaneous recovery
- B. Treat now with pegIFN-RBV
- C. Treat later with pegIFN
- D. Do not treat till DAAs available
- E. Treat now with RBV



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Cuenta regresiva

Q&A 4

What is the best attitude now?:

- A- Hold therapy, good chances for spontaneous recovery
- B- Treat now with pegIFN-RBV
- C- Treat later with pegIFN
- D- Do not treat till DAAs available
- E- Treat now with RBV

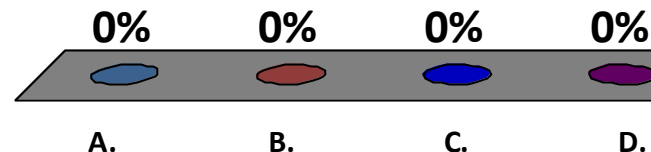
Acute HCV Infection in HIV Coinfection

- Wait 12 weeks for possible spontaneous HCV clearance (10-15%). Predictors:
 - Symptoms
 - Women, younger age
 - Genotype 1
 - IL28B CC
 - High CD4 counts
 - Rate of HCV-RNA decay after 4-8 weeks
 - >2 log HCV-RNA decay at week 4, PPV of 85%
 - HCV-RNA detectable at week 12, NPV of 90%

Q&A 5

What is not true for treatment of acute hepatitis C in HIV?:

- A. Shorter therapy for good genotypes (HCV 2-3)
- B. Always pegIFN plus RBV
- C. Shorter therapy for RVR
- D. IL28 B predictor of response
- E. Treat no later than 24 weeks after infection



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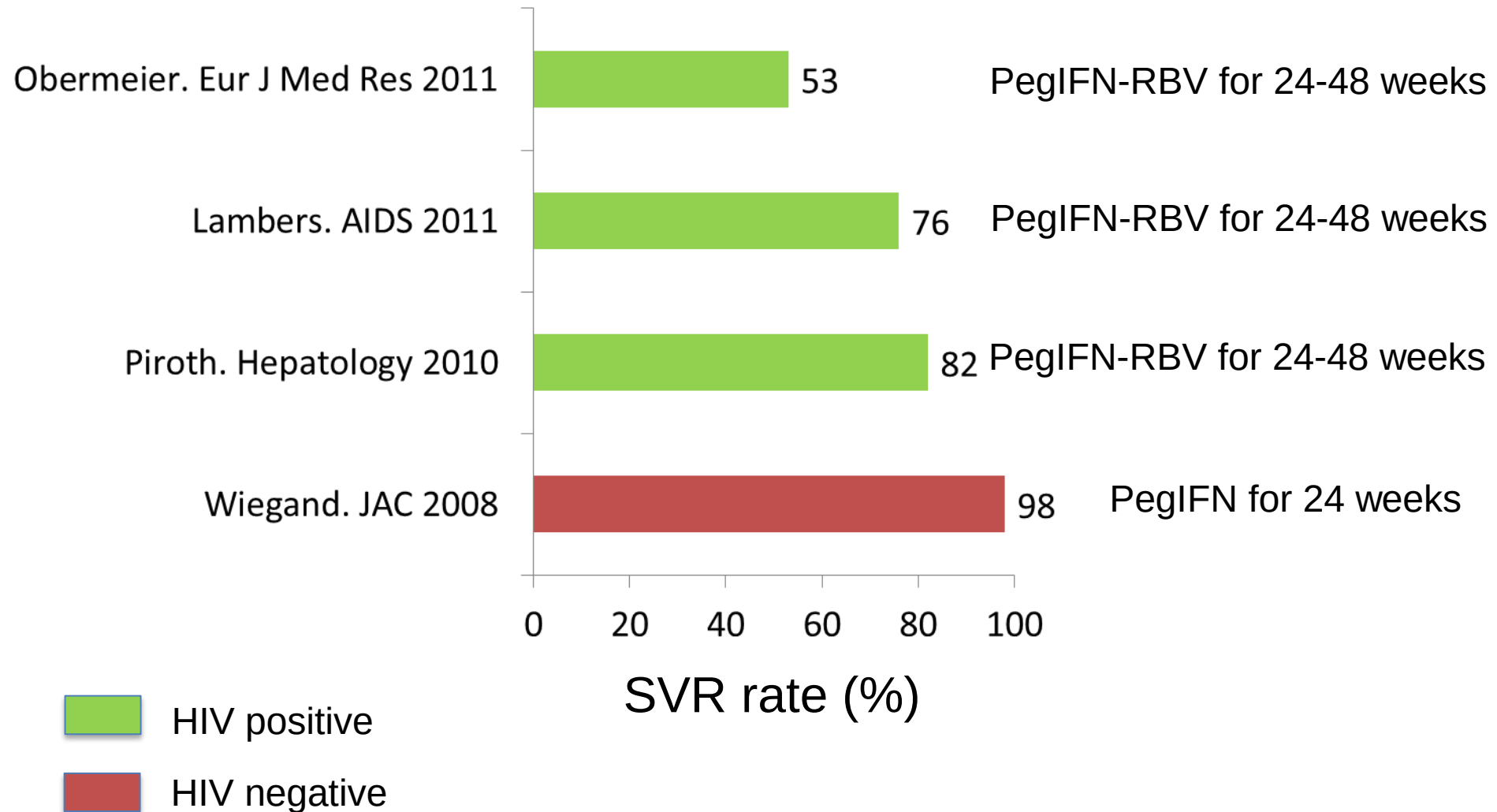
Cuenta regresiva

Q&A 5

What is not true for treatment of acute hepatitis C in HIV?:

- A- Shorter therapy for good genotypes (HCV 2-3)
- B- Always pegIFN plus RBV
- C- Shorter therapy for RVR
- D- IL28 B predictor of response
- E- Treat no later than 24 weeks after infection

Acute HCV Infection. Main Studies



Clinical Case

- Evolution of HCV-RNA:
 - @ week 4: 5,795 IU/mL
 - @ week 12: 986 IU/mL

Reluctant to IFN therapy

Another sample in 2 weeks:

HCV-RNA detectable

pegIFN-RBV started

Acute HCV Infection in HIV Coinfection

Onset: Treat between 12-24 weeks after diagnosis

Regimen: Peg-IFN plus RBV

- RVR better predictor of response
- HCV G2-3 and IL28B CC other predictors

Duration:

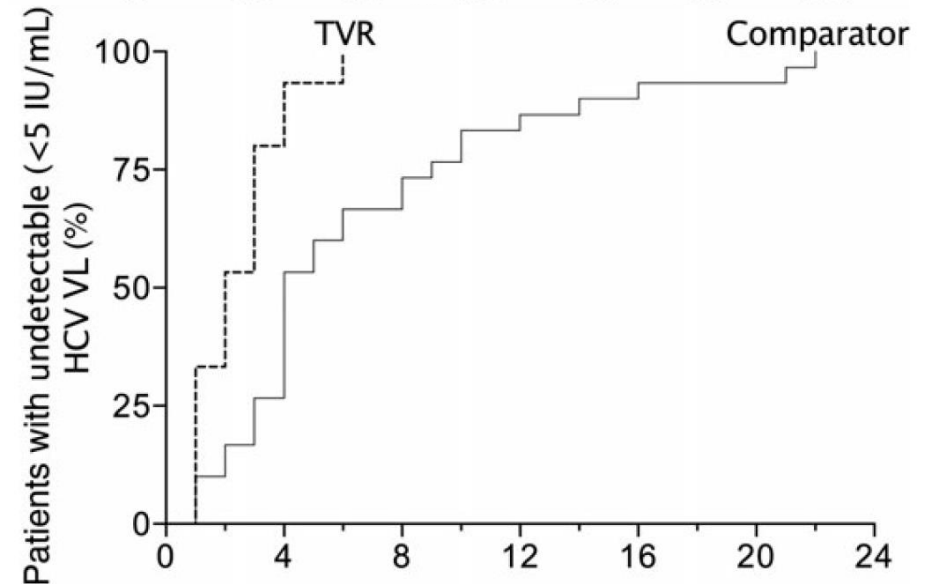
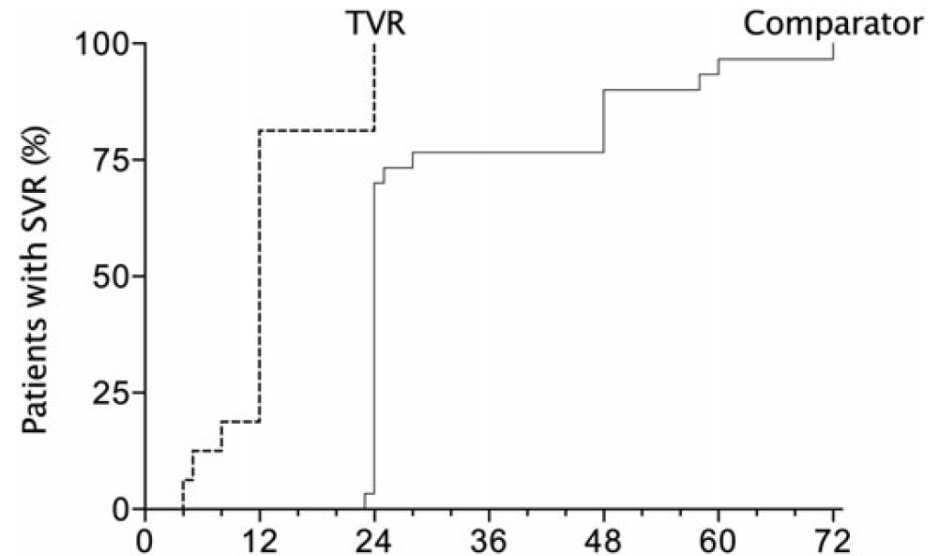
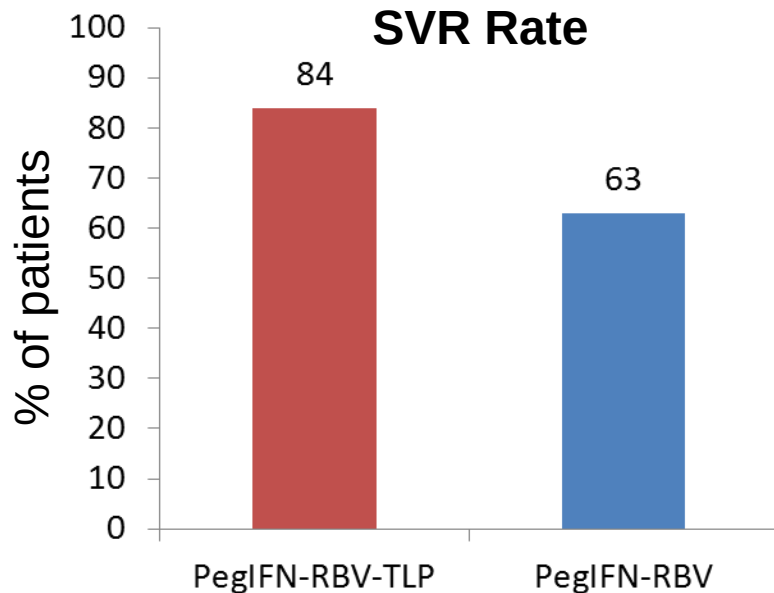
- 24 weeks in RVR
- 48 weeks in no RVR
- Stop in no RVR no EVR

Indications regardless of HCV genotype

Shorter and Curative Triple Therapy with Telaprevir for Acute HCV Infection in HIV Patients

Acute HCV G1 in HIV MSM at Mount Sinai (NYC) in 2011-12:

- 48 patients pegIFN-RBV for 24 to 72 weeks by RGT
- 19 patients pegIFN-RBV-TVR for 12 weeks



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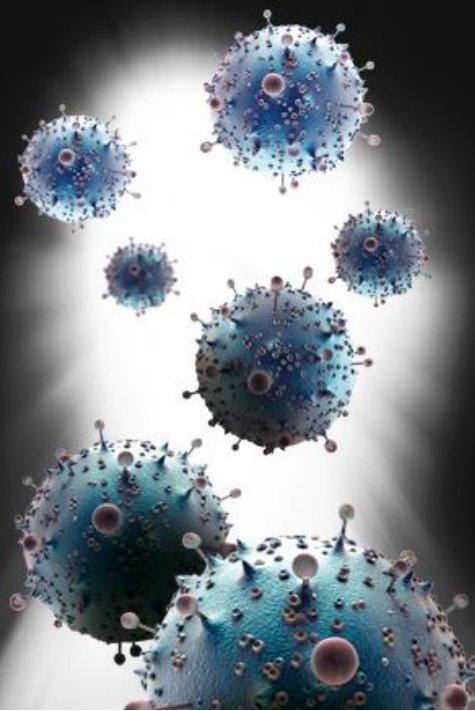
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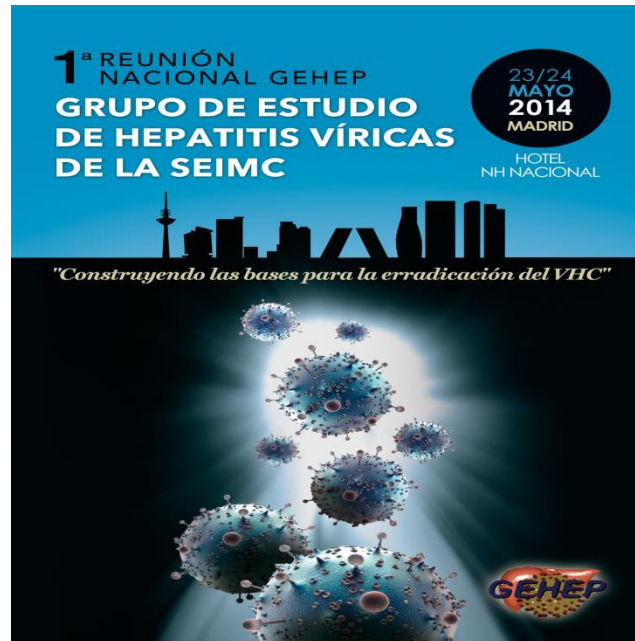
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"Construyendo las bases para la erradicación del VHC"



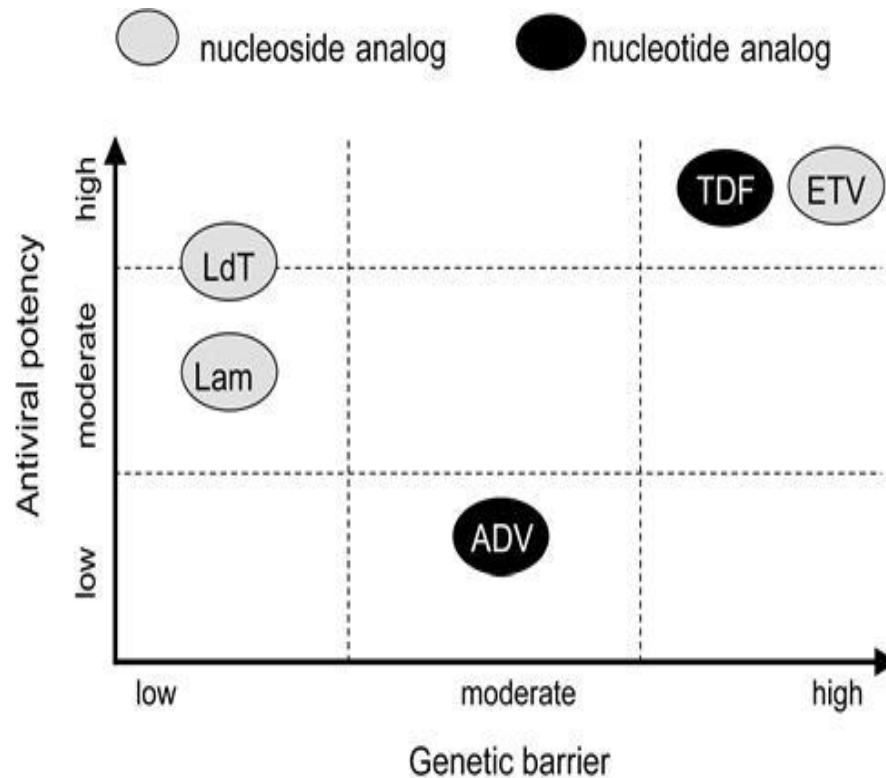
Fallo a Entecavir como primera línea de tratamiento en un paciente con hepatitis crónica B



Antonio Aguilera .

Servicio Microbiología CHUS y Departamento de Microbiología USC.

La terapia antiviral oral con los agentes de mayor potencia y barrera genética se ha convertido en el pilar del tratamiento de la HCB.



Características del paciente



Hombre

28 años

Hipertransaminasemia leve

Hepatitis crónica B HBeAg positivo

Nivel basal de ADN-VHB > 7.0 log UI/mL

Hepatitis leve en biopsia hepática (F1)

Múltiples parejas sexuales (HSH)

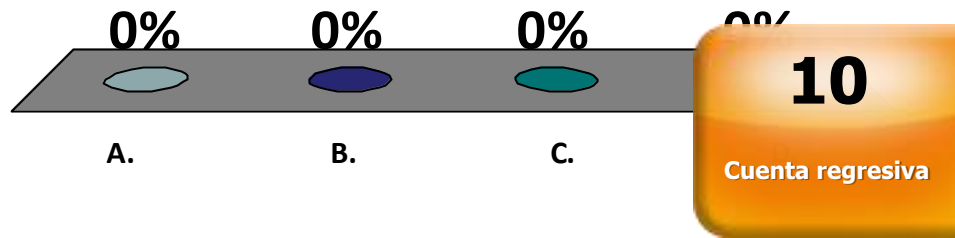
Asintomático

Serologías negativas para VHD, VHC y VIH

Sin otros datos de interés

En la hepatitis crónica B ¿Qué marcadores virológicos del VHB contribuyen en la caracterización de la historia natural y en la decisión y tipo de tratamiento?

- A. Niveles de ADN-VHB (Carga Viral)**
- B. Niveles de HBsAg (HBsAg QT)**
- C. Genotipo viral**
- D. Todas son correctas**



1-Characterización de la historia natural y decisión de tratar

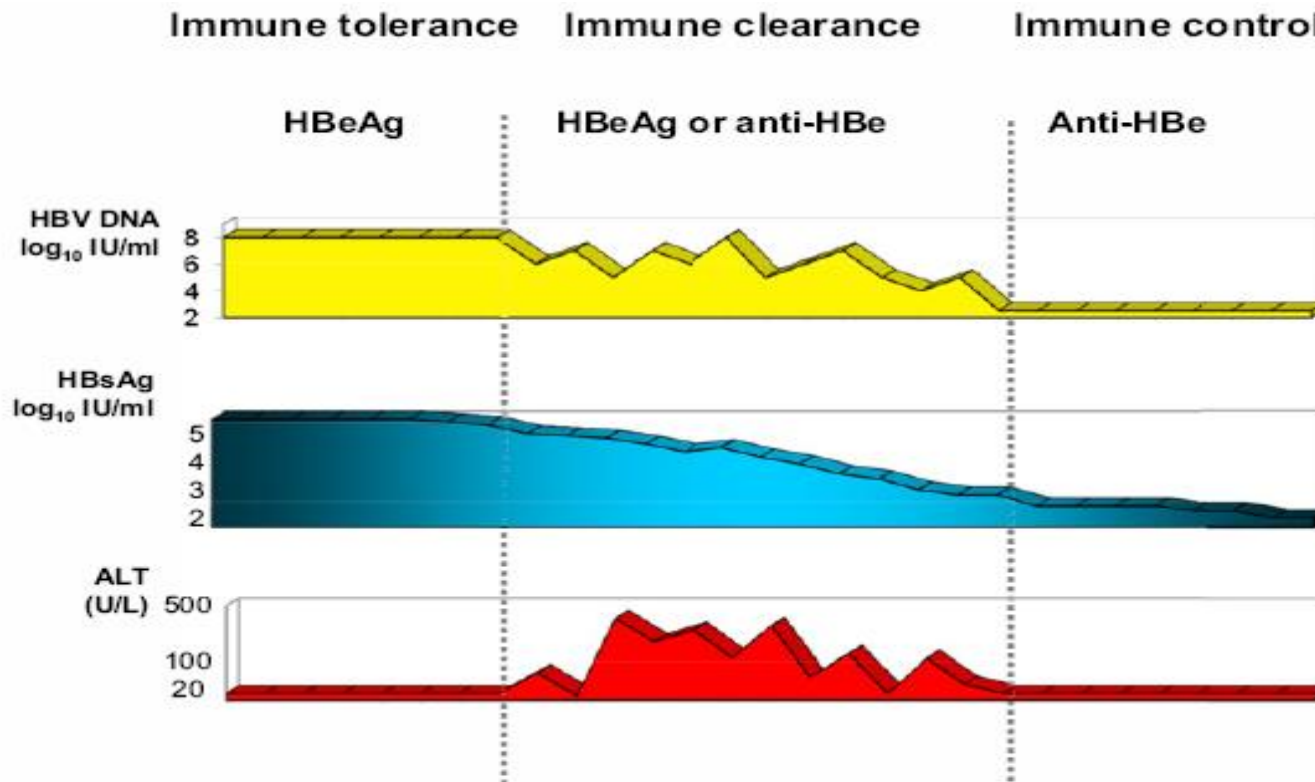
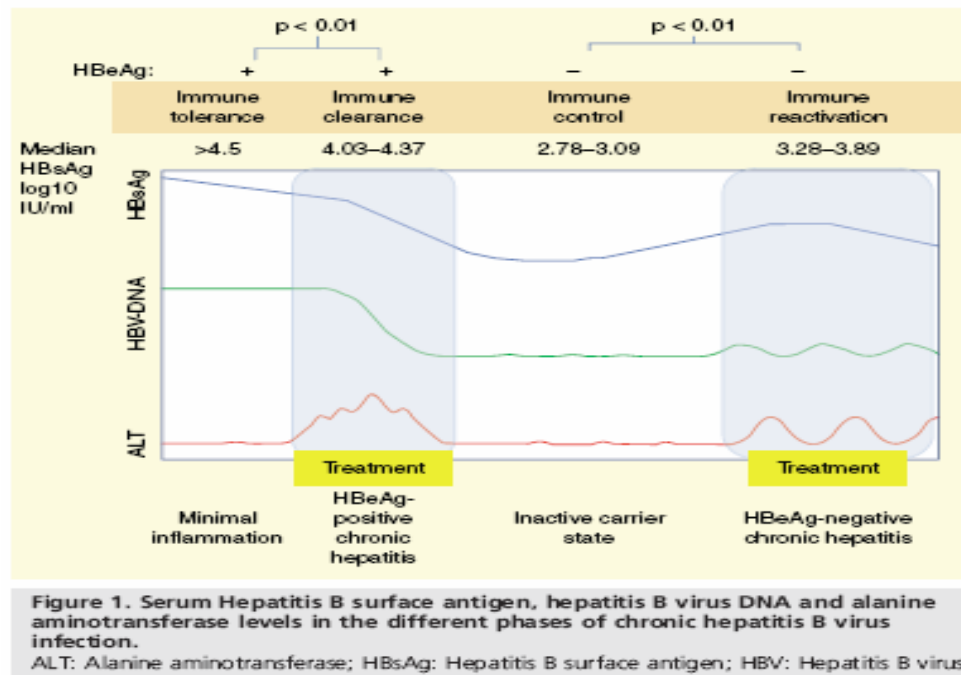


Figure 1 Serum levels of HBV DNA, hepatitis B virus surface antigen (HBsAg) and alanine transaminase (ALT) during the different phases of hepatitis B virus (HBV) infection. HBeAg, hepatitis B 'e' antigen.

Estudios de monitorización de los niveles de HBsAg durante la historia natural de la HCB

La combinación de los niveles simultáneos del HBsAg y de la carga viral puede permitir:

- 1-Diferenciar las fases de la historia natural de la HCB.
- 2-Identificar a los verdaderos portadores inactivos.
- 3-Predecir la pérdida de HBsAg o la progresión de la enfermedad.



Niveles de HBsAg durante la historia natural de la HCB: Diferenciación de inmunotolerancia e inmunoeliminación

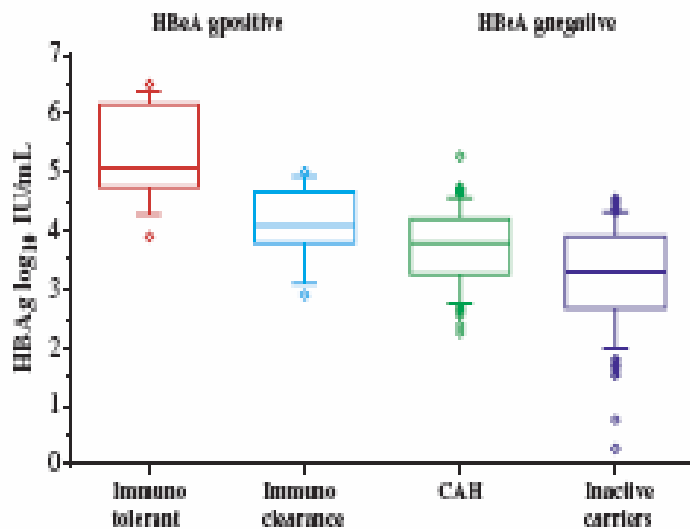


Fig. 1. Serum HBsAg levels during the natural history of HBV infection. Median values with 95% CI. Serum HBsAg levels are higher in HBsAg(+) (immune-tolerant and immune-clearance) than in AgHBe (-) chronic hepatitis B (17).

El HBsAg puede proporcionar información adicional para diferenciar inmunotolerancia e inmunoeliminación cuando la carga viral es alta y las ALT son normales o mínimamente elevadas.

Características del paciente



Hombre

28 años

Hipertransaminasemia leve

Hepatitis crónica B HBeAg positivo

Nivel basal de ADN-VHB > 7.0 log UI/mL

Hepatitis leve en biópsia hepática (F1)

Múltiples parejas sexuales (HSH)

Asintomático

Serologías negativas para VHD, VHC y VIH

Sin otros datos de interés

Nivel de HBsAg de 4.2 log UI/mL

2-Elección del tratamiento

La hipervariabilidad en el Gen S, a nivel de los residuos de AAs 25-43, 69-109 y 144-157 caracteriza al VHB en genotipos y subgenotipos

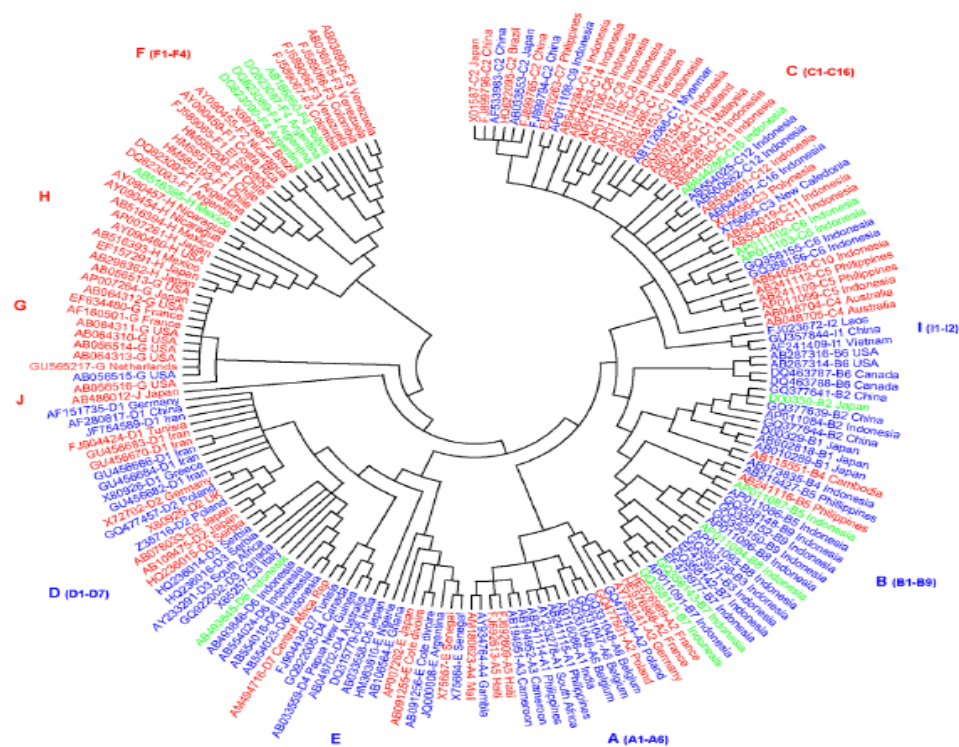


Figure 2. Dendrogram based on 176 complete genomic sequences of HBV with genotypes A-J. The phylogenetic tree was constructed using the UPGMA method. The genotypes are marked by the letters A through J. Each sequence is identified by the GenBank accession number, followed by the genotype/subgenotype and the country of origin of the isolates. HBV genomes containing three, two, and four CpG islands are shown in blue, red, and green, respectively.
doi:10.1371/journal.pone.0056711.g002

El genotipo es una variable que potencialmente puede influir en el resultado de la HCB y en el éxito de la terapia antiviral debido a sus diferentes propiedades biológicas.

CL Lin and JH Kao

HBV genotype and clinical outcomes

Table 2 Comparison of clinical and virologic differences among hepatitis B virus genotypes. Due to the unique distribution of HBV genotypes in Asian and Western countries, the available data could only be reliably compared between genotype B and C or genotype A and D

Genotype	B	C	A	D	E-J
Clinical characteristics					
Modes of transmission	perinatal	vertical	perinatal	vertical	horizontal
Tendency of chronicity	Lower	Higher	Higher	Lower	ND
Positivity of HBeAg	Lower	Higher	Higher	Lower	ND
HBeAg seroconversion	Earlier	Later	Earlier	Later	ND
HBeAg seroclearance	More	Less	More	Less	ND
Histologic activity	Lower	Higher	Lower	Higher	ND
Clinical outcome (cirrhosis and hepatocellular carcinoma)	Better	Worse	Better	Worse	Worse in Genotype F
Response to interferon alpha	Higher	Lower	Higher	Lower	Lower in Genotype G
Response to nucleos(t)ide analogues	No significant difference between genotype A to D				ND
Virologic characteristics					
Serum HBV DNA level	Lower	Higher	ND	ND	ND
Frequency of precore A1896 mutation	Higher	Lower	Higher	Higher	ND
Frequency of basal core promoter	Lower	Higher	Lower	Lower	ND
T1762A1764 mutation					
Frequency of pre-S deletion mutation	Lower	Higher	ND	ND	ND

ND, no available data

genotype B patients.^{23,24} Furthermore, a long-term follow-up study with 460 Taiwanese HBV chronically-infected children indicated that the seropositive rate of HBeAg after 20 years of follow-up was 70% in genotype C and 40% in genotype B carriers.²⁵ Taking these lines of evidence together, genotype C patients may experience delayed HBeAg seroconversion and thus a longer duration of high HBV replication than genotype B patients. With these adverse factors, genotype C patients are correspondingly more prone to develop advanced fibrosis, cirrhosis and HCC than genotype B patients. Similar observations have been reported from Hong Kong and Japan.²⁶⁻²⁸

Regarding genotypes A and D, one prospective study evaluated the clinical outcomes of 258 Spanish patients with chronic HBV infection; mean follow-up was 94 months.²⁷ Although no differences were observed in the probability of HBeAg seroconversion between patients infected with genotype A and D, the rate of sustained remission after HBeAg seroconversion was higher in genotype A than genotype D (55% versus 32%, $P < 0.01$). As for spontaneous HBeAg seroclearance, compared to genotypes C and D, genotype A and B patients had a higher rate of HBeAg seroclearance.^{13,28} Taken together, these facts suggest the phenotype of HBeAg seroconversion differs between genotypes B and C as well as genotypes A and D during the early phase of chronic HBV infection. Further, genotype C and D patients, compared to genotype A and B patients, have late or absent HBeAg seroconversion after multiple hepatitis flares that may accelerate the progression of chronic hepatitis, thereby conferring a poor clinical outcome.

Disease progression to cirrhosis or hepatocellular carcinoma (HCC)

Most retrospective or case-control studies indicated that patients with genotype C infection have more severe liver disease, including cirrhosis and HCC, than those with genotype B.²⁹⁻³² Recently, a community-based prospective cohort study on 2762 Taiwanese

HBV carriers demonstrated that HBV genotype C was associated with an increased risk of HCC than genotype B; the adjusted hazard ratio was 2.35 (95% CI = 1.68 to 3.30; $P < 0.001$).³³ These findings confirm that genotype C correlates with a higher risk of HCC development. Of interest, several reports showed HBV genotype B was associated with the early onset of HCC, whereas genotype C was associated with HCC development at older ages.^{23,34,35} The predominance of HBV genotype B in HCC patients was more prominent in those younger than 35 years, and most were cases of non-cirrhotic chronic hepatitis B.

HBV genotype also influences the clinicopathological features of patients with resectable HCC. In Taiwan, among 193 resectable HBV-related HCC patients, genotype B patients had a higher rate of solitary tumor (94% versus 86%, $P = 0.048$) but more satellite nodules (22% versus 12%, $P = 0.05$) than genotype C patients. These characteristics may contribute to the recurrence patterns and prognosis of HBV-related HCC patients with genotype B or C infection.^{36,38} As for other genotypes, death related to liver disease is more frequent in patients infected with HBV genotype D and F than those with genotype A infection.^{37,39,40}

Interactions between HBV genotypes, viral load and viral mutants

In addition to HBV genotypes, emerging data reveal that HBV viral load and naturally occurring mutant strains are closely associated with long-term outcomes of HBV-related chronic liver disease.^{41,42} In an earlier study, we found that genotype C infections conferred a higher frequency of basal core promoter (BCP) A1762G1764A mutation than genotype B.³³ In another prospective study with 4841 Taiwanese male HBV-infected patients without HCC at enrollment, Yu *et al.* found that HBV viral load was higher in genotype C than genotype B patients, while genotype C-infected patients who also had very high viral load had a 26-fold higher risk of HCC than those with other genotypes and

Evidencias en términos de progresión de la enfermedad: Mayor severidad y mayor riesgo de progresión a CHC para el genotipo C frente al resto.

Evidencias en términos de respuesta al tratamiento antiviral: Los genotipos C y D se asocian a una peor respuesta al tratamiento basado en IFN que los genotipos B y A, en términos de seroconversión del HBeAg. No demostrada relación con los análogos de nucleós(t)ido.

EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection

European Association for the Study of the Liver*

Introduction

Our understanding of the natural history of hepatitis B virus (HBV) infection and the potential for therapy of the residual disease is continuously improving. New data have become available since the previous EASL Clinical Practice Guidelines (CPGs) were published in 2008 and published in early 2009 [1]. The objective of this manuscript is to update the recommendations for the optimal management of chronic HBV infection. The CPGs do not fully address prevention including vaccination. In addition, despite the increasing knowledge, areas of uncertainty still exist and therefore clinicians, patients, and public health authorities must continue to make choices on the basis of the evolving evidence.

Context

Epidemiology and public health burden

Approximately one third of the world's population has serological evidence of past or present infection with HBV and 350–400 million people are chronic HBV surface antigen (HBsAg) carriers. The spectrum of disease and natural history of chronic HBV infection are diverse and variable, ranging from an inactive carrier state to progressive chronic hepatitis B (CHB), which may evolve to cirrhosis and hepatocellular carcinoma (HCC) [2–4]. HBV-related end-stage liver disease or HCC are responsible for over 65–1 million deaths per year and currently represent 5–10% of cases of liver transplantation [5–8]. Host and viral factors, as well as coinfection with other viruses, in particular hepatitis C virus (HCV), hepatitis D virus (HDV), or human immunodeficiency virus (HIV) together with other co-morbidities including alcohol abuse and obesity, can affect the natural course of HBV infection as well as efficacy of antiviral strategies [2–8]. CHB may present either as hepatitis B e antigen (HBeAg)-positive or HBeAg-negative CHB. The prevalence of the HBeAg-negative form of the disease has

been increasing over the last decade as a result of aging of the HBV-infected population and predominance of specific HBV genotypes and represents the majority of cases in many areas, including Europe [4,9,10]. Morbidity and mortality in CHB are linked to persistence of viral replication and evolution to cirrhosis and/or hepatocellular carcinoma (HCC). Longitudinal studies of untreated patients with CHB indicate that, after diagnosis, the 5-year cumulative incidence of developing cirrhosis ranges from 8% to 20%. The 5-year cumulative incidence of hepatic decompensation is approximately 20% for untreated patients with compensated cirrhosis [2,4,11–13]. Untreated patients with decompensated cirrhosis have a poor prognosis with a 14–30% probability of survival at 5 years [2–4,12]. The worldwide incidence of HCC has increased, mostly due to persistent HBV and/or HCV infection; presently it constitutes the fifth most common cancer, representing around 5% of all cancers. The annual incidence of HBV-related HCC in patients with CHB is high, ranging from 2% to 5% when cirrhosis is established [13]. However, the incidence of HBV-related HCC appears to vary geographically and correlates with the underlying stage of liver disease and possibly exposure to environmental carcinogens such as aflatoxin. Population movements and migration are currently changing the prevalence and incidence of the disease in several low endemic countries in Europe and elsewhere. Substantial healthcare resources will be required for control of the worldwide burden of disease.

Natural history

Chronic HBV infection is a dynamic process. The natural history of chronic HBV infection can be schematically divided into five phases, which are not necessarily sequential.

- (1) The "immune tolerant" phase is characterized by HBeAg positivity, high levels of HBV replication (reflected by high levels of serum HBV DNA), normal or low levels of aminotransferases, mild or no liver necroinflammation and no or slow progression of fibrosis [2,3,6,8]. During this phase, the rate of spontaneous HBeAg loss is very low. This first phase is more frequent at more prolonged in subjects infected perinatally or in the first years of life. Because of high levels of viremia, these patients are highly contagious.
- (2) The "immune active HBeAg-positive phase" is characterized by HBeAg positivity, relatively lower level of replication compared to the immune tolerant phase (as reflected by lower serum HBV DNA levels), increased or

Keywords: Hepatitis B virus; EASL guidelines; Treatment; Interferon alpha; Nucleoside/nucleotide analogues.
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Journal of Hepatology 2012 vol. 57 | 167–185

El genotipo viral en la hepatitis crónica B posee un pobre valor predictivo individual en cuanto a la respuesta al tratamiento antiviral, por lo que sólo con él no se deben de tomar decisiones vinculadas al tratamiento.

EASL J Hepatol 2012; 57:167-85

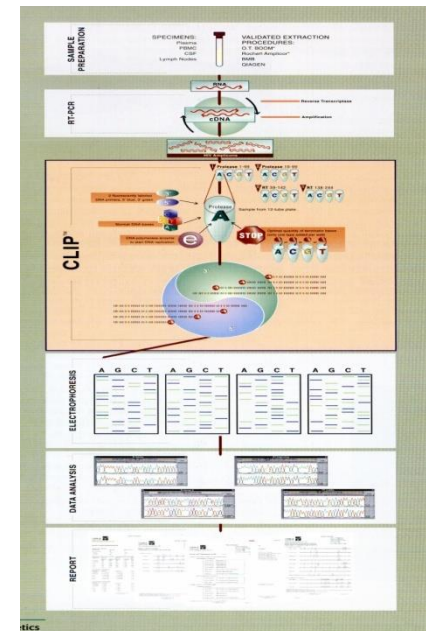
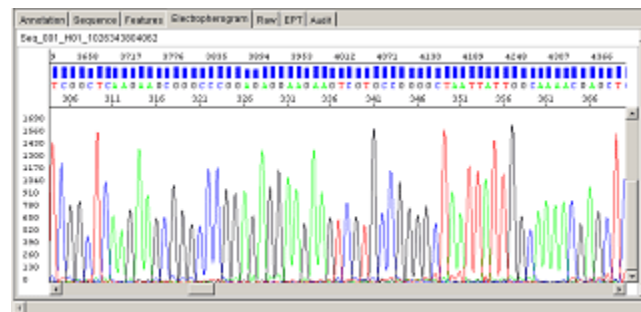
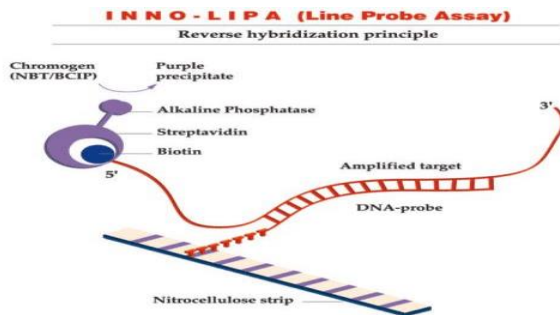
Determinación del genotipo viral del VHB:

1-Ensayos de secuenciación directa y análisis filogenético.

- Diseñados en el propio laboratorio y basados en la secuenciación completa o parcial del gen S y posterior análisis filogenético (PHYLYP software, HepSeq, HIV-DB, Geno2pheno, Bioafrica, etc.)
- Comerciales (TRUGENE HBV Genotyping kit, Siemens Medical Solutions Diagnostics y HBV Sequencing Assay de Abbott Molecular)

2-Otros ensayos.

- Hibridación reversa mediante sondas específicas (INNO-LiPA HBV Genotyping, Innogenetics).
- PCR a tiempo real alelo específica y mixta genotipo específica.
- RFLP
- Ensayos serológicos
- Ensayos en desarrollo no comerciales: Chips de ADN, RFMP, etc



Características del paciente



Hombre

28 años

Hipertransaminasemia leve

Hepatitis crónica B HBeAg positivo

Nivel basal de ADN-VHB > 7.0 log UI/mL

Hepatitis leve en biópsia hepática (F1)

Múltiples parejas sexuales (HSH)

Asintomático

Serologías negativas para VHD, VHC y VIH

Sin otros datos de interés

Nivel de HBsAg de 4.2 log UI/mL

Infección por el Genotipo A2 del VHB

Características del paciente



Hombre

28 años

Hipertransaminasemia leve

Hepatitis crónica B HBeAg positivo

Nivel basal de ADN-VHB > 7.0 log UI/mL

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Múltiples parejas sexuales (HSH)

Asintomático

Serologías negativas para VHD, VHC y VIH

Sin otros datos de interés

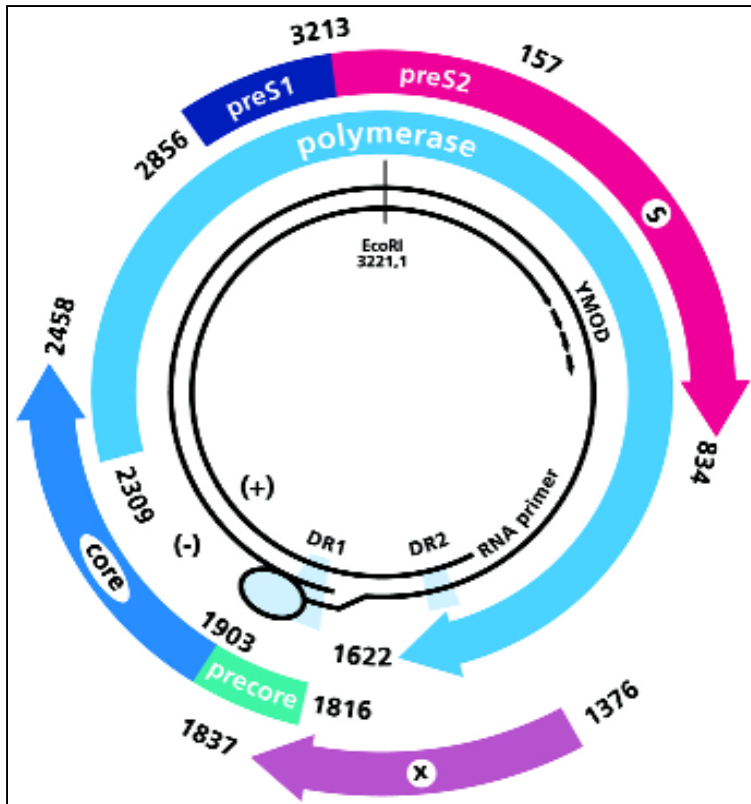
Nivel de HBsAg de 4.2 log UI/mL

Infección por el Genotipo A2 del VHB

Infección por cepa salvaje en POL

Genoma viral del VHB

El genoma del VHB consiste en una molécula circular de ADN bicatenario de 3,2 kb, cuya cadena positiva se haya incompleta en su extremo 3'. Contiene siete señales de iniciación de la transcripción que definen genes parcialmente solapantes.



geno2pheno®



HBV resistance prediction from genotype (version 2.0)

I. General information

Patient:	Study Id:
Birth date:	Viral load:
Sample received:	Sample collected:
Sample ID: SCQETVr - B384	Predicted genotype: A (A2)
Sample type:	Report date:
Physician:	Reported by:

II. Substitutions

RT domain:	
SHB protein:	
Escape:	

III. Resistance analysis

Drug	Prediction	Scored Mutations
Lamivudine	susceptible	none
Adefovir	susceptible	none
Entecavir	susceptible	none
Tenofovir	susceptible	none
Telivudine	susceptible	none

Comments:

(signature)

3- Tratamiento: ETV

Journal of Viral Hepatitis, 2012, 19, 377-386
doi:10.1111/j.1365-2893.2012.01602.x

REVIEW

First-line treatment of chronic hepatitis B with entecavir or tenofovir in 'real-life' settings: from clinical trials to clinical practice

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Received December 2011; accepted for publication February 2012

SUMMARY. Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are potent nucleos(tide) analogues (NUCs) recommended as first-line monotherapies for chronic hepatitis B. In Phase III trials, ETV and TDF demonstrated superior efficacy, and comparable safety compared with other NUCs. In long-term clinical studies, both drugs achieved virologic response rates of around 95%, with very low rates of resistance development and good safety profiles. Clinical trials are conducted under standardized conditions with strict enrolment criteria that limit the heterogeneity of study populations. 'Real-life' populations tend to be composed of a wider range of patients, often older and with different morbidities, combinations that may impact treatment efficacy and co-factors, such as smoking and alcohol intake, which can have

a direct impact on disease progression. Real-life studies provide better representations of everyday clinical practice and are important to confirm the results reported in clinical studies and to identify rare or late-emerging adverse events. In five 'real-life' studies of ETV in more than 1000 patients, up to 4 years of treatment resulted in virologic responses in 76-96% of patients. Two real-life studies of TDF reported response rates of 71-92% after up to 21 months of treatment. Low incidences of drug resistance and favourable tolerabilities were reported for both drugs, thus confirming the results from registration trials.

Keywords: entecavir, hepatitis B virus, nucleoside/nucleotide analogues, tenofovir.

INTRODUCTION

It is estimated that one-third of the world's population has serologic evidence of a past or present hepatitis B virus (HBV) infection, with around 370 million being chronically infected [1,2]. HBV-related liver failure, cirrhosis and hepatocellular carcinoma (HCC) currently account for over 1 million deaths annually [2]. The goal of chronic hepatitis B (CHB) treatment is to improve survival by preventing disease progression to decompensated cirrhosis and HCC [1-3]. It is now well established that the risk of disease progression is reduced through the sustained reduction in HBV DNA to undetectable levels [4-6]. The effective and

sustained suppression of HBV replication can result in regression of liver fibrosis and can even reverse liver cirrhosis [7]. Furthermore, maintaining undetectable levels of HBV DNA also increases the rate of hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg) seroconversion, which are also desired endpoints of CHB therapy [1,2]. However, HBV is not completely eradicated by treatment, even if HBeAg loss occurs. This is because of the persistence of nuclear covalently closed circular DNA and HBV DNA integrated into the host genome, which may trigger HBV reactivation or direct viral hepatocarcinogenesis, respectively. Long-term therapy is required in HBeAg(-) and in HBeAg(+) patients who cannot maintain virologic suppression off-treatment and for those with advanced liver disease. One barrier to the success of long-term therapy is the emergence of drug-resistant mutants, which are frequently observed during treatment of CHB with lamivudine (3T), adenofovir (ADN) or telbivudine as monotherapies [2]. Current guidelines, therefore, recommend that the most potent drugs with optimal resistance profiles (i.e. entecavir [ETV] and tenofovir disoproxil fumarate [TDF]) should be used as first-line monotherapies in CHB [2,3]. These two agents were approved by the US Food and Drug Administration (FDA) for

Abbreviations: ADV, adenofovir; ALT, alanine transaminase; CHB, chronic hepatitis B; eGFR, estimated glomerular filtration rate; ETV, entecavir; HBeAg, hepatitis B e antigen; HBeAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LVD, lamivudine; NUCs, nucleos(tide) analogues; TDF, tenofovir disoproxil fumarate.

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Long-Term Monitoring Shows Hepatitis B Virus Resistance to Entecavir in Nucleoside-Naïve Patients Is Rare Through 5 Years of Therapy

Daniel J. Tenney, Ronald E. Rose, Carl J. Baldick, Kevin A. Pokornowski, Betsy J. Eggers, Jie Fang, Michael J. Wichroski, Dong Xu, Joanna Yang, Richard B. Wilber, and Richard J. Colonna*

Patients with chronic hepatitis B virus (HBV) infection who develop antiviral resistance lose benefits of therapy and may be predisposed to further resistance. Entecavir (ETV) resistance (ETVr) results from HBV reverse transcriptase substitutions at positions T184, S202, or M250, which emerge in the presence of lamivudine (LVD) resistance substitutions M204I/V $\pm$ L180M. Here, we summarize results from comprehensive resistance monitoring of patients with HBV who were continuously treated with ETV for up to 5 years. Monitoring included genotypic analysis of isolates from all patients at baseline and when HBV DNA was detectable by polymerase chain reaction (≥ 300 copies/mL) from Years 1 through 5. In addition, genotyping was performed on isolates from patients experiencing virologic breakthrough ($\geq 1 \log_{10}$ rise in HBV DNA). *In vitro* phenotypic ETV susceptibility was determined for virologic breakthrough isolates, and for HBV containing novel substitutions emerging during treatment. The results over 5 years of therapy showed that in nucleoside-naïve patients, the cumulative probability of genotypic ETVr and genotypic ETVr associated with virologic breakthrough was 1.2% and 0.8%, respectively. In contrast, a reduced barrier to resistance was observed in LVD-refractory patients, as the LVD resistance substitutions, a partial requirement for ETVr, preexist, resulting in a 5-year cumulative probability of genotypic ETVr and genotypic ETVr associated with breakthrough of 51% and 43%, respectively. Importantly, only four patients who achieved < 300 copies/mL HBV DNA subsequently developed ETVr. **Conclusions:** Long-term monitoring showed low rates of resistance in nucleoside-naïve patients during 5 years of ETV therapy, corresponding with potent viral suppression and a high genetic barrier to resistance. These findings support ETV as a primary therapy that enables prolonged treatment with potent viral suppression and minimal resistance. (Hepatology 2009;49:1503-1514.)

Approximately 400 million people worldwide have chronic hepatitis B virus (HBV) infections, with a risk for chronic, life-threatening liver disease.¹ Antiviral therapy for HBV can provide suppression of

viral replication and halt disease progression.^{2,3} However, therapeutic benefits are diminished with the emergence of drug-resistant virus, which occurs most often with prolonged therapy and incomplete viral suppression.⁴

Resistance to nucleoside/nucleotide antivirals arises through substitutions in the HBV polymerase reverse transcriptase domain (RT), that arise spontaneously through low-fidelity replication and are enriched through drug-selective pressure.^{2,3} Antiviral therapies are characterized by their barrier to resistance, which includes three components: (1) the potency of the antiviral in suppressing viral replication, (2) a 'genetic barrier', i.e. the number of genetic changes required to effectively reduce drug susceptibility that results in virologic breakthrough, and (3) the replication fitness of the resistant virus. These factors act together to determine the levels of resistance which emerge during therapy. Other factors related to the particular binding site or mechanism of activity also contribute to determining the overall barrier to resistance.

Lamivudine (LVD) resistance (LVD_r) arises with changes in the HBV RT tyrosine-methionine-aspartate-

Abbreviations: ADV, adenofovir; ADVr, adenofovir-resistance; AS-PCR, allele-specific, single-nucleotide polymorphism polymerase chain reaction; EC₅₀, median effective concentration; ETV, entecavir; ETV_r, entecavir-resistance; entecavir-resistance; HBV, hepatitis B virus; LVD, lamivudine; LVD_r, lamivudine-resistance; lamivudine-resistance; nucleoside-naïve, nucleoside-naïve-naïve; RT, reverse transcriptase domain of the HBV polymerase; WT, wild type; YMDD, YMDD-mutated-aspartate-aspartate.

From Bristol-Myers Squibb Company Research and Development, Wallingford, CT. Received August 20, 2008; accepted December 25, 2008.

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Potential conflicts of interest: The studies were performed as Bristol-Myers Squibb employees of Bristol-Myers Squibb. Study participants have been informed of potential conflicts of interest. Drs. Wilber, Eggers, Colonna, Baldick, Tenney, Pokornowski, and Joann Yang are Bristol-Myers Squibb.



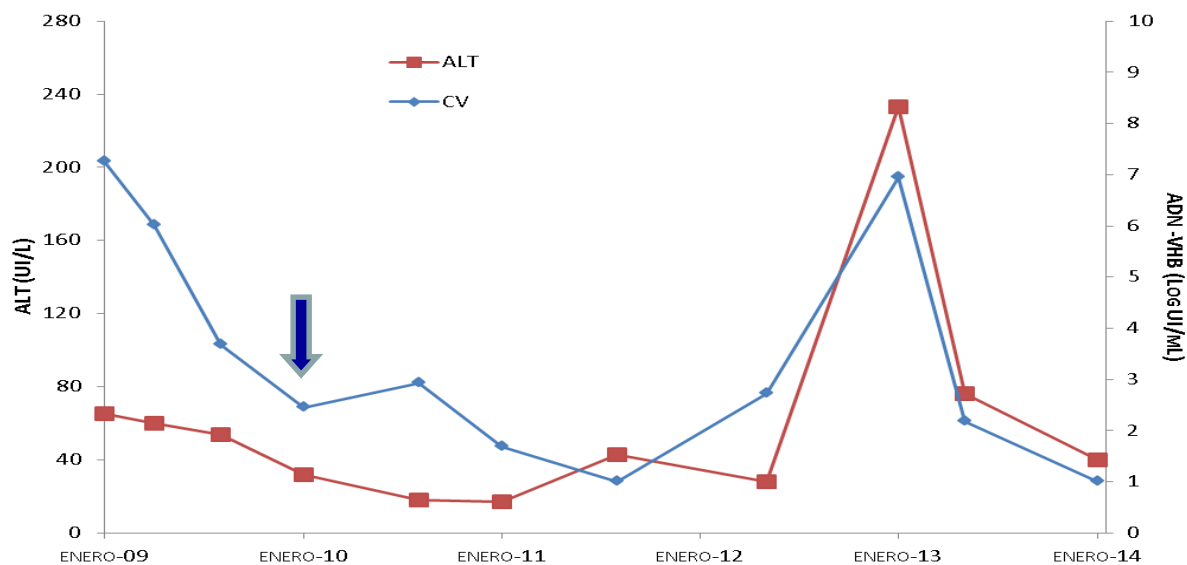
Evolución del tratamiento

Sem 1: ETV 0.5 mg/día

Sem 48: Respuesta bioquímica

Respuesta Viroológica Parcial (2.45 log UI/mL)

Cambio ETV 1 mg/día





Evolución del tratamiento

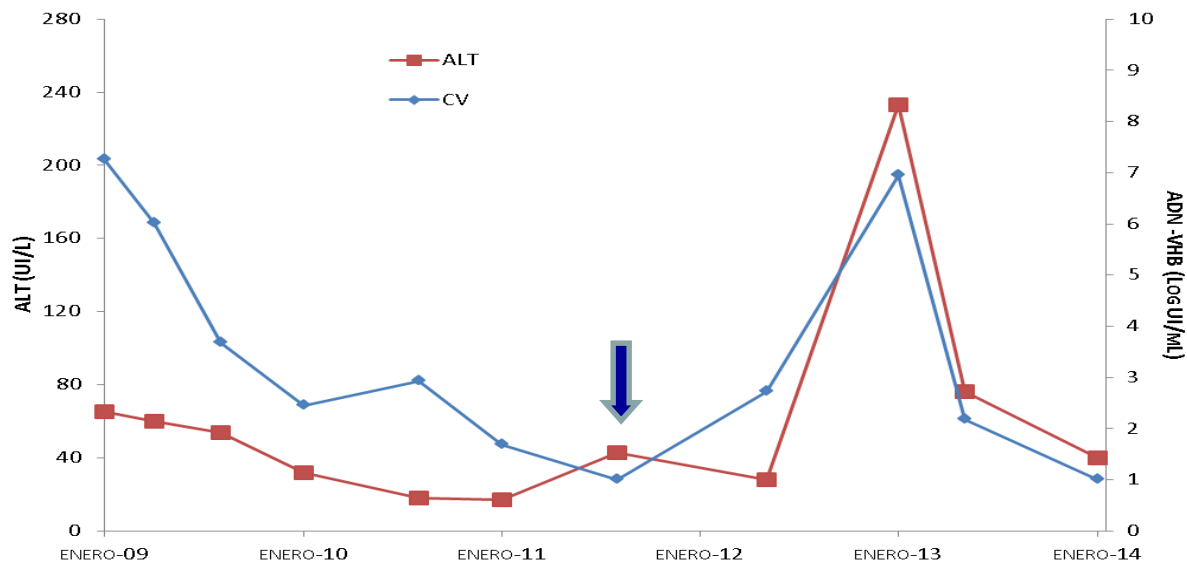
Sem 1: ETV 0.5 mg/día

Sem 48: Respuesta bioquímica

Respuesta Viroológica Parcial (2.45 log UI/mL)

Cambio ETV 1 mg/día

Sem 132: Respuesta Viroológica





Evolución del tratamiento

Sem 1: ETV 0.5 mg/día

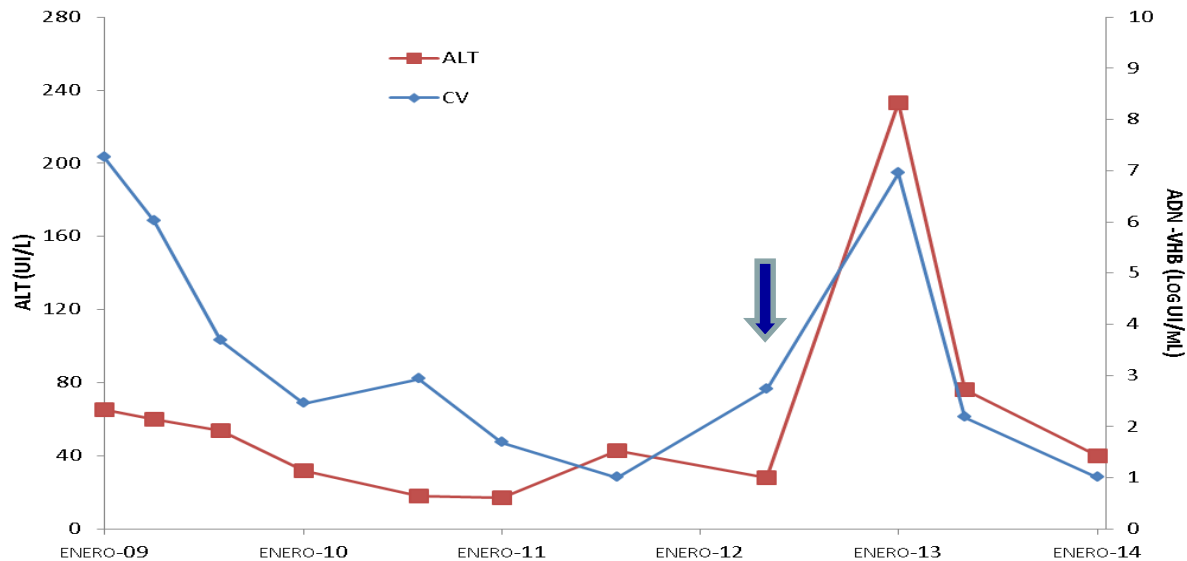
Sem 48: Respuesta bioquímica

Respuesta Viroológica Parcial (2.45 log UI/mL)

Cambio ETV 1 mg/día

Sem 132: Respuesta Viroológica

Sem 164: Rebote virológico (2.72 log UI/mL)





Evolución del tratamiento

Sem 1: ETV 0.5 mg/día

Sem 48: Respuesta bioquímica

Respuesta Viroológica Parcial (2.45 log UI/mL)

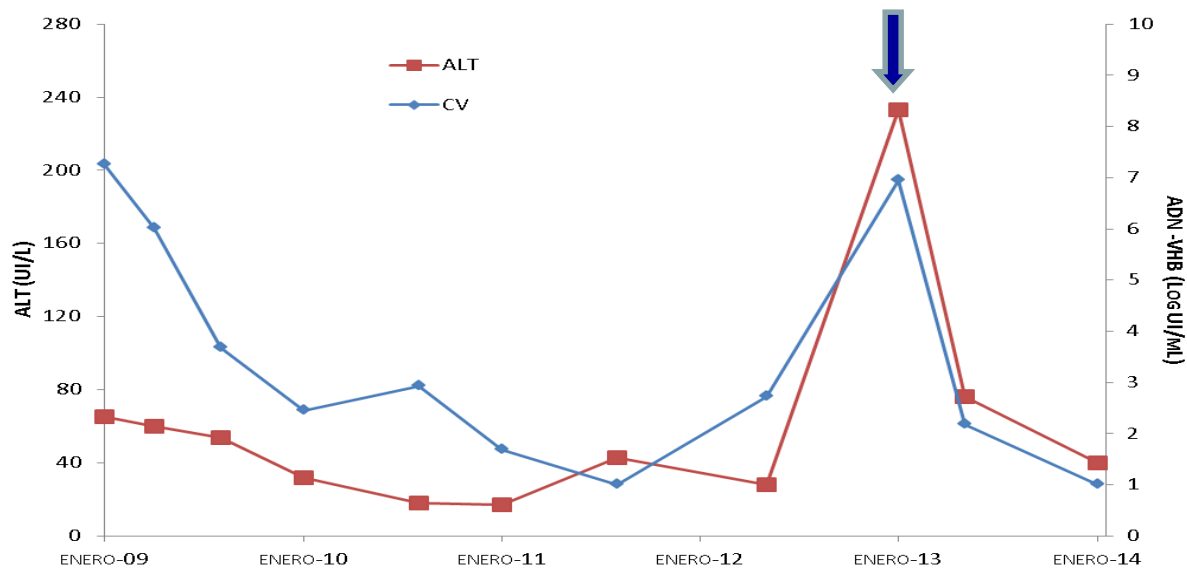
Cambio ETV 1 mg/día

Sem 132: Respuesta Viroológica

Sem 164: Rebote virológico (2.72 log UI/mL)

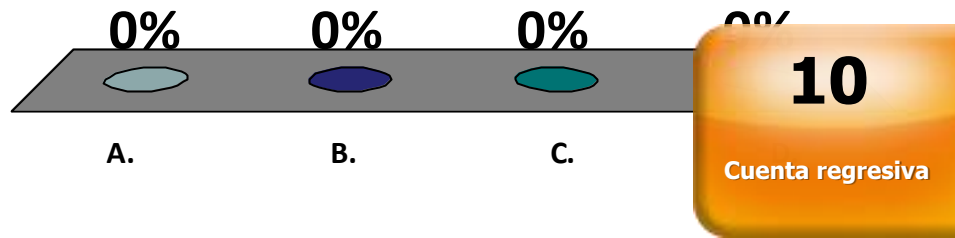
Sem 192: Rebote virológico? (6.94 log UI/mL)

Rebote bioquímico (ALT 233 UI/L)



De los siguientes perfiles de mutaciones de resistencia en la RT del gen POL del VHB ¿Cuál caracteriza la resistencia genotípica a Entecavir?

- A. rtL180M + rtM204V + rtA181T/V
- B. rtL180M + rtM204V + rtN236T
- C. rtL180M + rtM204V + rtS202G
- D. Todas son correctas



4-Resistencia al tratamiento

Las mutaciones de resistencia se seleccionan en diferentes regiones del gen de la polimerasa y son específicas de cada fármaco o familia de fármacos.

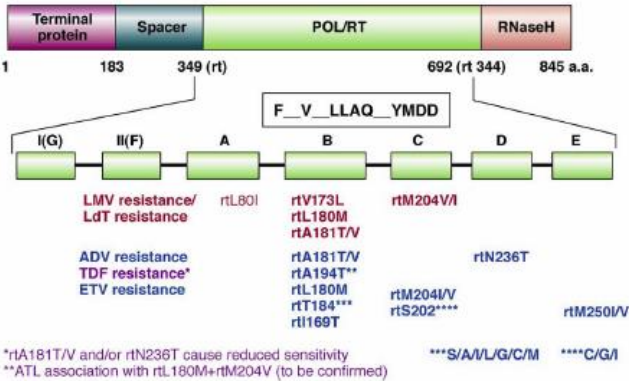
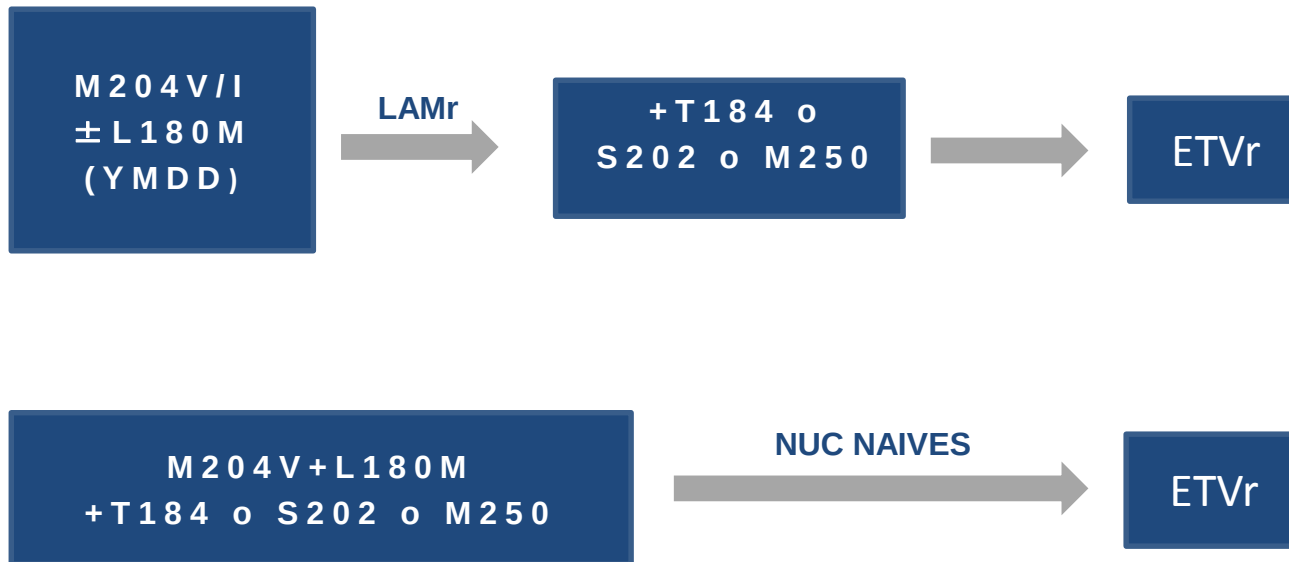


Table 1. Patterns and pathways of antiviral drug resistance in chronic hepatitis B in the context of cross-resistance.

Pathway	Amino acid substitution in the rt domain	LMV	LdT	ETV	ADV	TFV
WT		S	S	S	S	S
L-nucleoside (LMV/LdT)	M204I/V	R	R	I	S	S
Acyclic phosphonate (ADV)	N236T	S	S	S	R	I
Shared (LMV, LdT, ADV)	A181T/V	R	R	S	R	I
Double (ADV, TFV)	A181T/V + N236T	R	R	S	R	R
D-Cyclopentane (ETV)	L180M + M204V/I ± I169 ± T184 ± S202 ± M250	R	R	R	S	S

Modified from Zoulim and Locarnini (2009)[18], Copyright (2009), with permission from Elsevier. I, intermediate sensitivity; R, resistant; S, sensitive based on cell culture and clinical.

PATRONES DE MUTACIONES EN ETVr



Determinación de variantes resistentes

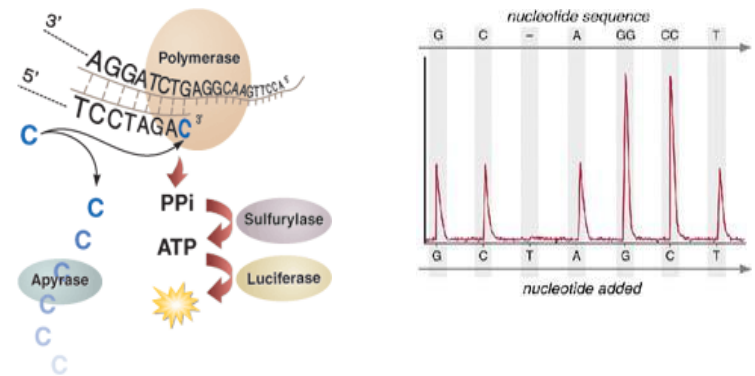
Métodos genotípicos:

1-Ensayos de secuenciación directa:

- Poblacional:** Elaborados en el propio laboratorio o Comerciales (TRUGENE HBV Genotyping kit de Siemens Medical Solutions Diagnostics y HBV Sequencing Assay de Abbott Molecular para variantes del gen POL)
- Clonal.**
- De Nueva Generación:** Pirosecuenciación (454 Life Sciences/Roche Diagnóstics), terminadores reversibles (Illumina), secuenciación a tiempo real (Applied Biosystems y Pacific Biosciences/Gen-Probe), etc.

2-Ensayos de detección de mutaciones puntuales (PMA).

- Hibridación mediante sondas específicas** (LiPA, Innogenetics).
- PCR selectiva** (alelo específica y a tiempo real).
- Minisecuenciación** (PCR + hibridación)
- RFLP.**
- Microarrays con oligonucleótidos** (Chips de ADN)
- Espectrometría de masas basada en RFMP**

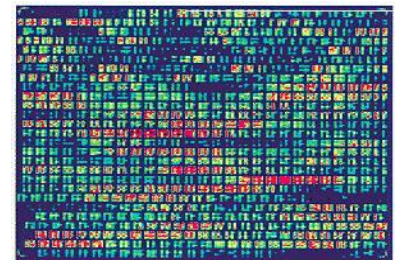
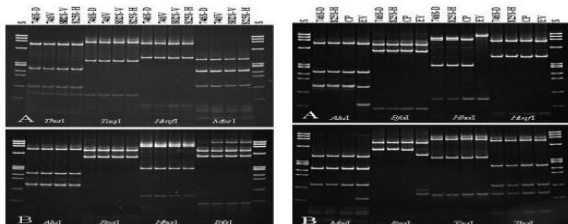


Métodos fenotípicos:

1-Ensayos enzimáticos de la polimerasa viral.

2-Modelos de cultivo celular para el análisis de la replicación viral en líneas HepG2 (Southern Research).

3-Aproximación al Fenotipo virtual (SeqHepB, Geno2pheno HBVSeq, HBV Grade, etc).





Evolución del tratamiento

Sem 1: ETV 0.5 mg/día

Sem 48: Respuesta bioquímica

Respuesta Viroológica Parcial (2.45 log UI/mL)

Cambio ETV 1 mg/día

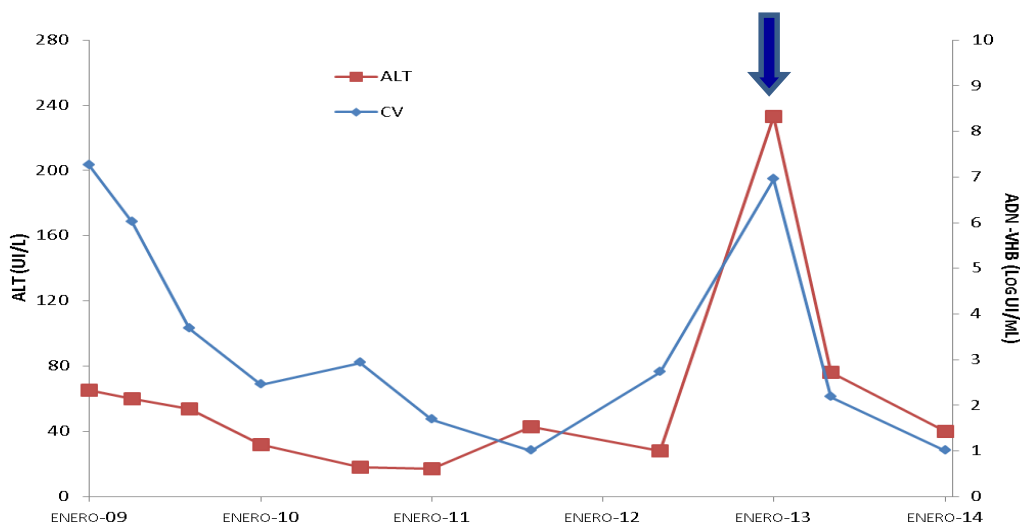
Sem 132: Respuesta Viroológica

Sem 164: Rebote virológico (2.72 log UI/mL)

Sem 192: Rebote virológico? (6.94 log UI/mL)

Rebote bioquímico (ALT 233 UI/L)

Genotipado POL: rtI180M, rtS202G y rt204V



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HBV resistance prediction from genotype (version 2.0)

I. General information

Patient:	Study id:
Birth date:	Viral load:
Sample received:	Sample collected:
Sample ID: SCQETV - B883	Predicted genotype: A (A2)
Sample type:	Report date:
Physician:	Reported by:

II. Substitutions

RT domain:	RT139-171: 171M, 172S, 173V, 174V
SHB protein:	SHB139-171: 171M, 172S, 173V, 174V
Escape:	

III. Resistance analysis

Drug	Prediction	Detected Mutations
Lamivudine	resistant	180M, 204V
Adelovir	susceptible	none
Entecavir	susceptible	204V, 204V, 180M
Tenofovir	susceptible	none
Telbivudine	resistant	204V

Comments:

(signature)

Características del paciente



Hombre

ALT casi normales

Alta carga viral ($> 7.0 \log \text{ UI/mL}$)

HBeAg positivo

Respuesta Viral Parcial

Lenta disminución de la CV

CV persistentemente detectable

Estudios de resistencia a ETV mediante SNG (HiSeq)

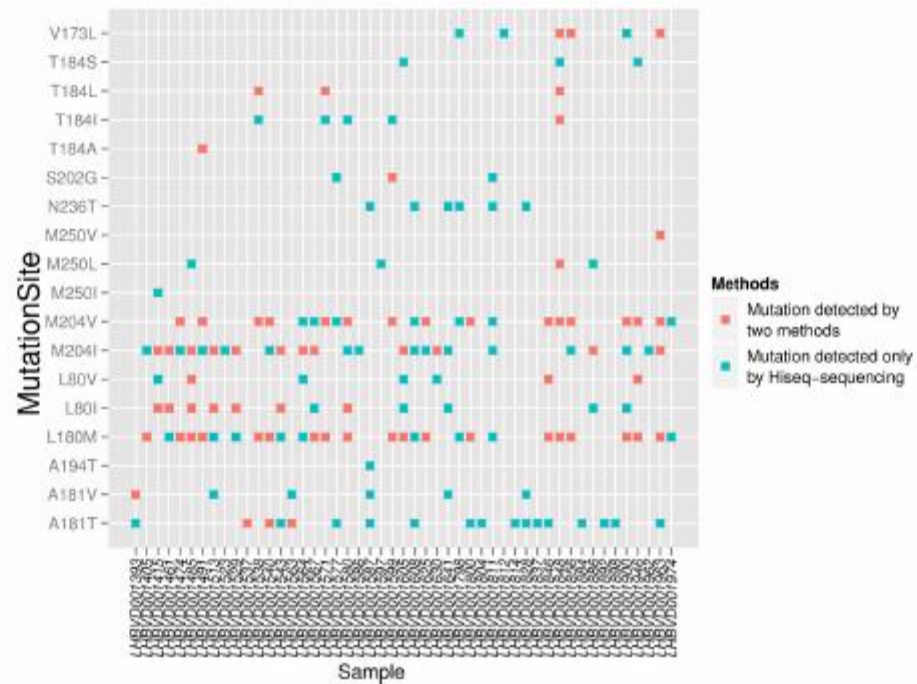


Fig. 2. Comparison of HiSeq sequencing and direct PCR sequencing on HBV test results from 49 patients. Thirteen patient samples were drug-resistance-mutation-positive using the HiSeq 2000 analysis but negative using the direct PCR sequencing analysis (3730 sequencing), and 36 patient samples showed more mutation sites in the HiSeq 2000 than in the 3730 analysis.

Estudios de resistencia a ETV mediante RFMP (MALDI-TOF)

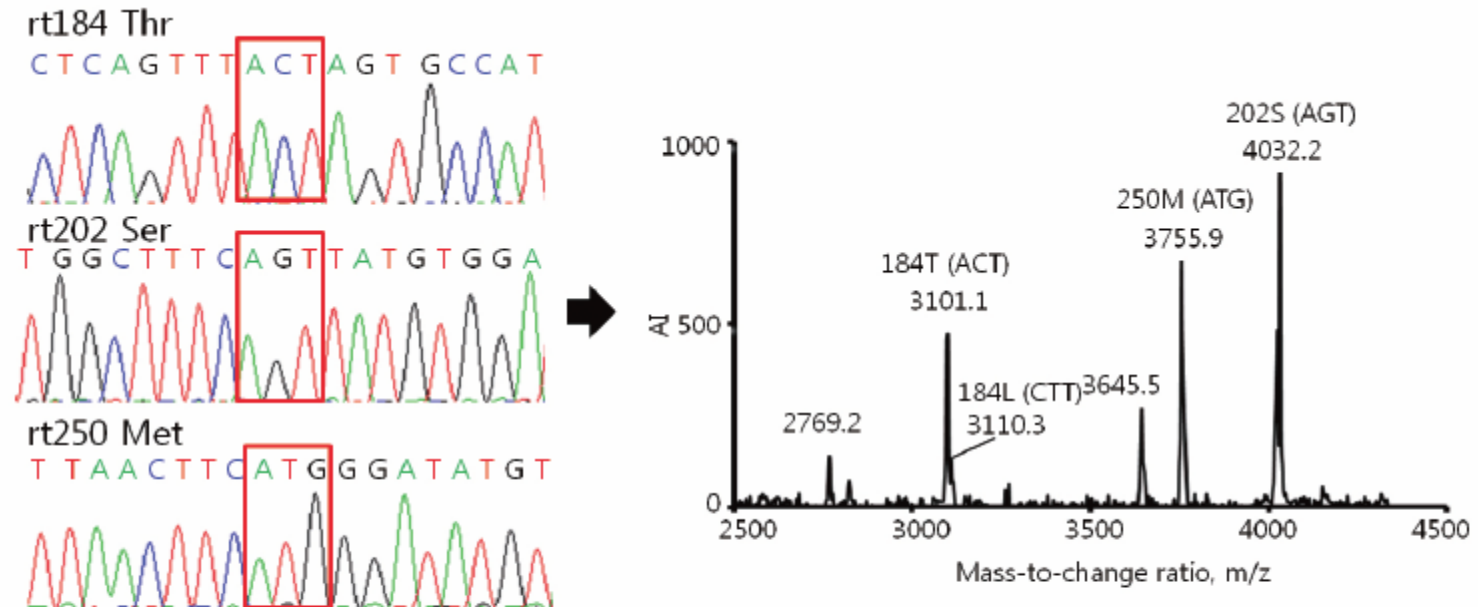


Figure 1. Comparison of the results of the HepB Typer-Entecavir kit and direct sequencing assays for detecting mixed genotypes. Sera were taken from patients infected with HBV and carrying entecavir resistance mutations, and examined using the HepB Typer-Entecavir kit and direct sequencing assays. (A) Molecular masses of 2769.2/3101.0 and 3046.7 represent Thr (ACT) and Leu (CTT) of codon rt184, respectively. However, the direct sequencing assay determined only the Thr (ACT) of codon rt184 in the clinical samples. Molecular mass of 4032.2 represents Ser (AGT) of codon rt202. Molecular masses of 3645.5/3755.9 represent Met (ATG) of codon rt250. Each codon is indicated by a red box in the sequencing chromatogram. AI, absolute intensity; m/z, mass-to-charge ratio.



Evolución del tratamiento

Sem 1: ETV 0.5 mg/día

Sem 48: Respuesta bioquímica

Respuesta Viroológica Parcial (2.45 log UI/mL)

Cambio ETV 1 mg/día

Sem 132: Respuesta Viroológica

Sem 164: Rebote virológico (2.72 log UI/mL)

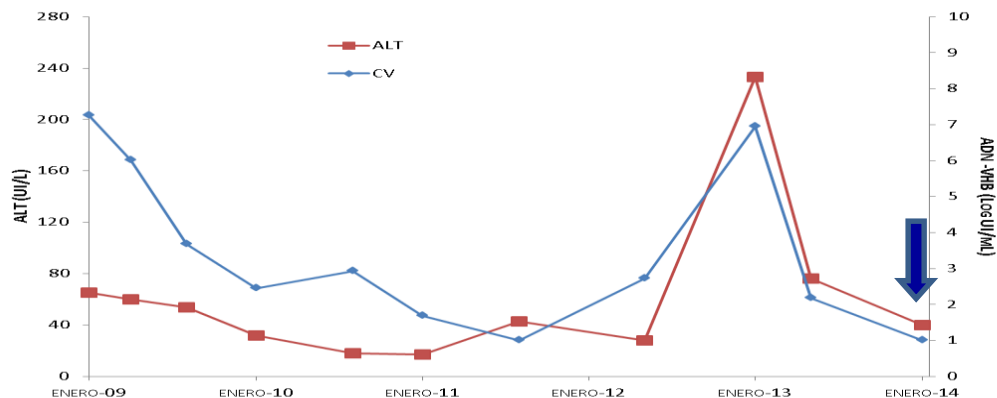
Sem 192: Rebote virológico? (6.94 log UI/mL)

Rebote bioquímico (ALT 233 UI/L)

Genotipado POL: rtI180M, rtS202G y rt204V

Rescate TDF 300 mg/día

Sem 48: Respuesta Viroológica



Consideraciones a la resistencia antiviral en la HCB

Las recomendaciones de manejo del tratamiento en la HCB dan poco valor clínico a la identificación de mutaciones asociadas a la resistencia antiviral, ya que esta información rara vez influye en la elección de la terapia.

Las pruebas de resistencia habitualmente no se están recomendando al asumirse que los incrementos de carga viral son indicativos de resistencia antiviral.

La resistencia a análogos de nucleós(t)idos sólo puede ser confirmada con ensayos genotípicos o fenotípicos en el laboratorio.

Tasas de resistencia a NUC(t) en pacientes con HCB

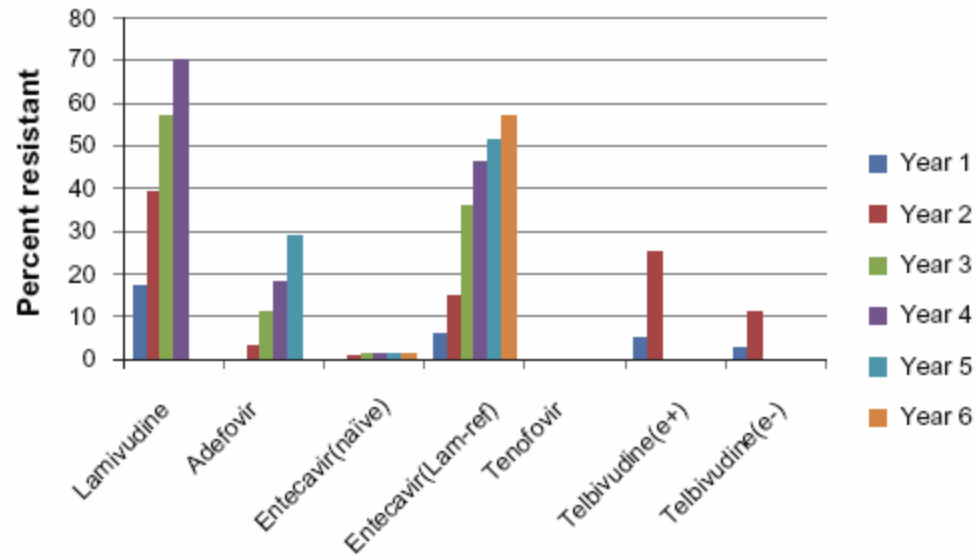


Figure 1 Resistance rates of available nucleos(t)ide analogs in hepatitis B patients. Note that no tenofovir resistance has been seen through 4 years of follow-up.^{21,24-46}
Abbreviations: e+, hepatitis B e-antigen positive; e-, hepatitis B e-antigen negative; lam-ref, lamivudine refractory.

Estudio Oriente: ETV en España

Original article 535

Efficacy and safety of entecavir in clinical practice in treatment-naïve Caucasian chronic hepatitis B patients

Maria Buti^a, Rosa Maria Morillas^b, Martín Prieto^{d,i}, Moisés Diago^a, Juan Pérez^j, Ricard Solà^c, Lucia Bonet^g, Antonio Palau^{h,i}, Milagros Testillanoⁱ, Javier García-Samaniego^j, Manuel Rodríguez^k and the ORIENTE Study Group

Background Entecavir is an effective treatment for chronic hepatitis B. However, data from clinical practice are limited, especially in hepatitis B e antigen (HBeAg)-positive patients.

Methods We retrospectively analysed data from 190 nucleos(t)ide-naïve chronic hepatitis B patients treated with entecavir (0.5 mg/day) in 25 Spanish centres. Virological response (hepatitis B virus DNA <50 IU/ml by PCR), biochemical response (alanine aminotransferase $\leq 1 \times$ upper limit of normal) and serological response were assessed at weeks 12, 24, 36 and 48.

Results The cohort was 73% male, 84% Caucasian, and 30% HBeAg-positive. Thirty-four per cent of the patients who underwent biopsy had advanced fibrosis/cirrhosis. At baseline, the median hepatitis B virus DNA was 5.94 (interquartile range = 4.64–7.39) $\log_{10}$ IU/ml. At week 48, 83% of the patients (61% HBeAg-positive; 92% HBeAg-negative) achieved a virological response and 82% (78% HBeAg-positive; 83% HBeAg-negative) of those with elevated baseline alanine aminotransferase showed a biochemical response. Twenty-six per cent (14/54) of the HBeAg-positive patients lost HBeAg and 22% (12/54) achieved seroconversion to anti-HBe. A significant correlation was observed between virological response at week 12 and the rate of seroconversion to anti-HBe at week 48 ($P=0.039$). This correlation was also noted at weeks 24, 36 and 48 ($P=0.003$, 0.002 and 0.017,

respectively). Three patients (2%) showed clearance of hepatitis B surface antigen. No resistance to entecavir was observed. Treatment with entecavir was generally well tolerated. No patients discontinued treatment due to adverse events.

Conclusion Entecavir monotherapy in clinical practice was well tolerated and resulted in a rapid and significant reduction in viral load. A virological response at week 12 correlated significantly with the rate of seroconversion to anti-HBe at week 48. *Eur J Gastroenterol Hepatol* 24:535–542 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

European Journal of Gastroenterology & Hepatology 2012; 24:535–542

Keywords: chronic hepatitis B, clinical practice, entecavir

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Received 10 September 2011 Accepted 5 January 2012

Introduction

Chronic hepatitis B (CHB) affects approximately 350 million individuals, and every year, around 600 000 people die from CHB-related liver diseases [1]. According to the European Centre for Disease Control [2], 6369 cases of hepatitis B infection were confirmed in Europe in 2008 (1.29 cases per 100 000 inhabitants). Spain accounted for over 10% of these cases (758). In contrast to several European countries, an increase in the incidence of hepatitis B virus (HBV) infection was observed in Spain between 2006 and 2008 (1.1–1.7 cases per 100 000 inhabitants).

Individuals suffering from CHB are at a greater risk of death and of developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma [3–5]. The Risk Evaluation of Viral Load Elevation and Associated Liver

Diseases/Cancer study demonstrated that progression to liver cirrhosis, hepatocellular carcinoma and liver-related mortality correlates strongly with the level of circulating HBV DNA [3,4]. The cumulative incidence of cirrhosis increased from 4.5% in patients with an HBV DNA level less than 300 copies/ml to 36.2% in patients with HBV DNA levels of at least 10^6 copies/ml ($P<0.001$) [4]. Consequently, one of the objectives of treatment is to suppress replication of HBV, thus reducing the necroinflammatory response and stopping or reversing progression of liver disease [6–8].

Hepatitis B e antigen (HBeAg) seroconversion is an important goal in clinical remission and in the transition to inactive carrier status [9]. It may be spontaneous or induced by treatment and is associated with reduced incidence of hepatic complications and improved survival,

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Tratamiento con NUC(t)s: Duración

Long-term hepatitis B surface antigen (HBsAg) kinetics during nucleoside/nucleotide analogue therapy: Finite treatment duration unlikely

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See Focus, pages 641–642

Background & Aims: Information regarding long-term HBsAg kinetics during treatment with nucleoside/nucleotide analogues is limited. The aim of the present study was to assess whether finite nucleoside/nucleotide analogue treatment duration could be envisaged during the patient's lifetime.

Methods: Patients with chronic hepatitis B receiving different schedules of nucleoside/nucleotide analogues were followed for a median duration of 102 months, i.e., 8.5 years (interquartile range: 88–119 months). Long-term HBV DNA and HBsAg level kinetics were modeled in order to estimate time to clear HBsAg during therapy in patients with undetectable HBV DNA.

Results: Antiviral therapy was associated with a slow but consistent reduction in the level of HBsAg in most of the patients. The patterns of HBsAg level declines were identified: decline during both the detectable and undetectable HBV DNA phases; decline during the HBV DNA detectable period only; decline during the HBV DNA undetectable period only. The mean HBsAg titer at the time when HBV DNA became undetectable was 3.29 ± 0.69 Log₁₀ international units (IU)/mL, and the mean slope was -0.007 ± 0.007 Log₁₀ IU/month, i.e., an average decline of 0.084 Log₁₀ IU/year. The corresponding calculated median number of years needed to clear HBsAg was 52.2 years (interquartile range: 30.8–84.2 years).

Conclusions: This study, based on the very long-term follow-up of patients with chronic hepatitis B treated with potent nucleoside/nucleotide analogues, shows that HBsAg clearance is unlikely to occur during the patient's lifetime, even if HBV replication is well controlled. Thus, lifetime therapy is required in the vast majority of HBV-infected patients.

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Introduction

Recent developments in the antiviral treatment of chronic hepatitis B virus (HBV) infection have emphasized the need for biomarkers that are predictive of treatment outcomes and can be used to tailor therapy to the individual patient. In chronic HBV carriers, hepatitis B surface antigen (HBsAg) is produced as a result of translation of messenger RNA generated from transcriptionally active cccDNA or integrated HBV DNA sequences in the host genome. HBsAg is present in the envelope of infectious HBV virions and in non-infectious spheres and tubules. The latter exceed infectious virions when replication is active; they remain produced in large amounts when replication is controlled, either spontaneously (inactive carriers) or by antiviral therapy [1–4].

A number of recent studies have demonstrated the clinical utility of HBsAg quantification in monitoring HBV therapy [1,5–14]. Indeed, early on-treatment serum HBsAg levels predict the sustained post-treatment response to therapy and the eventual subsequent HBsAg clearance in patients with both hepatitis B e antigen (HBeAg)-positive and HBeAg-negative chronic hepatitis B treated with a finite duration of pegylated interferon (IFN- α) [1,5–9]. HBsAg clearance, followed or not by HBe seroconversion (appearance of anti-HBe antibodies) characterizes a sustained remission of HBV infection.

Standardized quantitative HBsAg level assays are available. Three commercial assays, the HBsAg assay on Architect[®] device (Abbott Diagnostics, Chicago, Illinois), the HBsAg Q_{quant} assay on Elecsys[®] or Cobas[®] e devices (Roche Diagnostics GmbH, Mannheim, Germany), and the Liaison[®] HBsAg Quant assay on Liaison[®] XL device (DiaSorin, Saluggia, Italy) are approved in the European Union; they are available for research use only in

Keywords: Hepatitis B Virus; HBsAg level; Nucleoside/nucleotide analogues.
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Abbreviations: HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; cccDNA, covalently closed circular DNA; HBsAg, hepatitis B e antigen; IFN, interferon; IU, international units; HBV, hepatitis B virus; PCR, polymerase chain reaction; RFL, interquartile range.



Journal of Hepatology 2013 vol. 58 | 676–683

Serum HBsAg Decline During Long-term Potent Nucleos(t)ide Analogue Therapy for Chronic Hepatitis B and Prediction of HBsAg Loss

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Charles A. B. Brouwer⁴ and Harry L. A. Jansz⁵

¹Department of Gastroenterology and Hepatology, ²Department of Biostatistics, and ³Department of Virology, Erasmus MC University Medical Center, Rotterdam, the Netherlands

Nucleos(t)ide analogues strongly inhibit viral replication in chronic hepatitis B (CHB) infection, but knowledge of their long-term effect on serum hepatitis B surface antigen (HBsAg) levels and HBsAg loss is lacking. Seventy-five CHB patients with virological response (VR) to ETV or TDF were included. HBsAg decline 2 years after VR was most pronounced in HBeAg-positive patients. Age, alanine aminotransferase, and HBeAg loss were associated with HBsAg decline in HBeAg-positive patients. Predicted median time to HBsAg loss was 36 years for HBeAg-positive and 39 years for HBeAg-negative patients. Thus, most patients treated with ETV and TDF will probably need decades of therapy to achieve HBsAg loss.

Continuous therapy with entecavir (ETV) or tenofovir (TDF) results in durable suppression of viral replication in the majority of patients with chronic hepatitis B virus (HBV) [1,2]. Current treatment guidelines emphasize HBV DNA suppression as a prerequisite for the prevention of complications of HBV-related liver disease [3].

Serum hepatitis B surface antigen (HBsAg) loss is the preferred endpoint of HBV therapy and approximates clinical cure of the

infection. However, HBsAg loss is rarely observed during therapy with ETV and TDF up to 5 years [1,2].

Recent data indicate that HBsAg quantification during HBV treatment has additional value to HBV DNA quantification, and on-treatment HBsAg was shown to predict a sustained off-treatment response to pegylated interferon (PEG-IFN) therapy [4–7]. HBsAg levels reflect intrahepatic covalently closed circular DNA (cccDNA), the limiting factor in complete clearance of chronic HBV infection, and could probably be used as a surrogate marker for the interaction between the immune system and the virus [8,9].

However, data on the effect of nucleos(t)ide analogue (NA) therapy on HBsAg levels are unclear and predominantly described for less potent NA [5,8,10,11].

The kinetics of serum HBsAg levels during long-term potent suppression of HBV DNA by TDF and ETV therapy are currently unknown. The aims of our study were (1) to investigate HBsAg kinetics in patients successfully treated with long-term ETV or TDF, (2) to identify factors associated with HBsAg decline, and (3) to predict treatment duration required to achieve HBsAg loss.

METHODS

Study Population

All consecutive chronic HBV patients treated with ETV or TDF therapy at the Erasmus MC University Medical Center Rotterdam were included. Patients were eligible if they had a virological response (VR; HBV DNA <100 IU/mL) for at least 48 weeks between April 2009 and December 2009. Patients were excluded if they had viral coinfections (e.g. human immunodeficiency virus, hepatitis C virus, hepatitis D virus). A total of 169 patients were identified, of whom 85 did not fulfill entry criteria and were excluded: 27 had not achieved VR and 58 had < 48 weeks of follow-up after VR. A total of 75 patients were eligible for this analysis. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and principles of Good Clinical Practice. Patients gave written informed consent according to standards of the local ethics committees.

Laboratory Tests

Alanine aminotransferase (ALT) levels were expressed as ratio to the upper limit of the normal range (ULN); 30 U/L for females and 40 U/L for males). Hepatitis B e antigen (HBeAg) and antibody against HBeAg (anti-HBe) status was determined using enzyme immunoassays. Serum HBsAg was quantified at baseline, at VR and each year after VR using the Architect HBsAg assay (Abbott Laboratories, range: .05–250 IU/mL). Serum HBV

Gracias por su atención

Antonio Aguilera .

Servicio Microbiología CHUS y Departamento de Microbiología USC.

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1^a REUNIÓN
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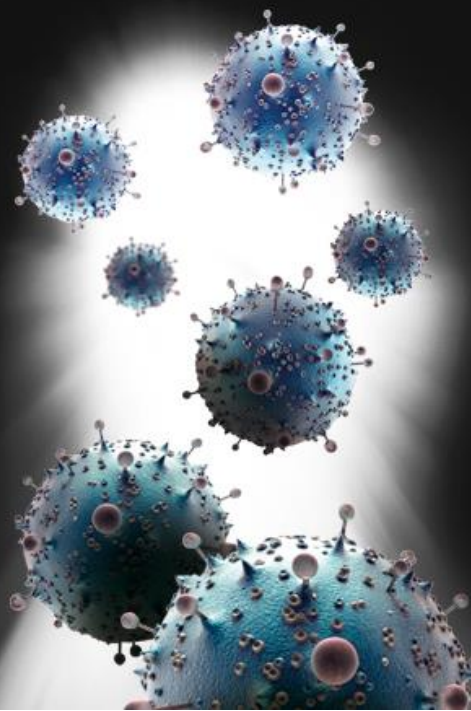
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"Construyendo las bases para la erradicación del VHC"



Caso clínico

Monoinfección

23/05/2014

Dra. Van den Eynde
Hospital de Bellvitge

Caso clínico: mono infección

Varón de 65 años.

- HTA en tratamiento con enalapril 20 mg y amlodipino 10 mg.
- DM tipo 2 en tratamiento con metformina.
- Valvulopatía aórtica con Insuficiencia aórtica II.
- FA paroxística de reciente diagnóstico en tto con warfarina.
- Amaurosis casi total por desprendimiento retiniano.
- Hepatitis crónica por VHC genotipo 1b diagnosticada en 1994.

Caso clínico: mono infección

Varón de 65 años.

- Hepatitis crónica por VHC genotipo 1b diagnosticada en 1994.

- Tratamiento en 2006 con Peg-IFN y RBV durante 48 semanas con Recidiva (PCR cualitativa negativa en semana 12, 24 y al final del tto).

- IL28B (CC).

- ARN-VHC 763.363 copias.

- Fibroscan 19.6.13: 12.4 kPa. (F3)

- AG: Hb 15.2, plaq 118000, L 4900, N 1900, ALT 101, ALB 4.1, creatinina 1.16, eGFR 73.

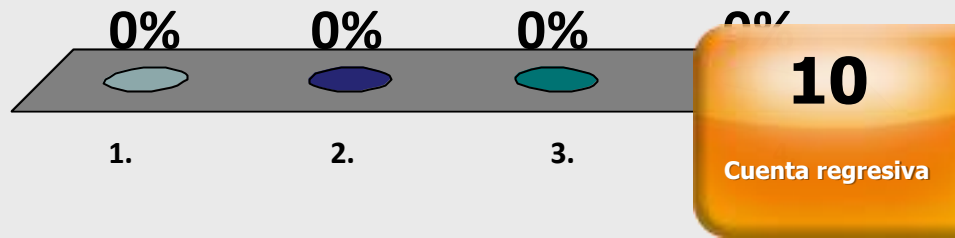
Caso clínico: monoinfección

EDAD	GEN	IL28B	Fibrosis	RESP.TTO
65	1b	CC	F3	RECIDIVA



Es Junio de 2013. Que harías?

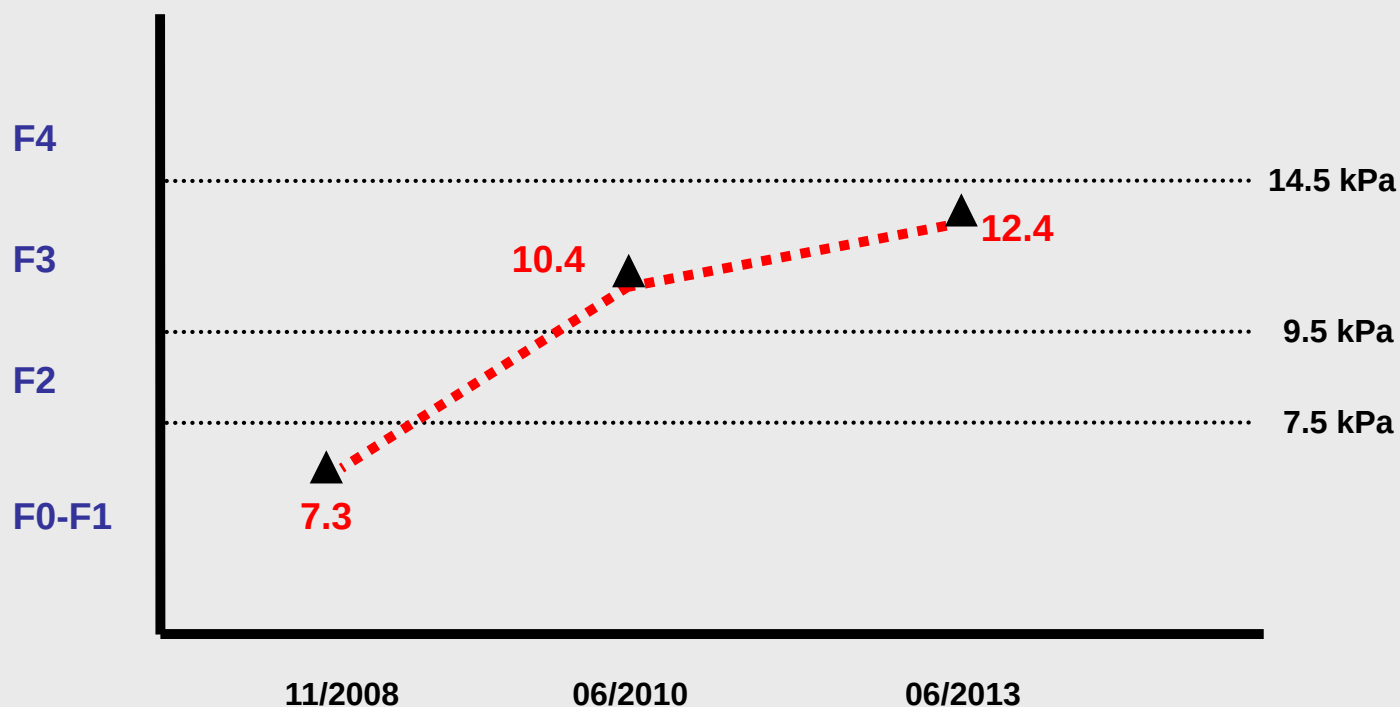
1. Esperar nuevos tratamientos libres de Interferon.
2. Solicitar uso compasivo de Sofosbuvir+RBV.
3. Iniciar re-tratamiento con Peg-IFN y RBV.
4. Tratamiento triple con Boceprevir/Telaprevir, Peg-IFN y RBV.



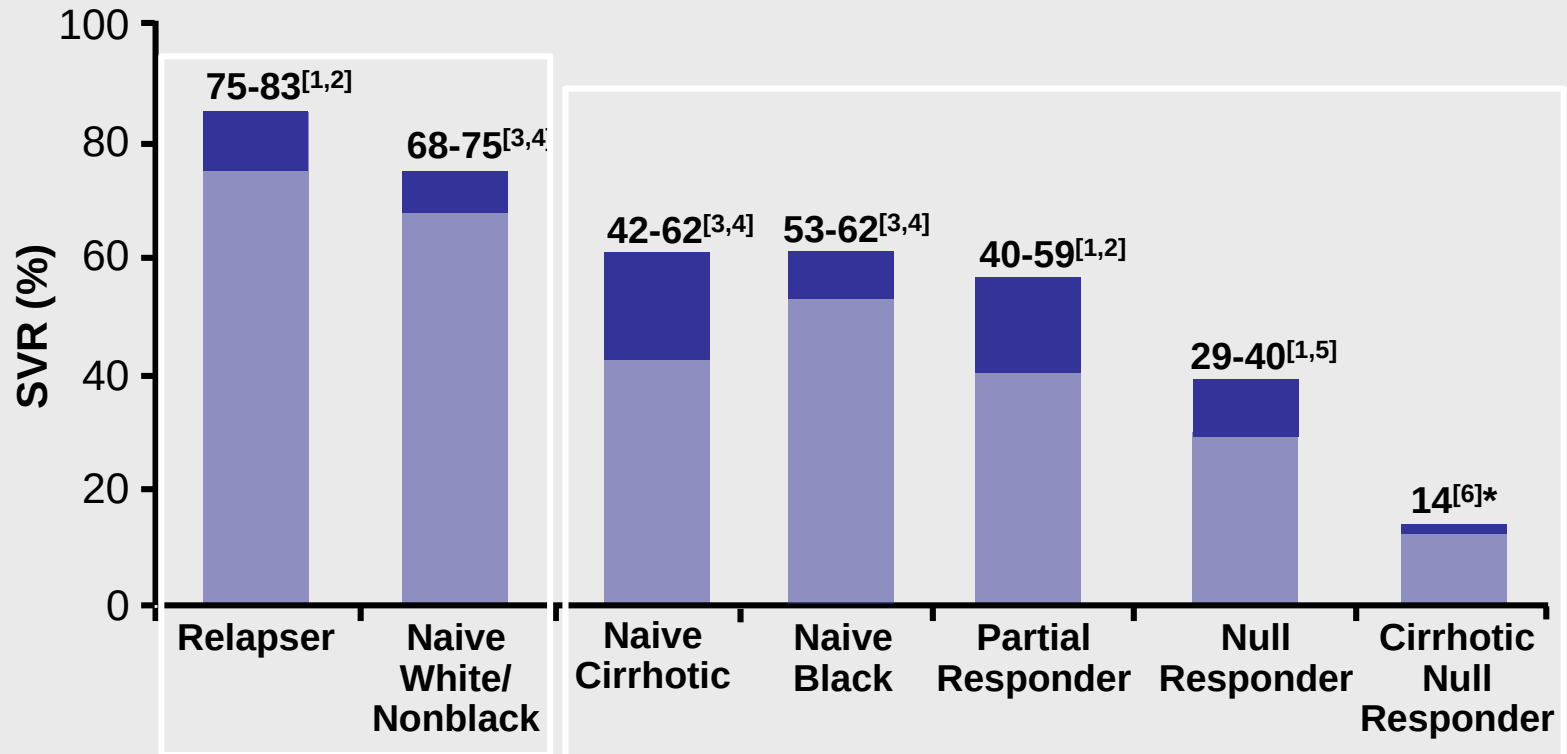
Caso clínico: monoinfección

EDAD	GEN	IL28B	Fibrosis	RESP.TTO
65	1b	CC	F3	RECIDIVA

Evolución de la fibrosis



Eficacia limitada de Telaprevir y Boceprevir en algunos subgrupos



*Pooled TVR arms of REALIZE trial.

1. Zeuzem S, et al. N Engl J Med. 2011;364:2417-2428. 2. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217.
3. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 4. Poordad F, et al. N Engl J Med. 2011;364:1195-1206. 5. Bronowicki J, et al. EASL 2012. Abstract 11. 6. Zeuzem S, et al. EASL 2011. Abstract 5.

Caso clínico: monoinfección

EDAD	GEN	IL28B	Fibrosis	RESP.TTO
65	1b	CC	F3	RECIDIVA

7/10/2013: Inicia tratamiento con Peg-IFN alfa-2a 180 mcg/sem, RBV 1000 mg/d, Telaprevir 1125 mg cada 12 h.

Sem 2: Rash



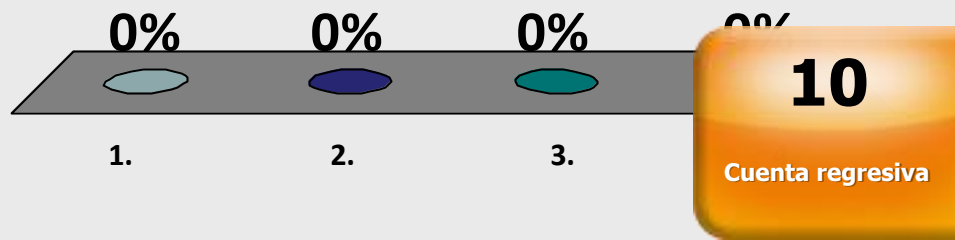
Caso clínico: monoinfección

EDAD	GEN	IL28B	Fibrosis	RESP.TTO
65	1b	CC	F3	RECIDIVA

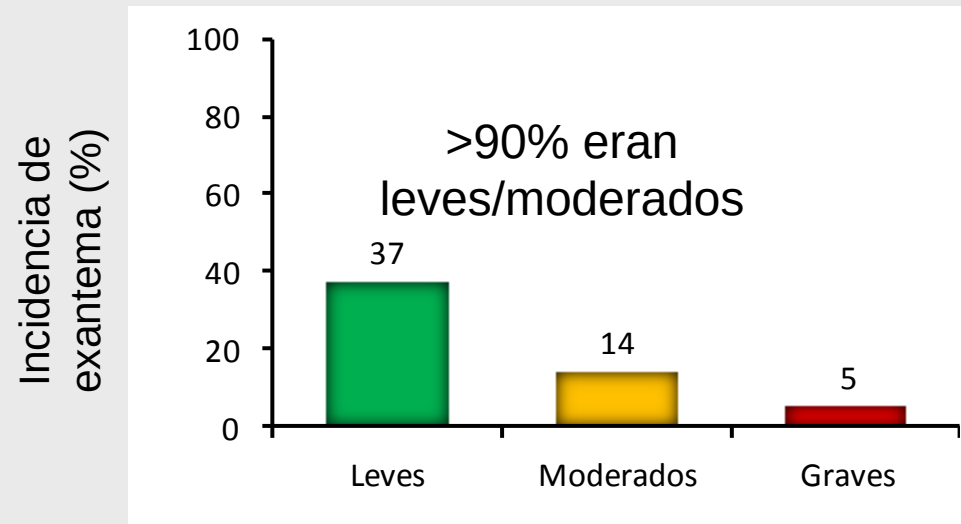
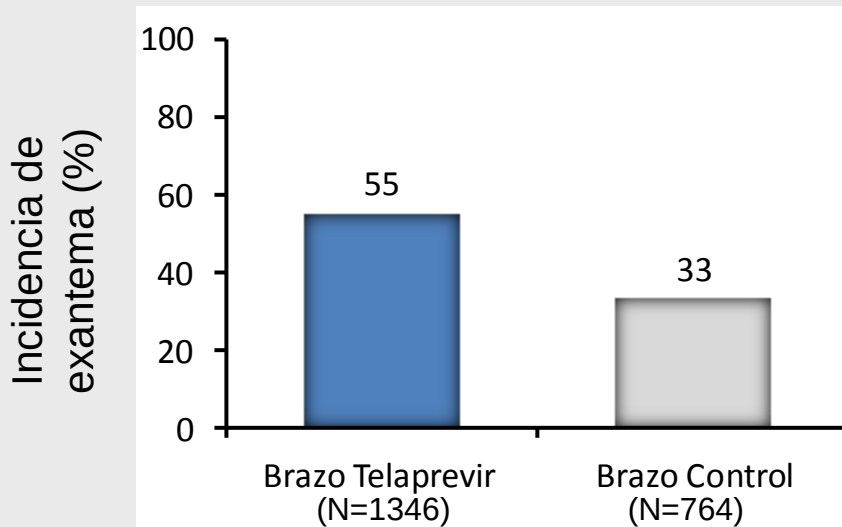


Ante este rash en semana 2. Que harías?

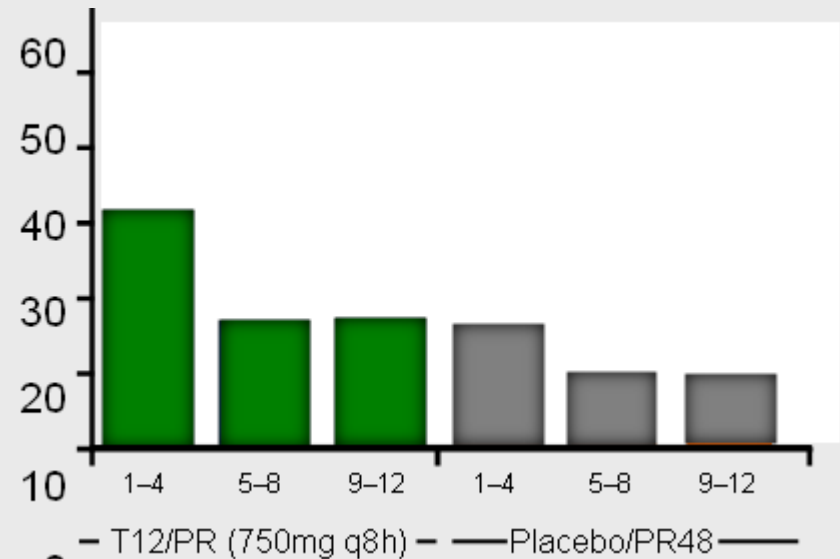
1. Ha presentado un rash muy precozmente, no podrá llegar a semana 12, suspendería todo el tratamiento.
2. Ha presentado un rash muy precozmente, no podrá llegar a semana 12, suspendería Telaprevir y continuaría Peg-IFN y RBV.
3. Iniciaría tratamiento con corticoides tópicos+antihistamínicos y seguiría el tratamiento.
4. De momento nada, vigilar.



Incidencia de Reacciones Cutáneas (Estudios fase II y III)



- Típicamente pruriginosa y ecematososa, afectando <30% de la superficie corporal
- Progresión infrecuente (< del 10% de los casos)
- La interrupción de TVR no suele ser necesaria.
- CORTICOIDES tópicos y ANTIHISTAMÍNICOS sistémicos
- Pueden ocurrir en cualquier momento durante el tratamiento con Telaprevir aunque el 50% comienzan durante las primeras 4 semanas.



Gradación de las reacciones dermatológicas según gravedad

- **Grado 1 (Leve):** erupción cutánea localizada o erupción cutánea con distribución limitada (hasta varios lugares aislados en el cuerpo).

La interrupción de telaprevir generalmente NO es necesaria

- **Grado 2 (Moderada):** erupción difusa que abarca $\leq 50\%$ de la superficie corporal.

La interrupción de telaprevir generalmente NO es necesaria.

Si la interrupción es necesaria por progresión, se recomienda suspender primero telaprevir y, si no se observa mejoría en 7 días, suspender ribavirina.

- **Grado 3 (Grave):** erupción extendida a $>50\%$ de la superficie corporal o asociada con síntomas sistémicos significativos, ulceración de mucosas, lesiones en escarapela, desprendimiento epidérmico.

Suspender telaprevir

Si la reacción cutánea no mejora a los 7 días de suspender TVR (o antes, si la reacción cutánea empeora), se debe interrumpir ribavirina

- **Grado 4 (SCAR):** término general para cuadros dermatológicos graves relacionados con exposición a fármacos, que pueden estar asociados a una significativa morbilidad.

Suspensión permanente de todos los fármacos: telaprevir, ribavirina, peginterferón

TELAPREVIR no se debe volver a administrar una vez ha sido suspendido

Caso clínico: monoinfección

EDAD	GEN	IL28B	Fibrosis	RESP.TTO
65	1b	CC	F3	RECIDIVA

	TVR initiation	wk 2	wk 3	wk 4					
Hemoglobin, mg/dL	15.2	13.8	12.5						
White blood cells, x10E ⁶ /L	4900	3900	3200						
Neutrophils, x10E ⁶ /L	1900	1400	1200						
Platelets, x10E ⁶ /L	118000	110000	131000						
HCV-RNA , IU/mL	763363								
Plasma Creatinine, mg/dL	1.16	1.42	1.42						
eGFR, mL/min	73	56	57						
Urine analysis	Neg	Neg							
ALT, IU/L	101	65							

Sem 3: TA 98/60, astenia. STOP amlodipino.

Caso clínico: monoinfección

EDAD	GEN	IL28B	Fibrosis	RESP.TTO
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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2011, p. 4569–4574

Vol. 55, No. 10

0066-4804/11/\$12.00 doi:10.1128/AAC.00653-11

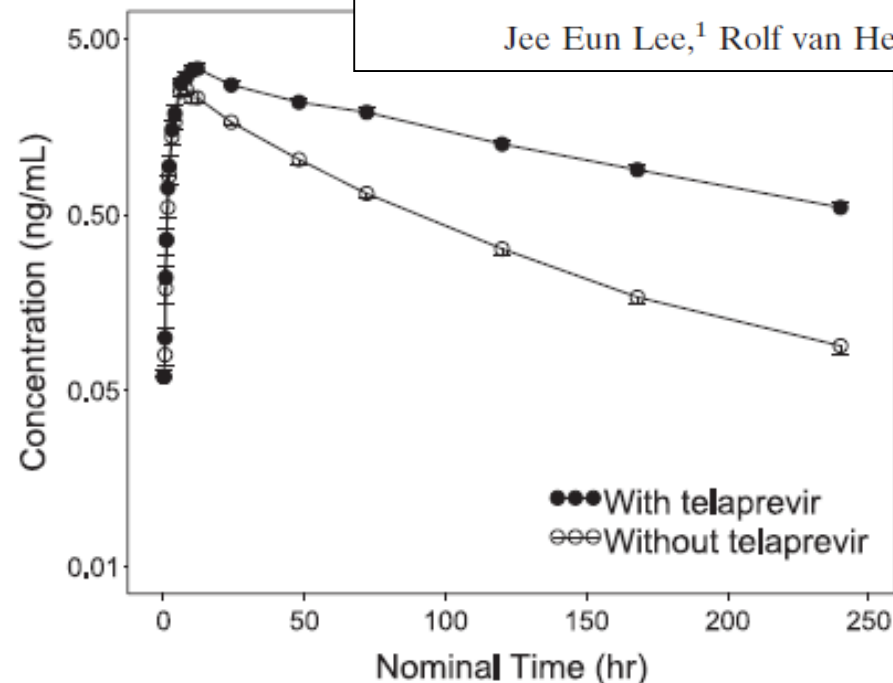
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Interac

Effect of the Hepatitis C Virus Protease Inhibitor Telaprevir on the Pharmacokinetics of Amlodipine and Atorvastatin[▽]

Jee Eun Lee,¹ Rolf van Heeswijk,² Katia Alves,¹ Frances Smith,¹ and Varun Garg^{1*}

Anti-coagulant & Anti-platelet



	□	◇	□
	Boceprevir	Sofosbuvir	Telaprevir
	n/a	□	n/a
	□	n/a	□
	n/a	□	n/a
	Boceprevir	Sofosbuvir	Telaprevir
	◇	◇	◇

e 3 meses.

may increase concentrations of amlodipine. Amlodipine is a weak inhibitor

concentrations. Monitor INR closely.

Significant interaction is unlikely.

Telaprevir and Amlodipine: increased amlodipine C_{max} by 27% and AUC by 2.79-fold. Use with caution and consider a dose reduction for amlodipine. A clinically significant effect on telaprevir is unlikely.

Telaprevir and Warfarin: Coadministration may alter warfarin concentrations. Monitor INR.

Caso clínico: mono infección

EDAD	GEN	IL28B	Fibrosis	RESP.TTO
65	1b	CC	F3	RECIDIVA

	TVR initiation	wk 2	wk 3	wk 4					
Hemoglobin, mg/dL	15.2	13.8	12.5	10					
White blood cells, x10E ⁶ /L	4900	3900	3200	3800					
Neutrophils, x10E ⁶ /L	1900	1400	1200	2000					
Platelets, x10E ⁶ /L	118000	110000	131000	117000					
HCV-RNA , IU/mL	763363			65					
Plasma Creatinine, mg/dL	1.16	1.42	1.42	1.86					
eGFR, mL/min	73	56	57	43					
Urine analysis	Neg	Neg							
ALT, IU/L	101	65		36					

Sem 3: TA 98/60, astenia. STOP amlodipino.

Sem 4: TA 100/55, astenia, náuseas, deterioro de la función renal.

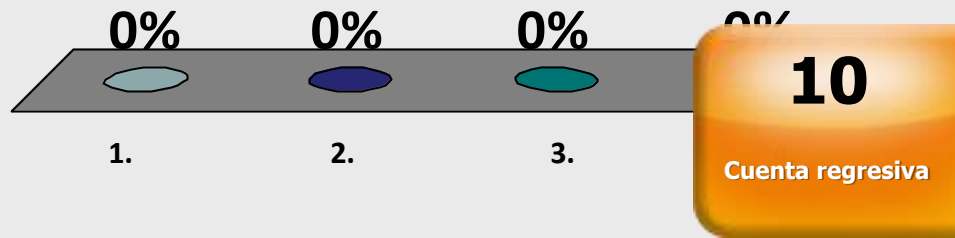
Caso clínico: monoinfección



EDAD	GEN	IL28B	Fibrosis	RESP.TTO
65	1b	CC	F3	RECIDIVA

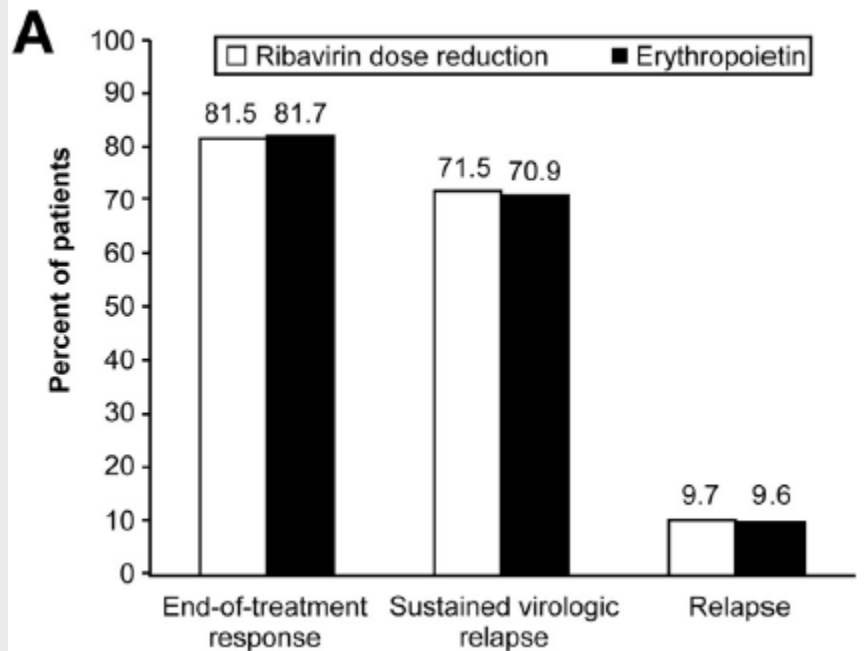
Sem 4: Anemia y empeoramiento de la función renal. Que harías?

1. Suspender todo el tratamiento.
2. Suspender Telaprevir y continuar Peg-IFN 180 mcg/sem y RBV 1000 mg/d.
3. Suspender Telaprevir, bajar RBV a 800 mg/d y Peg-IFN 180 mcg/sem.
4. Seguir igual, este tratamiento no provoca insuficiencia renal y hay que mantener dosis altas de RBV para lograr la curación.



Effects of Ribavirin Dose Reduction vs Erythropoietin for Boceprevir-Related Anemia in Patients With Chronic Hepatitis C Virus Genotype 1 Infection—A Randomized Trial

FRED POORDAD,¹ ERIC LAWITZ,¹ K. RAJENDER REDDY,² NEZAM H. AFDHAL,³ CHRISTOPHE HÉZODE,⁴ STEFAN ZEUZEM,⁵ SAMUEL S. LEE,⁶ JOSE LUIS CALLEJA,⁷ ROBERT S. BROWN, JR.,⁸ ANTONIO CRAXI,⁹ HEINER WEDEMAYER,¹⁰ LISA NYBERG,¹¹ DAVID R. NELSON,¹² LORENZO ROSSARO,¹³ LUIS BALART,¹⁴ TIMOTHY R. MORGAN,¹⁵ BRUCE R. BACON,¹⁶ STEVEN L. FLAMM,¹⁷ KRIS V. KOWDLEY,¹⁸ WEIPING DENG,¹⁹ KENNETH J. KOURY,¹⁹ LISA D. PEDICONE,¹⁹ FRANK J. DUTKO,¹⁹ MARGARET H. BURROUGHS,¹⁹ KATIA ALVES,¹⁹ JANICE WAHL,¹⁹ CLIFFORD A. BRASS,¹⁹ JANICE K. ALBRECHT,¹⁹ and MARK S. SULKOWSKI,²⁰ for the Protocol 6086 Investigators

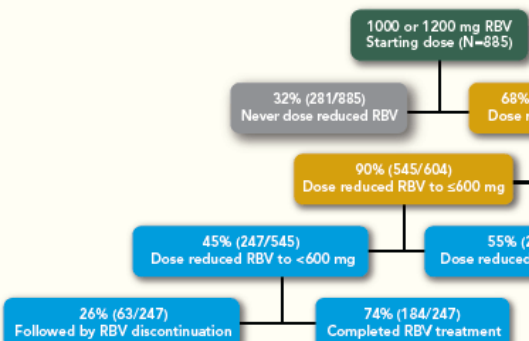


RBV Dose Reduction for First-line Anemia Management Did Not Impact SVR

- 82% of RBV dose reduction group vs 62% in EPO group did not require secondary anemia intervention

Ribavirin Dose Modification in Treatment-naïve and Previously Treated Patients Who Received Telaprevir Combination Treatment: No Impact on Sustained Virologic Response in Phase 3 Studies

(A) ADVANCE and ILLUMINATE (T12PR, N=885)



(B) REALIZE (T12PR48, N=259)

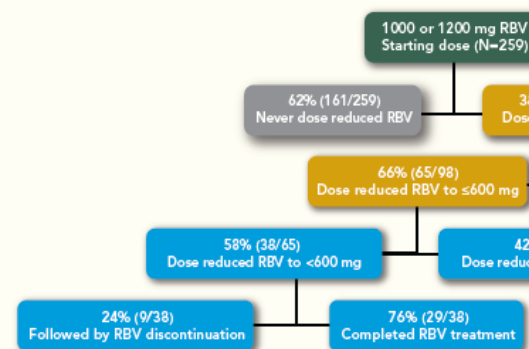
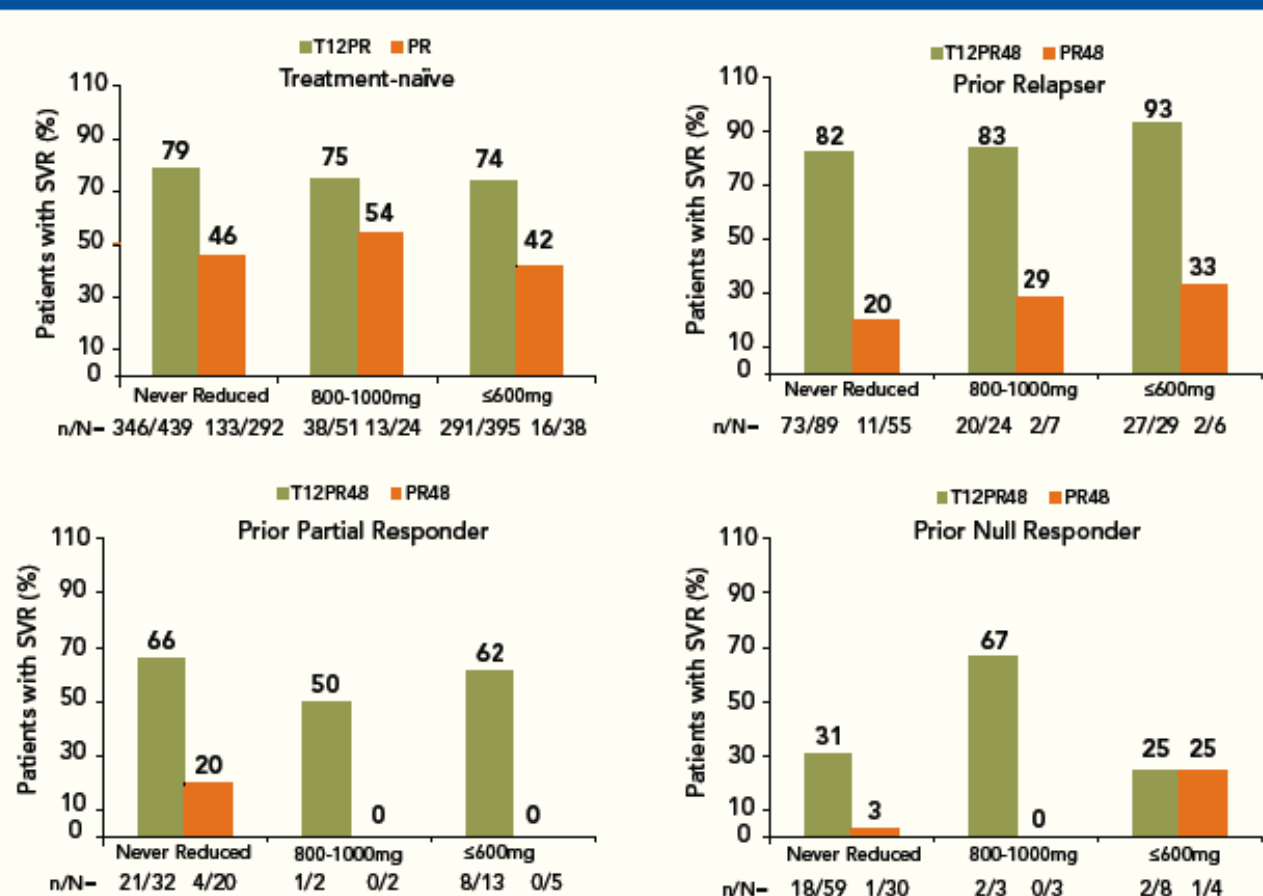


Figure 3: Overall Proportion of Treatment-naïve Patients, and Patients with Prior Relapse, Prior Partial, and Prior Null Response with SVR According to Minimum Ribavirin Dose/Day During the Telaprevir Treatment Phase



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- ☐ [Renal impairment during the treatment of telaprevir with peginterferon and ribavirin in patients with chronic hepatitis C.](#)

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- ☐ [Reply to: Renal impairment is frequent in chronic hepatitis C patients under triple therapy with telaprevir or boceprevir.](#)

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Renal impairment during the treatment of telaprevir with peginterferon and ribavirin in patients with chronic hepatitis C

Manuscript type: Original Article

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25 pacientes VHC 1

TVR 12+PR

TVR dosis (14 ptes.2250 vs.11ptes.1500 mg/d)

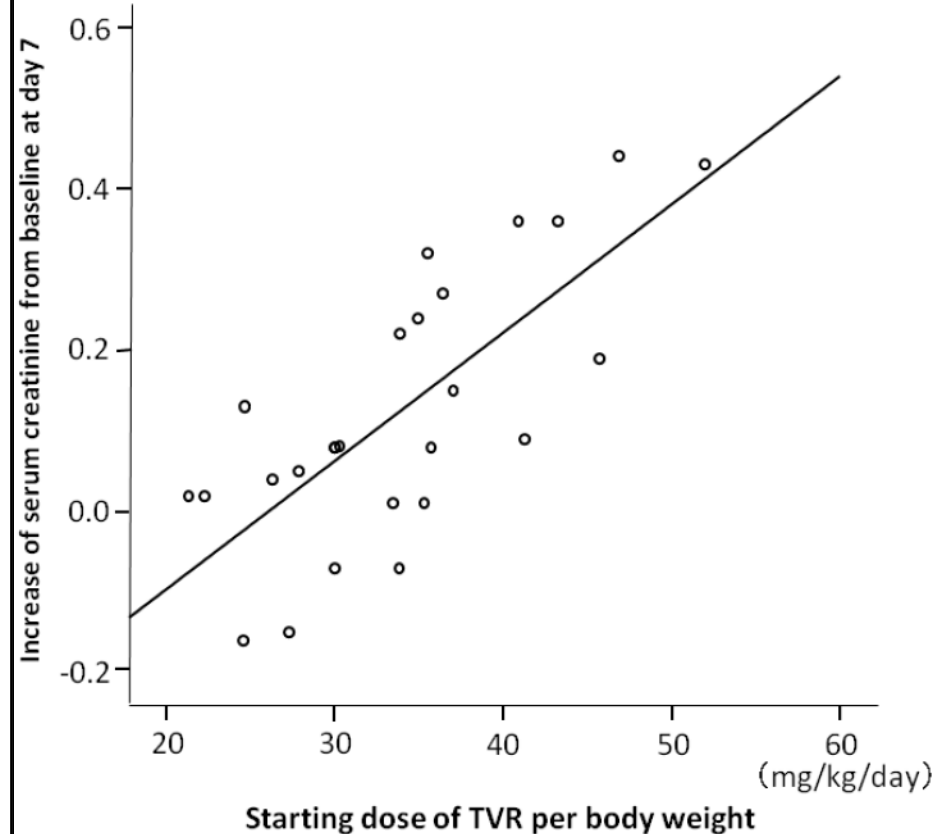
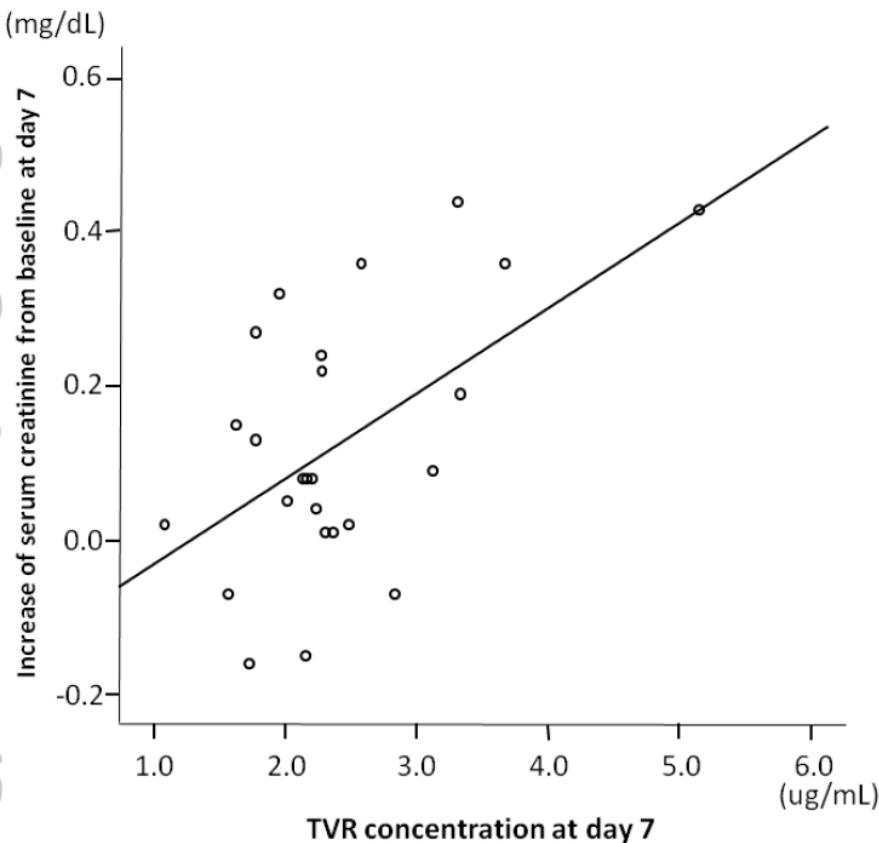
	Basal	Día 7	p
Clearance (mL/min/1.73m ²)	84.4 ± 21.2	69.9 ± 17.6	P<0.001
Creatinina	0.78 ± 0.19	0.90 ± 0.21	P<0.001
Cistatina C	1.03 ± 0.15	1.21± 0.25	P<0.001

Renal impairment during the treatment of telaprevir with peginterferon and ribavirin in patients with chronic hepatitis C

25 pacientes VHC 1

TVR 12+PR

TVR dosis (14 ptes.2250 vs.11ptes.1500 mg/d)



- Los niveles de creatinina y cistatina C se correlacionaron con los de TVR en suero el día 7.
- Al estratificar por dosis TVR/Kg peso, sólo en pacientes con dosis inicial de TVR >33 mg/Kg/día el cambio en el aclaramiento renal fue significativo.

Renal impairment is frequent in chronic hepatitis C patients under triple therapy with telaprevir or boceprevir

895 pacientes tto VHC
(TVR 575, BOC 211 y PR 109)

Table 1: Baseline demographics

	Dual therapy N=109	Boceprevir N=211	Telaprevir N=575
Mean age (years)	41,6 +/-11.5	48.9 +/- 10.5	48.5 +/-11.0
Female sex	39%	39%	33%
Body mass index (kg/m ²), mean ± SD	25.4 ± 4.2	27.0 ± 5.0	26.4 ± 4.4
smoking	53%	50%	41%
Median creatinine (mg/dL)	0,8	0,8	0,8
eGFR >60- 90 ml/min	25%	31%	24%
eGFR >90 ml/min	75%	69%	76%
ALT U/L mean ± SD	110.± 63	89 ± 61	97 ± 81
HCV-RNA ≤400.000 IU/mL	49,5%	28,6%	23,4%
Arterial hypertension	9%	26%	16%
Diabetes mellitus	2%	9%	7%
APRI Score >1.5	12%	17%	18%

	TVR+PR	BOC+PR	PR
Week 12			
Clearance reduction to <60 mL/min/1.73m ²	38/575 (6.6%) (p<0.05)	10/211 (4.7%) (p<0.05)	1/109 (0.9%)
Week 24			
Clearance reduction to <60 mL/min/1.73m ²	5/398 (1.3%)	5/113 (4.4%)	1/80 (1.3%)

Factores asociados con el descenso del aclaramiento renal:

- Creatinina basal
- TVR o BOC vs. PR
- HTA

Reply to: Renal impairment is frequent in chronic hepatitis C patients under triple therapy with telaprevir or boceprevir.

Loustaud-Ratti Véronique^{1,2}, MD, Carrier Paul¹, MD, Vong Chanlina¹, MD, Essig Marie^{3,4}, MD, PhD.

- TVR inhibe transportador renal OCT2 interfiriendo en la secreción de creatinina a nivel del túbulo distal e incrementando secundariamente la concentración de creatinina en suero.
- Este efecto es reversible cuando cesa la inhibición del transportador por parte de TVR

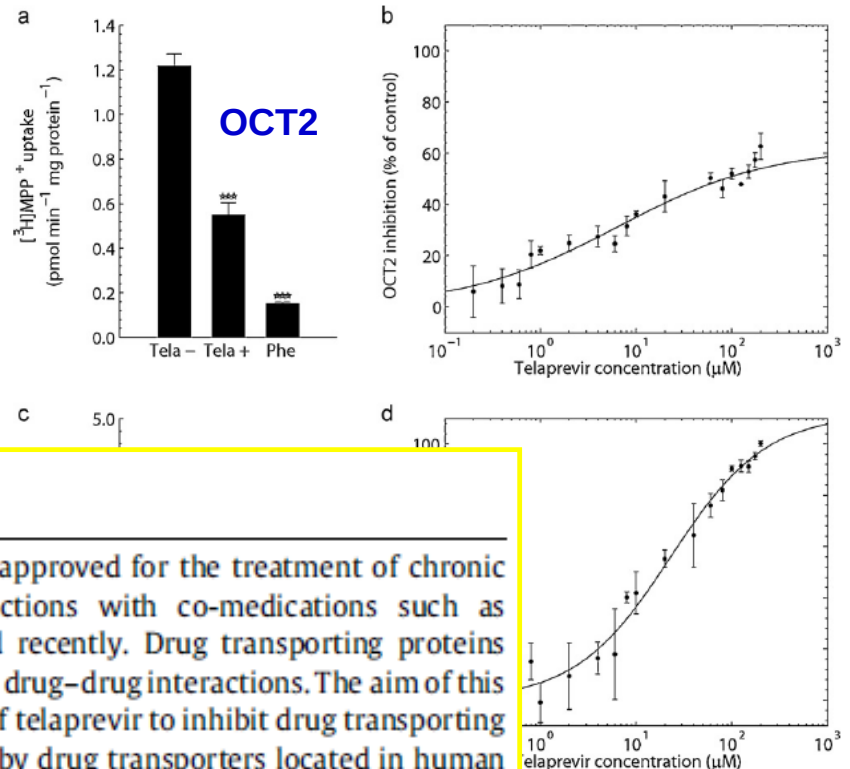


Interaction of the antiviral drug telaprevir with renal drug transporters

Annett Kunze^a, Jörg Huwyler^b, Gian Camenisch^a, Heike Gutmann^{a,*}

^a Division of Drug Metabolism and Pharmacokinetics, Drug–Drug Interactions Section, Novartis Institutes for BioMedical Research, Basel, Switzerland

^b Department of Pharmaceutical Sciences, Division of Pharmaceutical Technology, University of Basel, CH-4056 Basel, Switzerland



ABSTRACT

Telaprevir is a new, direct-acting antiviral drug that has been approved for the treatment of chronic hepatitis C viral infection. First data on drug–drug interactions with co-medications such as cyclosporine, tacrolimus and atorvastatin have been reported recently. Drug transporting proteins have been shown to play an important role in clinically observed drug–drug interactions. The aim of this study was therefore to systematically investigate the potential of telaprevir to inhibit drug transporting proteins. The effect of telaprevir on substrate uptake mediated by drug transporters located in human kidney and liver was investigated on a functional level in HEK293 cell lines that over-express single transporter. Telaprevir was shown to exhibit significant inhibition of the human renal drug transporters OCT2 and MATE1 with IC₅₀ values of 6.4 μM and 23.0 μM, respectively, whereas no inhibitory effect on OAT1 and OAT3 mediated transport by telaprevir was demonstrated. Liver drug transporters were inhibited with an IC₅₀ of 2.2 μM for OATP1B1, 6.8 μM for OATP1B3 and 20.7 μM for OCT1. Our data show that telaprevir exhibited significant potential to inhibit human drug transporters. In view of the inhibitory potential of telaprevir, clinical co-administration of telaprevir together with drugs that are substrates of renal or hepatic transporters should be carefully monitored.

proximal.

lo contorneado distal.

•OATPs: membrana basolateral hepatocitos.

664LB Telaprevir Increases Ribavirin Toxicity Through eGFR Decrease in HIV-HCV Coinfected Patients

Laurent Cotte^{1,2}, Aurélie Barrail-Tran^{3,4}, Corine Vincent⁵, Marc-Antoine Valantin^{6,7}, Isabelle Fournier⁵, Karine Lacombe⁸, Stéphane Chevaliez^{9,10}, Jean-Pierre Aboulker⁵, Anne-Marie Taburet^{3,4}, Jean-Michel Molina^{11,12}

¹Infectious Diseases, Hospices Civils de Lyon, Lyon, France, ²U1052, INSERM (AP-HP), Paris, France, ³Ea4123, Faculty of Pharmacy, Paris-Sud University, Assistance Publique Hôpitaux de Paris (AP-HP), Paris, France, ⁴UMR-S 943, Paris, France, ⁵Henri Mondor Hospital, Assistance Publique - Hôpitaux de Paris, Paris, France, ⁶UMR-S 943, Paris, France, ⁷UMR-S 943, Paris, France, ⁸Henri Mondor Hospital, Assistance Publique - Hôpitaux de Paris, Paris, France, ⁹Henri Mondor Hospital, Assistance Publique - Hôpitaux de Paris, Paris, France, ¹⁰Henri Mondor Hospital, Assistance Publique - Hôpitaux de Paris, Paris, France, ¹¹University of Paris VII De

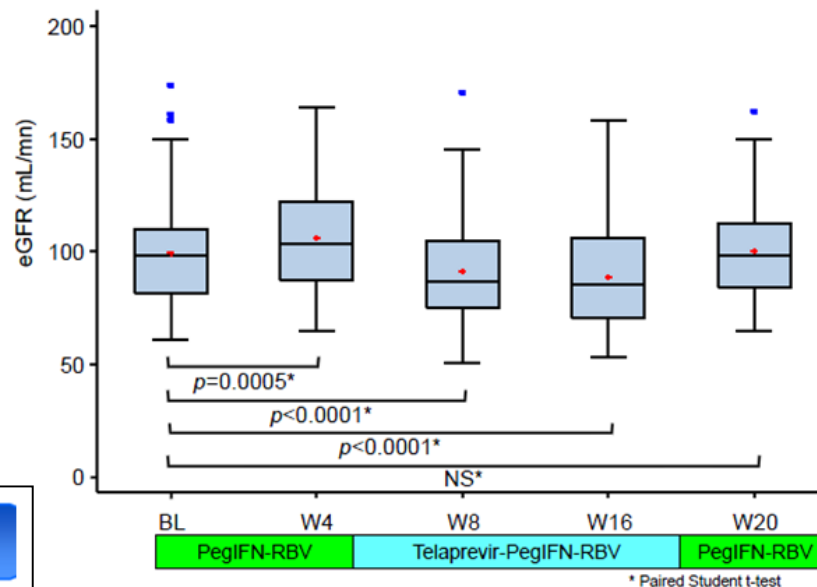
Descenso del aclaramiento renal e incremento de la concentración de RBV con TVR

eGFR basal 97.9 mL/mn [81.4-110]

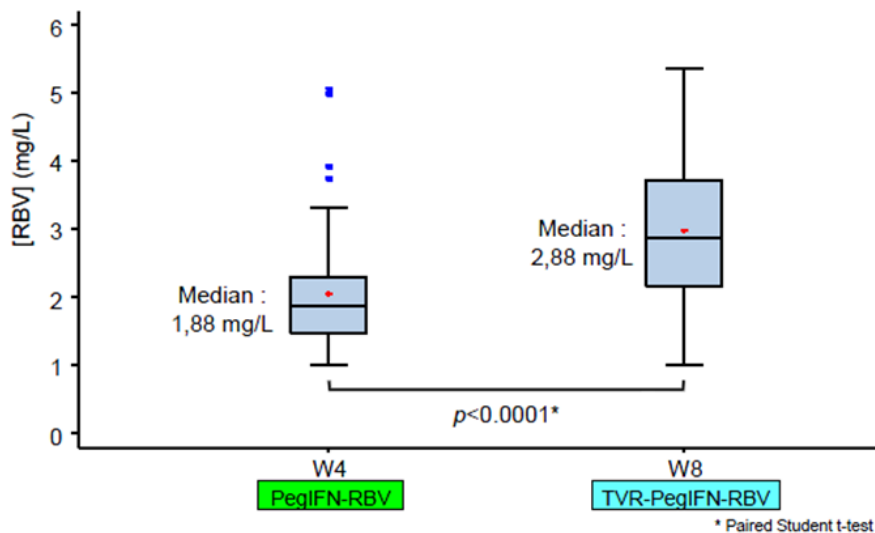
eGFR w4 103.4 mL/mn [87.4-122.1]

eGFR w8 86.3 mL/mn [74.8-104.5]

Evolution of eGFR



RBV trough concentrations



Caso clínico: monoinfección

EDAD	GEN	IL28B	Fibrosis	RESP.TTO
65	1b	CC	F3	RECIDIVA

	TVR initiation	wk 2	wk 3	wk 4	wk 5	wk 7	wk 12	w 24	wk 36
Hemoglobin, mg/dL	15.2	13.8	12.5	10		8.8	9.8	10.1	10
White blood cells, x10E ⁶ /L	4900	3900	3200	3800		3300	3100	3800	3600
Neutrophils, x10E ⁶ /L	1900	1400	1200	2000		1800	1600	2000	1900
Platelets, x10E ⁶ /L	118000	110000	131000	117000		97000	103000	102000	113000
HCV-RNA , IU/mL	763363			65	N.D.				
Plasma Creatinine, mg/dL	1.16	1.42	1.42	1.86	1.6	1.44			1.2
eGFR, mL/min	73	56	57	43	49	56			68
Urine analysis	Neg	Neg							
ALT, IU/L	101	65		36	32	41			39

STOP TVR+IFN+RBV

REINICIO IFN+RBV

Sem 3: TA 98/60, astenia. STOP amlodipino.

Sem 4: TA 100/55, astenia, náuseas, deterioro de la función renal.

Ecografía RV normal.

Caso clínico: monoinfección

EDAD	GEN	IL28B	Fibrosis	RESP.TTO
65	1b	CC	F3	RECIDIVA

	TVR initiation	wk 2	wk 3	wk 4	wk 5	wk 7	wk 12	w 24	wk 36
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STOP TVR+IFN+RBV

REINICIO IFN+RBV

Caso clínico: monoinfección

EDAD	GEN	IL28B	Fibrosis	RESP.TTO
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Neutrophils, x10E ⁶ /L	1900	1400	1200	2000		1800	1600	2000	1900
Platelets, x10E ⁶ /L	118000	110000	131000	117000		97000	103000	102000	113000
HCV-RNA , IU/mL	763363			65	N.D.		N.D.	<30	
Plasma Creatinine, mg/dL	1.16	1.42	1.42	1.86	1.6	1.44			1.2
eGFR, mL/min	73	56	57	43	49	56			68
Urine analysis	Neg	Neg							
ALT, IU/L	101	65		36	32	41			39

STOP TVR+IFN+RBV

REINICIO IFN+RBV



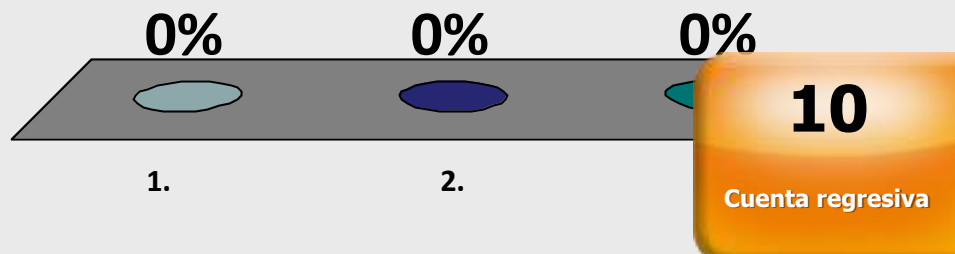
Caso clínico: monoinfección

EDAD	GEN	IL28B	Fibrosis	RESP.TTO
65	1b	CC	F3	RECIDIVA



En semana 24 ARN-VHC <30. Que harías?

1. Nada, la cantidad de virus es muy baja.
2. Suspendería todo el tratamiento. Se trata de un fracaso viral.
3. Confirmar con una nueva determinación que no se trate de un fracaso tipo breakthrough.



Uso e interpretación de los niveles de ARN-VHC: LLOQ vs. LLOD

HEPATOLOGY, Vol. 55, No. 4, 2012

Clinical Relevance of Detectable but Not Quantifiable Hepatitis C Virus RNA During Boceprevir or Telaprevir Treatment

Patrick R. Harrington,¹ Wen Zeng,² and Lisa K. Naeger¹

Response-guided therapy

•TELAPREVIR:

Sem 4 LLOQ (<25) but detected: Recidiva 28

•BOCEPREVIR:

Sem 8 LLOQ (<25) but detected: Recidiva 17%

SVR 15-20% menor que los pacientes indetectables

AASLD PRACTICE GUIDELINE

An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection: 2011 Practice Guideline by the American Association for the Study of Liver Diseases

Marc G. Ghany,¹

Recommendations:

18 An HCV assay with a lower limit of quantification of equal to or less than 25 IU/mL and a limit of HCV RNA detection of approximately 10-15 IU/mL should be used for monitoring response to therapy and decision making during triple therapy. Class 2a, Level A.

19. Response-guided therapy should only be considered when no virus is detected by a sensitive assay four weeks after initiation of the HCV protease inhibitor. Class 1, Level A.

Caso clínico: monoinfección

EDAD	GEN	IL28B	Fibrosis	RESP.TTO
65	1b	CC	F3	RECIDIVA

Cinética viral

	TVR initiation	wk 2	wk 3	wk 4	wk 5	wk 7	wk 12	w 24	wk 36
Hemoglobin, mg/dL	15.2	13.8	12.5	10		8.8	9.8	10.1	10
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HCV-RNA , IU/mL	763363			65	N.D.		N.D.	<30	N.D.
Plasma Creatinine, mg/dL	1.16	1.42	1.42	1.86	1.6	1.44			1.2
eGFR, mL/min	73	56	57	43	49	56			68
Urine analysis	Neg	Neg							
ALT, IU/L	101	65		36	32	41			39

LLOQ (<20,<25,<30) vs. LLOD (NOT DETECTABLE)

Caso clínico: monoinfección

EDAD	GEN	IL28B	Fibrosis	RESP.TTO
65	1b	CC	F3	RECIDIVA

Varón de 65 años.

- Hepatitis crónica por VHC genotipo 1b.
 - ARN-VHC 763.363 copias.
 - RVR.
 - Anemia, deterioro del filtrado renal reversible tras suspender Telaprevir en sem 4. Inhibición del OCT2?
 - Interacción con amlodipino.
 - Ongoing: Indetectable en semana 36 (desde semana 5).

Muchas gracias



1^a REUNIÓN
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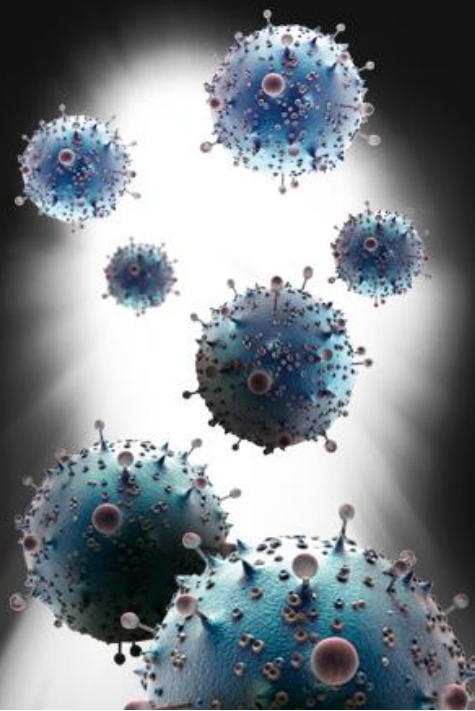
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23/24
MAYO
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MADRID

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NH NACIONAL



"Construyendo las bases para la erradicación del VHC"



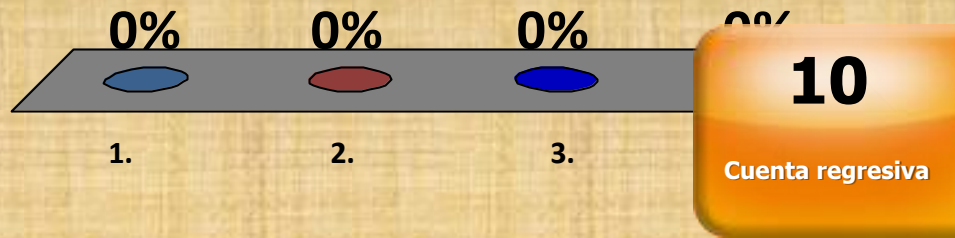
¿Donde celebraríais el próximo Congreso de GEHEP 2015 ?

1. VIGO

2. MADRID

3. VALENCIA

4. SEVILLA



1^a REUNIÓN
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