HEPATİTLERDE GÜNCEL LİTERATÜR: HEPATİT A, E VE D

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Malatya

Literatür seçimi

- Pubmed veritabanı
- “Hepatitis A”, “Hepatitis E” ve “Hepatitis D” anahtar kelimeleri
- 1 Ocak 2015 - 20 Şubat 2016
- Ulaşılan yayın sayısı
  - Hepatit A: 402
  - Hepatit E: 473
  - Hepatit D: 72

HEPATİT A

International Journal of Clinical and Experimental Medicine
Home Editorial Board Info for Authors Submission

Int J Clin Exp Med. 2015; 8(10): 19394–19399.
Published online 2015 Oct 15.
PMCID: PMC4694481

Seroprevalence of hepatitis a and associated factors among 1-15 year old children in Eastern Turkey

Serap Karaman,[1] Kamuran Karaman,[1] Baran Serdar Kızılyıldız,[2] Nesrin Ceylan,[1] Sultan Kaba,[1] Mehmet Parlak,[3] Burhan Beger,[4] and Abdullah Ceylan[1]

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Abstract

Go to:

Background: Hepatitis A is a common infectious disease during childhood worldwide. Recently, great deal of changes in the epidemiology has been reported. The seroepidemiologic studies of this infection are not sufficient in Eastern region of Turkey. Objective: To investigate the seroprevalence and association with socio-demographic variables of hepatitis A in 1-15 year old children in Van. Patients and Methods: This study was performed on 510 one to fifteen year old children from outpatient pediatric clinics in Yüzüncü Yıl University, Faculty of Medicine during last three months of 2009. Anti-HAV IgG was measured in sera by enzyme-linked immunosorbent assay. The information about subjects was recorded on standardized forms and a chart review survey was performed. Results: The overall ratio for seropositivity was 54.9%. Statistical significance was found between hepatitis A seroprevalence and age, collective use of domestic items, fresh water resources, localization and type of toilet and the number of households. Conclusion: This study provided the most recent data of seropositivity and revealed the preliminary indication of epidemiological shift in seroprevalence of Hepatitis A virus in a region with high endemicity.

Table 1. Association between demographic features and the prevalance seropositivity among study population

Variables	N (total)	Anti-HAV IgG (+) n (%)	*P* value
Gender			
Female	209	120 (41)	x^2: 0.904, P=0.342
Male	301	160 (59)	
Age (years)			
1-4 years	141	37 (26.2)	
5-8 years	151	79 (52.3)	x^2: 84.799, P=0.001*
9-12 years	146	106 (72.6)	
13-15 years	72	58 (80.6)	

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Appl Environ Microbiol. 2016 Jan 29. pii: AEM.03573-15.

Thermal inactivation of enteric viruses and bioaccumulation of enteric foodborne viruses in live oysters (Crassostrea virginica).

Araud E[1], DiCaprio E[1], Ma Y[1], Lou F[2], Gao Y[3], Kingsley D[4], Hughes JH[5], Li J[6].

Author information

Abstract

Human enteric viruses are one of the main causative agents of shellfish associated outbreaks. In this study, the kinetics of viral bioaccumulation in live oysters and the heat stability of the most predominant enteric viruses were determined in both tissue culture and in oyster tissues. A human norovirus (HuNoV) GII.4 strain, HuNoV surrogates [murine norovirus (MNV-1); Tulane virus (TV)], hepatitis A virus (HAV), and human rotavirus (RV) were bioaccumulated to a high titer within the oyster tissues with different patterns of bioaccumulation for each virus. We tested the thermal stability of each virus at 62, 72, and 80°C in culture medium. The viruses can be ranked from the most heat resistant to the least stable as: HAV>RV>TV>MNV-1. In addition we found that oyster tissues provided a protective effect to the virus during heat treatment. To decipher the mechanism underlying viral inactivation by heat, purified TV was treated at 80°C for increasing time intervals. It was found that the integrity of viral capsid was disrupted whereas viral genomic RNA remained intact. Interestingly, heat treatment leading to complete loss of TV infectivity was not sufficient to completely disrupt the receptor binding activity of TV as determined by the porcine gastric mucin magnetic bead binding assay. Similarly, HuNoV VLPs and a HuNoV GII.4 strain retained some receptor binding ability following heat treatment. Although foodborne viruses have variable heat stability, 80°C for >6 min was sufficient to completely inactivate most enteric viruses in oysters, with the exception of HAV.

Canlı istiridyelerde birikebilen norovirüs, Tulane virüs, hepatit A virüsü ve rotavirüs gibi enterik virüslerden hepatit A virüsü dışındakilerin 80°C'de 6 dakika ısıtıldıklarında inaktive oluyor.

Outbreak of hepatitis A in the USA associated with frozen pomegranate arils imported from Turkey: an epidemiological case study

Lancet Infect Dis 2014; 14: 976–81

Melissa G Collier, Yury E Khudyakov, David Selvage, Meg Adams-Cameron, Erin Epson, Alicia Cronquist, Rachel H Jervis, Katherine Lamba, Akiko C Kimura, Rick Sowadsky, Rashida Hassan, Sarah Y Park, Eric Garza, Aleisha J Elliott, David S Rotstein, Jennifer Beal, Thomas Kuntz, Susan E Lance, Rebecca Dreisch, Matthew E Wise, Noele P Nelson, Anil Suryaprasad, Jan Drobeniuc, Scott D Holmberg, Fujie Xu, for the Hepatitis A Outbreak Investigation Team

Summary

Background In May, 2013, an outbreak of symptomatic hepatitis A virus infections occurred in the USA. Federal, state, and local public health officials investigated the cause of the outbreak and instituted actions to control its spread. We investigated the source of the outbreak and assessed the public health measures used.

Methods We interviewed patients, obtained their shopping information, and did genetic analysis of hepatitis A virus recovered from patients' serum and stool samples. We tested products for the virus and traced supply chains.

Findings Of 165 patients identified from ten states, 69 (42%) were admitted to hospital, two developed fulminant hepatitis, and one needed a liver transplant; none died. Illness onset occurred from March 31 to Aug 12, 2013. The median age of patients was 47 years (IQR 35–58) and 91 (55%) were women. 153 patients (93%) reported consuming product B from retailer A. 40 patients (24%) had product B in their freezers, and 113 (68%) bought it according to data from retailer A. Hepatitis A virus genotype IB, uncommon in the Americas, was recovered from specimens from 117 people with hepatitis A virus illness. Pomegranate arils that were imported from Turkey—where genotype IB is common—were identified in product B. No hepatitis A virus was detected in product B.

Interpretation Imported frozen pomegranate arils were identified as the vehicle early in the investigation by combining epidemiology—with data from several sources—genetic analysis of patient samples, and product tracing. Product B was removed from store shelves, the public were warned not to eat product B, product recalls took place, and postexposure prophylaxis with both hepatitis A virus vaccine and immunoglobulin was provided. Our findings show that modern public health actions can help rapidly detect and control hepatitis A virus illness caused by imported food. Our findings show that postexposure prophylaxis can successfully prevent hepatitis A illness when a specific product is identified. Imported food products combined with waning immunity in some adult populations might make this type of intervention necessary in the future.

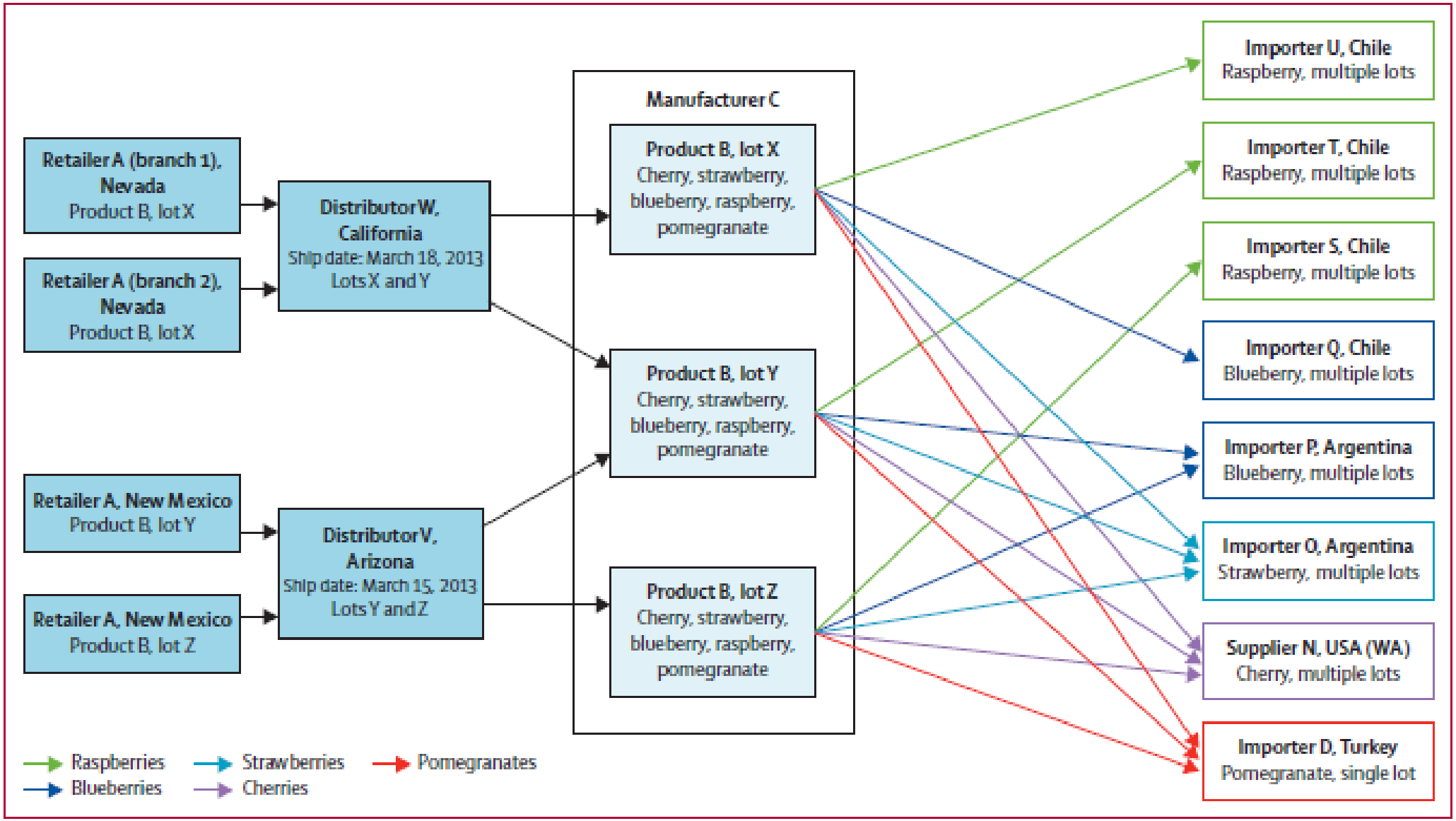


Figure 2: Tracing the ingredients of product B

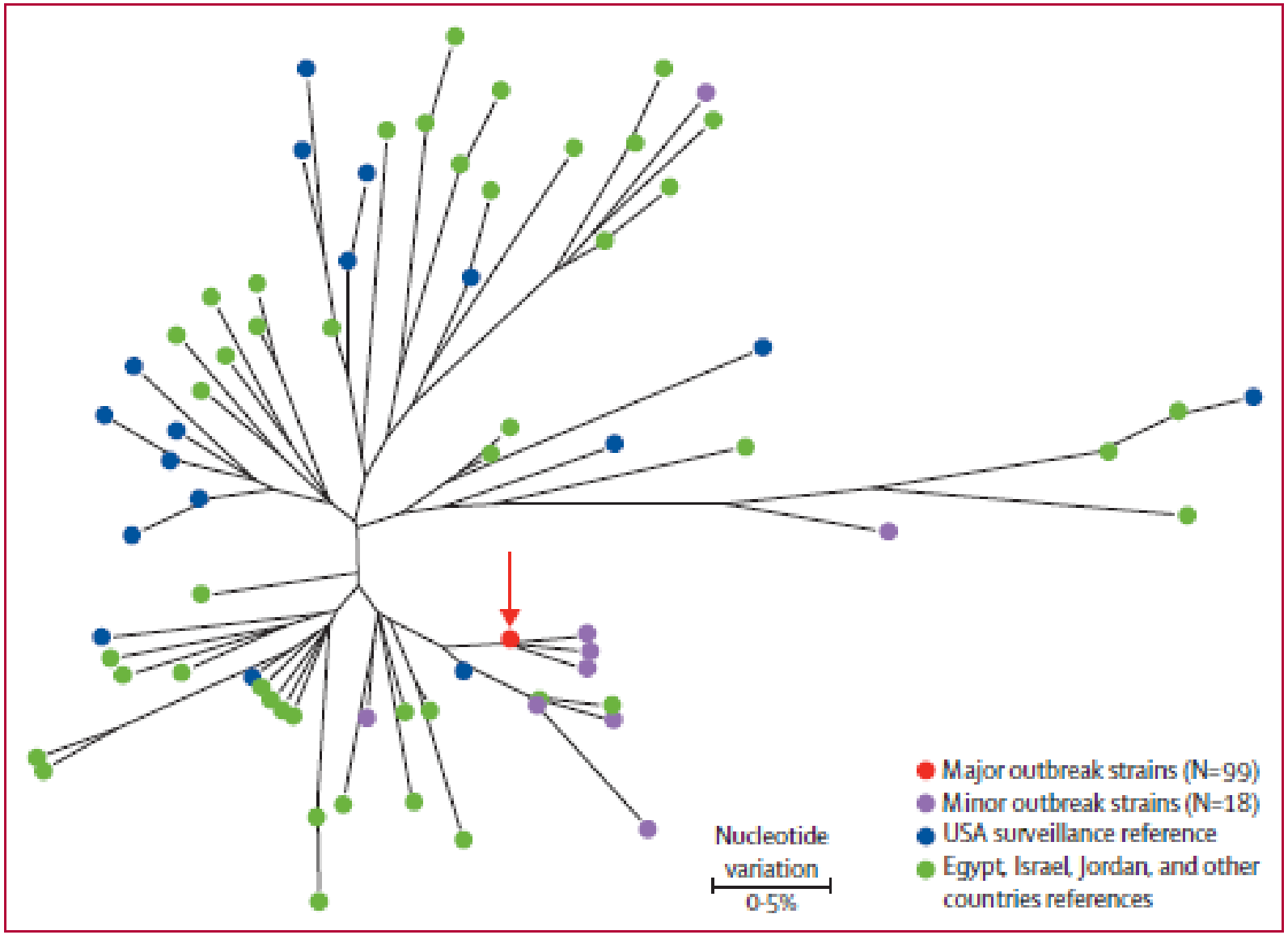


Figure 3: Hepatitis A virus genotype IB genetic analysis

Compares the sequence of the 315 bp segment (VP1/P2B) among outbreak related and non-outbreak related genotype IB positive specimens.

ORIGINAL ARTICLE

Gut 2015;**64**:1303–1313.

Liver injury in acute hepatitis A is associated with decreased frequency of regulatory T cells caused by Fas-mediated apoptosis

Yoon Seok Choi,[1,2] Jeewon Lee,[1] Hyun Woong Lee,[3] Dong-Yeop Chang,[1] Pil Soo Sung,[1] Min Kyung Jung,[1] Jun Yong Park,[4] Ja Kyung Kim,[4] Jung Il Lee,[4] Hana Park,[5] Jae Youn Cheong,[6] Kyung-Suk Suh,[7] Hyung Joon Kim,[3] June Sung Lee,[8] Kyung-Ah Kim,[8] Eui-Cheol Shin[1]

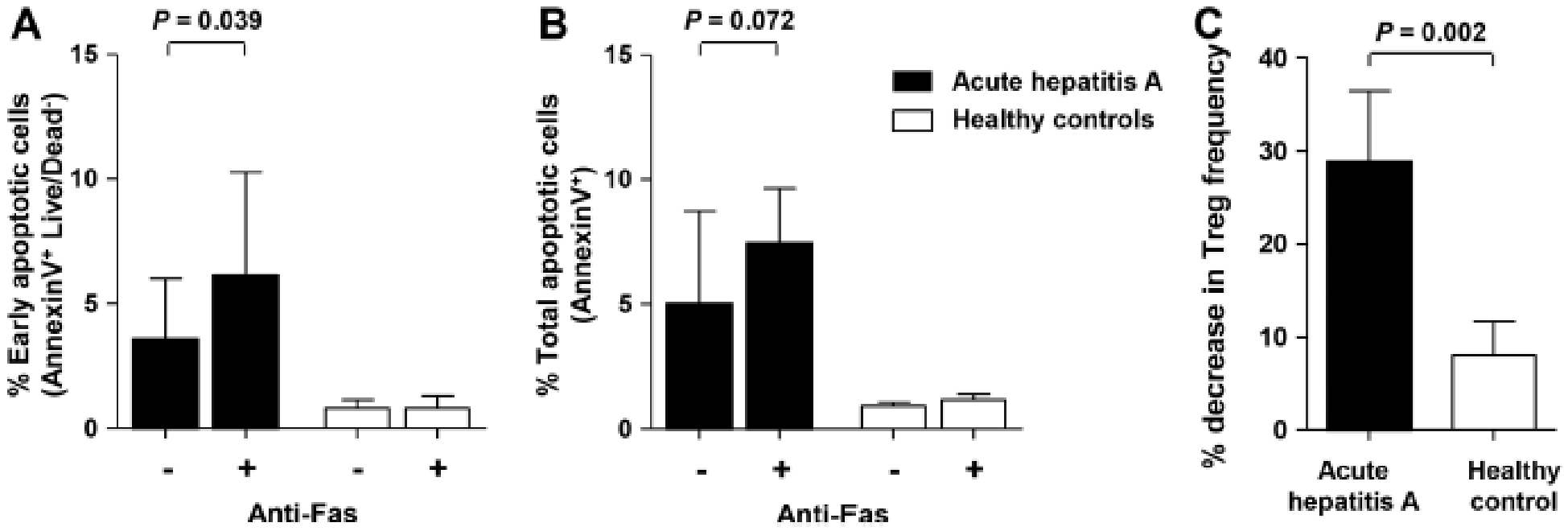
ABSTRACT

Objective $Foxp3^+CD4^+CD25^+$ regulatory T cells (Tregs) control immune responses, but their role in acute viral hepatitis remains elusive. Herein, we investigated alteration in the peripheral blood Treg population during acute hepatitis A (AHA) and its implication in the immune-mediated liver injury.

Design The study included 71 patients with AHA, and peripheral blood mononuclear cells (PBMCs) were isolated. The suppressive activity of Treg population was determined by assessing anti-CD3/CD28-stimulated proliferation of Treg-depleted and reconstituted PBMCs. Treg cell frequency, phenotype and apoptosis in PBMCs were analysed by flow cytometry.

Results The frequency of circulating Tregs was reduced during AHA. Moreover, the suppressive activity of the total Treg pool in the peripheral blood was attenuated during AHA. Treg frequency and suppressive activity of the Treg population inversely correlated with the serum alanine aminotransferase level. Fas was overexpressed on Tregs during AHA, suggesting their susceptibility to Fas-induced apoptosis. Indeed, increased apoptotic death was observed in Tregs of patients with AHA compared with healthy controls. In addition, agonistic anti-Fas treatment further increased apoptotic death of Tregs from patients with AHA. The decreased Treg frequency and Fas overexpression on Tregs were not observed in other acute liver diseases such as acute hepatitis B, acute hepatitis C and toxic/drug-induced hepatitis.

Conclusions The size of the Treg pool was contracted during AHA, resulting from apoptosis of Tregs induced by a Fas-mediated mechanism. Decrease in Treg numbers led to reduced suppressive activity of the Treg pool and consequently resulted in severe liver injury during AHA.



Akut hepatit A sırasında görülen Treg sıklığında azalma ve Treg aracılı Fas aşırı ifadesinin, diğer akut viral hepatit türlerinden farklı olarak Treg sayısının azalmasına ve Treg'in baskılayıcı aktivitesinin azalmasına yol açtığı; dolayısıyla akut hepatit A sırasında ciddi karaciğer hasarı ile sonuçlandığı bildirilmiştir.

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

HEPATOLOGY, VOL. 63, NO. 3, 2016

Persistence of Seropositivity Among Persons Vaccinated for Hepatitis A During Infancy by Maternal Antibody Status: 15-Year Follow-up

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The effect of passively transferred maternal antibody to hepatitis A virus (anti-HAV) on the duration of seropositivity after hepatitis A vaccination during infancy and early childhood is unclear. We obtained levels of anti-HAV at intervals through age 15-16 years among three groups of Alaskan Native children who initiated a two-dose inactivated hepatitis A vaccination series at ages 6 months (group 1), 12 months (group 2), and 15 months (group 3), each group randomized according to maternal anti-HAV status. Seropositivity (anti-HAV ≥20 mIU/mL) 30 years after the second vaccine dose among the three groups was predicted using a random effects model. One hundred eighty-three children participated in the study; follow-up did not differ significantly by vaccine group or maternal anti-HAV status. Although the frequency of seropositivity among all participants through age 10 years was high (100% among groups 2 and 3 and >90% among group 1), there was a decrease thereafter through age 15-16 years among group 1 children, who initiated vaccination at age 6 months (50%-75%), and among maternal anti-HAV-positive children in groups 2 and 3 (67%-87%), who initiated vaccination at ages 12 months and 15 months, respectively. Nonetheless, the model indicated that anti-HAV seropositivity should persist for ≥30 years after vaccination in 64% of all participants; among those seropositive at age 15-16 years, 84% were predicted to remain so for ≥30 years. *Conclusion*: Most children vaccinated during early childhood available for sampling maintained seropositivity through age 15-16 years; however, seropositivity was less frequent among those starting vaccination at age 6 months and among maternal antibody-positive participants who started vaccination at age 12 months or 15 months; overall, our findings support current vaccine recommendations and continued follow-up of this cohort. (HEPATOLOGY 2016;63:703-711)

TABLE 2. Anti-HAV Levels After Two Doses of Hepatitis A Vaccine Among Group 1 Infants, by Maternal Anti-HAV Status and Follow-up Period

		1 Month After Dose 2		3 Years of Age		7 Years of Age		10 Years of Age		12-14 Years of Age		15-16 Years of Age	
Group*	Maternal Anti-HAV Status	*n*	GMC, mIU/mL (95% CI)	*n*	GMC, mIU/mL (95% CI)	*n*	GMC, mIU/mL (95% CI)	*n*	GMC, mIU/mL (95% CI)	*n*	GMC, mIU/mL (95% CI)	*n*	GMC, mIU/mL (95% CI)
1	Neg	40	1196 (855-1673)	36	219 (139-346)	33	65 (44-97)	31	45 (31-65)	22	37 (22-62)	20	49 (31-77)
	Pos: Natural	17	299 (125-717)	18	76 (41-139)	15	44 (23-83)	9	31 (12-79)	11	13.7 (7-26)	6	36 (8-167)
	Pos: Vaccine	16	1636 (971-2756)	17	194 (111-342)	16	57 (40-83)	13	34 (21-56)	13	28 (18-44)	12	23 (14-36)

Long-term antibody persistence after vaccination with a 2-dose *Havrix*™ (inactivated hepatitis A vaccine): 20 years of observed data, and long-term model-based predictions

Heidi Theeten[a,1,2], Koen Van Herck[a,b,2], Olivier Van Der Meeren[c], Priya Crasta[c], Pierre Van Damme[a,*], Niel Hens[a,d]

Vaccine 33 (2015) 5723–5727

ABSTRACT

Antibody persistence in two cohorts of adults, who received inactivated hepatitis A (HAV) vaccine (1440El.U; *Havrix*™; GSK Vaccines) according to a 0–6 or 0–12 month schedule in 1992–1993, has been measured annually. After 20 years, >97% of the subjects in both studies were seropositive for anti-HAV antibodies. Geometric mean concentrations in the according-to-protocol cohorts were 312 mIU/ml in 34/36 subjects vaccinated initially at 0–6 months (NCT00289757) and 317 mIU/ml in 85/86 subjects vaccinated at 0–12 months (NCT00291876). Over the whole follow-up period, seven subjects (2+5, respectively) lost circulating anti-HAV antibodies but mounted a strong response after HAV booster administration (1440El.U). Mathematical modelling, which was applied to assess true persistence at Year 20 (accounting for drop-outs and missing data), and to predict longer-term persistence confirmed previous estimates that seropositive anti-HAV levels would persist in ≥95% vaccinees at Year 30 and ≥90% at Year 40.

HEPATİT E

Mikrobiyol Bul. 2015 Oct;49(4):554-564.

[Investigation of the hepatitis E virus seroprevalence in cases admitted to Hacettepe University Medical Faculty Hospital].

[Article in Turkish]

Aydın NN, Ergünay K, Karagül A, Pınar A, Us D[1].

Author information

Abstract

Hepatitis E virus (HEV), classified in Hepeviridae family, Hepevirus genus, is a non-enveloped virus with icosahedral capsid containing single-stranded positive sense RNA genome. HEV infections may be asymptomatic especially in children, however it may present as fulminant hepatitis in pregnant women, as well as chronic hepatitis in immunocompromised patients. There are four well-known genotypes of HEV that infect humans and many mammalian species. Genotype 1 and 2 are frequently responsible for water-borne infections transmitted by fecal-oral way in developing countries, while genotype 3 and 4 cause zoonotic infections in developed countries. Turkey is considered as an endemic country with a total seroprevalence rate of 6.3% for normal population, showing significant variation (0-73%) according to the regions and study groups. The aims of this study were to investigate the HEV seropositivity in cases admitted to Hacettepe University Medical Faculty Hospital (HUMFH), to evaluate the results according to the demographic features of patients, and to determine the current HEV seroprevalence in our region, contributing seroepidemiological data in Turkey. A total of 1043 serum samples (514 female, 529 male; age range: 1-90 years, mean age: 38.03) obtained from 327 blood donors (32 female, 295 male; age range: 19-59 years, mean age: 31.1) who were admitted to HUMFH Blood Center, and 716 sera (482 female, 234 male; age range: 1-90 years, mean age: 41.7) that were sent to HUMFH Central Laboratory from various outpatient/inpatient clinics, between November 2012 to November 2013, were included in the study. The presence of HEV-IgG antibodies in serum samples was detected by a commercial ELISA method (Euroimmun, Germany), and the presence of HEV-IgM antibodies was also investigated in the sera with IgG-positive results. The overall HEV-IgG seropositivity rate was determined as 4.4% (46/1043), and the seropositivity rates for blood donors and in/outpatients were as 0.92% (3/327) and 6.0% (43/716), respectively. HEV-IgM antibody was not detected in any of the cases. The HEV-IgG seropositivity was 3.2% among male, and 5.6% among female, yielding no statistically significant difference between the gender (p= 0.056). HEV-IgG antibodies were detected in none (0/118) of the pediatric age group (0-18 years), while the seropositivity rates were 1.9% (14/731) and 16.5% (32/194) in 19-55 and ≥ 56 years-old groups, respectively. The difference between the age groups was statistically significant (p< 0.001), indicating the age-related pattern of HEV exposure. In conclusion, the total HEV seroprevalence rate found as 4.4% in our study, is comparable to the average results reported from Turkey. Our data is also in agreement with the result of a previous report (3.8%) that performed from Ankara province in 2002 with similar study groups, emphasizing that there was no significant changes for HEV exposure have occured over more than the last decade in Ankara, Cental Anatolia, Turkey.

Incidence and duration of hepatitis E virus infection in Dutch blood donors

Boris M. Hogema,[1,2] Michel Molier,[1] Margret Sjerps,[2] Mirjam de Waal,[2] Peter van Swieten,[2] Thijs van de Laar,[1,2] Marijke Molenaar-de Backer,[1,2] and Hans L. Zaaijer[1,3]

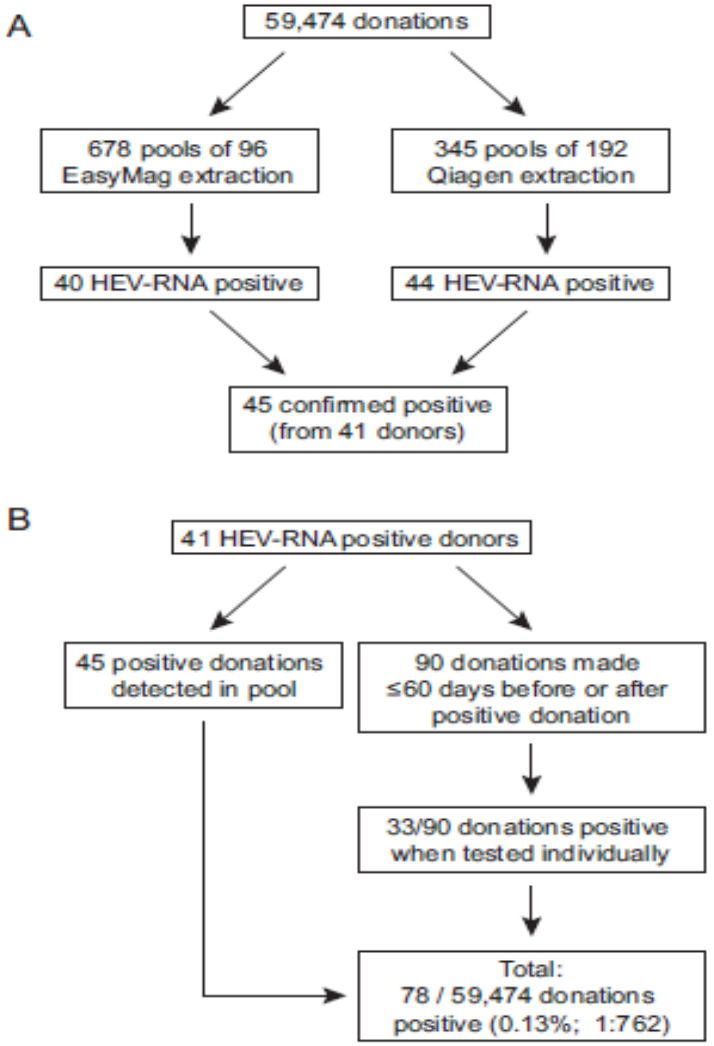
TRANSFUSION 2015;00;00–00

BACKGROUND: The incidence of hepatitis E virus (HEV) infection in the Netherlands is high. Blood donors are not routinely screened for HEV infection, but since January 2013, donations used for the production of solvent/detergent (S/D)-treated plasma have been screened for HEV RNA.

STUDY DESIGN AND METHODS: Donations were screened for HEV RNA in pools of 96 and 192 donations. In addition, all donations made between 60 days before and after each HEV RNA-positive donation were tested individually for HEV RNA and anti-HEV immunoglobulin G.

RESULTS: The screening of 59,474 donations between January 2013 and December 2014 resulted in identification of 45 HEV RNA-positive donations (0.076%) from 41 donors. HEV RNA loads ranged from 80 to 2.3×10^6 IU/mL. The number of positive donations increased significantly over time ($p = 0.03$). Thirty-three of 90 donations made up to 60 days before or after HEV RNA-positive donations were positive when tested individually, while they had not been detected in the pool screening. The mean duration of HEV viremia in the healthy blood donor is estimated to be 68 days.

CONCLUSION: The incidence of HEV infection in the Netherlands is high and increased during the study period. In 2013 and 2014, HEV RNA was detected in 1 per 762 donations intended for production of S/D plasma.



Annals of Hepatology

ORIGINAL ARTICLE

January-February, Vol. 15 No. 1, 2016: 33-40

Hepatitis E virus serum antibodies and RNA prevalence in patients evaluated for heart and kidney transplantation

Alberto Unzueta, Riccardo Valdez, Yu-Hui H. Chang, Yvonne M. Desmarteau, Raymond L. Heilman, Robert L. Scott, David D. Douglas, Jorge Rakela

ABSTRACT

Background. Acute hepatitis E virus (HEV) infection in solid organ transplant recipients is rare, but can cause severe hepatic and extrahepatic complications. We sought to identify the pretransplant prevalence of HEV infection in heart and kidney candidates and any associated risk factors for infection. **Material and methods.** Stored frozen serum from patients undergoing evaluation for transplant was tested for HEV immunoglobulin G (IgG) antibodies and HEV RNA. All patients were seen at Mayo Clinic Hospital, Phoenix, Arizona, with 333 patients evaluated for heart (n = 132) or kidney (n = 201) transplant. HEV IgG antibodies (anti-HEV IgG) were measured by enzyme-linked immunosorbent assay, and HEV RNA by a noncommercial nucleic acid amplification assay. **Results.** The prevalence of anti-HEV IgG was 11.4% (15/132) for heart transplant candidates and 8.5% (17/201) for kidney transplant candidates, with an overall seroprevalence of 9.6% (32/333). None of the patients tested positive for HEV RNA in the serum. On multivariable analysis, age older than 60 years was associated with HEV infection (adjusted odds ratio, 3.34; 95% CI, 1.54-7.24; P = 0.002). **Conclusions.** We conclude that there was no evidence of acute HEV infection in this pretransplant population and that older age seems to be associated with positive anti-HEV IgG.

Detection and assessment of infectivity of hepatitis E virus in urine

Yansheng Geng[1], Chenyan Zhao[2], Weijin Huang[2], Tim J. Harrison[3], Hongxin Zhang[1], Kunjing Geng[4], Youchun Wang[2,*]

Journal of Hepatology 2016 vol. 64 | 37–43

Background & Aims: Hepatitis E virus (HEV) is known to be excreted in the stool but there has been no report of its presence in urine. This study investigated the presence of HEV RNA and antigen (HEV-Ag) in urine and its possible transmission.

Methods: Serum and urine samples from patients with chronic or acute HEV infection and HEV infected monkeys were tested for viral and biochemical markers. Liver and kidney biopsies from the infected monkeys were analyzed by histopathology and immunohistochemistry. The infectivity of HEV from urine was assessed by inoculation into monkeys.

Results: HEV RNA and HEV-Ag were detected persistently in the urine of a patient with chronic HEV infection. Subsequently, HEV RNA was detected in the urine of three of the eight (37.5%) acute patients, all of whom had detectable HEV-Ag in their urine. HEV RNA and HEV-Ag were also detectable in the urine of HEV infected monkeys. The ratio of HEV-Ag to RNA in the urine of the infected monkeys was significantly higher than in their sera and feces. The parameters of routine urinalysis remained within the normal ranges in the hepatitis E patients and infected monkeys, however, pathological changes and HEV-Ag were observed in the kidneys of the infected monkeys. Furthermore, one of two monkeys became infected with HEV after inoculation with urine from another infected monkey.

Conclusions: HEV infection may result in kidney injury and the urine may pose a risk of transmission. HEV-Ag detection in urine may be valuable for diagnosis of ongoing HEV infection.

Seroprevalence of Hepatitis E Virus Infection Among Dogs in Several Developed Cities in the Guangdong Province of China

Accepted 5 January 2016
DOI 10.1002/jmv.24468
Journal of Medical Virology

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Hepatitis E virus (HEV), as a zoonotic disease virus, was seldom studied in dogs especially in stray dogs. As previously reported, dog might be an accidental host of HEV for human beings and some risk factors might play an important role in HEV transmission. Thus, we designed this study to evaluate the seroprevalence of HEV infection among dogs in several cities in Guangdong province of China. This surveillance may help us understand risk factors including location, gender, live type, and diet habit for HEV transmission. The overall seroprevalence of anti-HEV antibodies in dogs was 19.00%. Positive rate of anti-HEV antibodies in other food groups (21.13%) was higher than that in dog food groups (9.77%) ($P < 0.05$), which suggested that diet habit might be a vital element of infecting HEV for dogs and play an important role in living environment. However, the analysis indicated that no strong relationship was observed among different cities, gender groups, and live type. Our study demonstrated that HEV is prevalent in dogs in the Guangdong province of China. As diet habit might become a vital element of infecting HEV for dogs and play an important role in living environment, similar studies of dogs should be conducted in the future. ***J. Med. Virol.***

Long-Term Efficacy of a Hepatitis E Vaccine

Jun Zhang, M.Sc., Xue-Feng Zhang, M.Sc., Shou-Jie Huang, M.Sc., Ting Wu, Ph.D., Yue-Mei Hu, M.Sc., Zhong-Ze Wang, B.Sc., Hua Wang, M.D., Han-Min Jiang, B.Sc., Yi-Jun Wang, M.Sc., Qiang Yan, M.Sc., Meng Guo, B.Sc., Xiao-Hui Liu, B.Sc., Jing-Xin Li, M.Sc., Chang-Lin Yang, B.Sc., Quan Tang, B.Sc., Ren-Jie Jiang, M.Sc., Hui-Rong Pan, Ph.D., Yi-Min Li, M.D., J. Wai-Kuo Shih, Ph.D., Mun-Hon Ng, Ph.D., Feng-Cai Zhu, M.Sc., and Ning-Shao Xia

N ENGL J MED 372;10 NEJM.ORG MARCH 5, 2015

ABSTRACT

BACKGROUND

Hepatitis E virus (HEV) is a leading cause of acute hepatitis. The long-term efficacy of a hepatitis E vaccine needs to be determined.

METHODS

In an initial efficacy study, we randomly assigned healthy adults 16 to 65 years of age to receive three doses of either a hepatitis E vaccine (vaccine group; 56,302 participants) or a hepatitis B vaccine (control group; 56,302 participants). The vaccines were administered at 0, 1, and 6 months, and the participants were followed for 19 months. In this extended follow-up study, the treatment assignments of all participants remained double-blinded, and follow-up assessments of efficacy, immunogenicity, and safety were continued for up to 4.5 years.

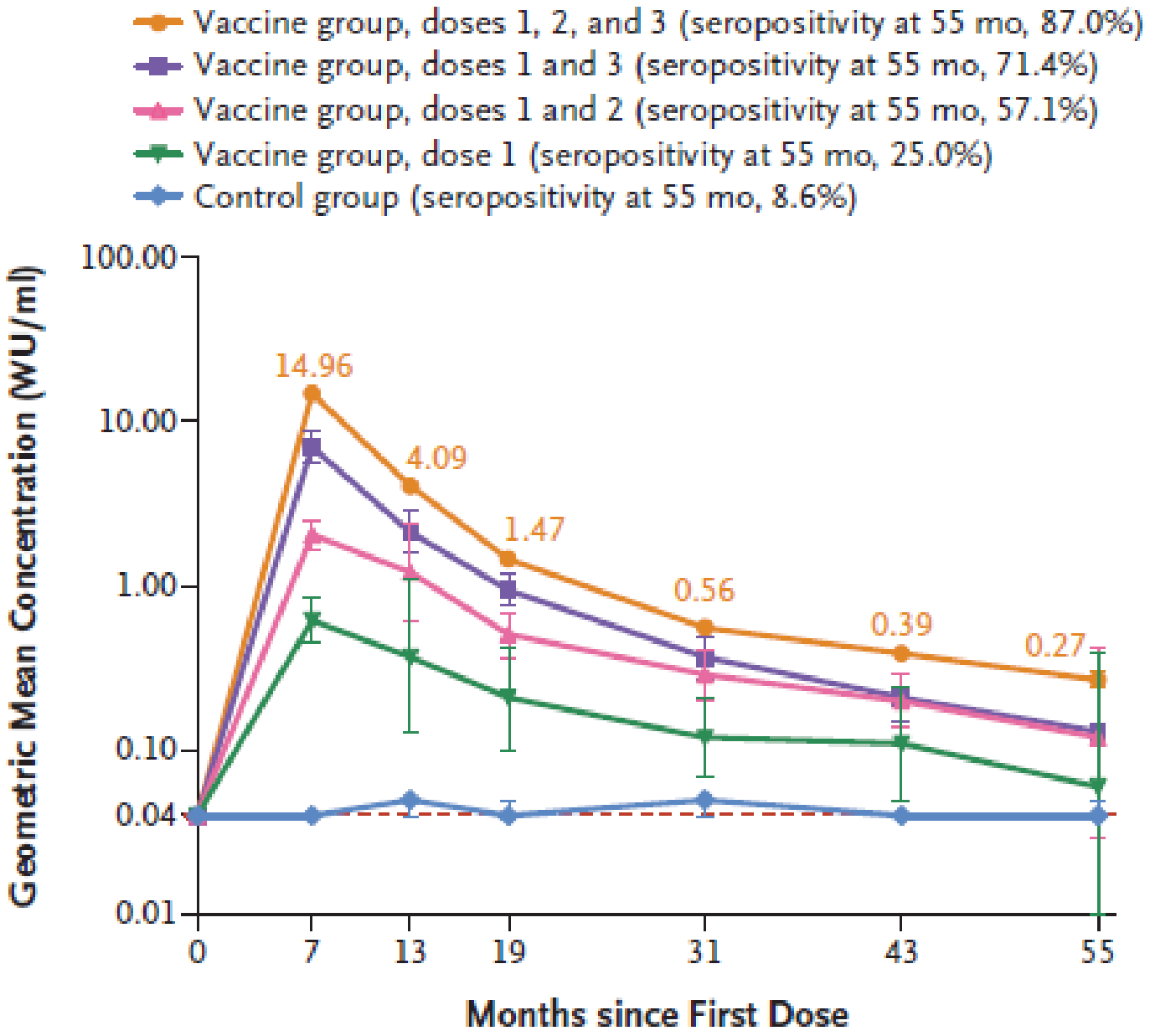
RESULTS

During the 4.5-year study period, 60 cases of hepatitis E were identified; 7 cases were confirmed in the vaccine group (0.3 cases per 10,000 person-years), and 53 cases in the control group (2.1 cases per 10,000 person-years), representing a vaccine efficacy of 86.8% (95% confidence interval, 71 to 94) in the modified intention-to-treat analysis. Of the participants who were assessed for immunogenicity and were seronegative at baseline, 87% of those who received three doses of the hepatitis E vaccine maintained antibodies against HEV for at least 4.5 years; HEV antibody titers developed in 9% in the control group. The rate of adverse events was similar in the two groups.

CONCLUSIONS

Immunization with this hepatitis E vaccine induced antibodies against HEV and provided protection against hepatitis E for up to 4.5 years. (Funded by the Chinese Ministry of Science and Technology and others; ClinicalTrials.gov number, NCT01014845.)

A **Participants Who Were Seronegative at Baseline**



A trivalent vaccine candidate against hepatitis E virus, norovirus, and astrovirus

Ming Xia[a,1], Chao Wei[a,1], Leyi Wang[a,2], Dianjun Cao[c], Xiang-Jin Meng[c], Xi Jiang[a,b], Ming Tan[a,b,*]

Vaccine 34 (2016) 905–913

ABSTRACT

Hepatitis E virus (HEV), norovirus (NoV), and astrovirus (AstV) are enterically-transmitted viral pathogens causing epidemic or endemic hepatitis (HEV) and gastroenteritis (NoV and AstV) respectively in humans, leading to significant morbidity and mortality worldwide. While a recombinant subunit vaccine against HEVs is available in China, there is no commercial vaccine or antiviral against NoV or AstV. We report here our development of a trivalent vaccine against the three viral pathogens through our new polymer vaccine technology. All HEV, NoV, and AstV are non-enveloped RNA viruses covered by a protein capsid, featuring surface protruding (P) proteins that are responsible for virus–host interaction. These dimeric P proteins elicit neutralizing antibody and are good targets for subunit vaccine development. The trivalent subunit vaccine was developed by fusion of the dimeric P domains of the three viruses together that formed tetramers. This trivalent vaccine elicited significantly higher antibody responses in mice against all three P domains than those induced by a mixture of the three free P domains (mixed vaccine). Furthermore, the post-immune antisera of the trivalent vaccine showed significantly higher neutralizing titers against HEV infection in cell culture and higher blocking activity against NoV binding to HBGA ligands than those of the post-immune sera of the mixed vaccine. Thus, the trivalent vaccine is a promising vaccine candidate against HEV, NoV, and AstV.

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Antimicrob Agents Chemother. 2016 Jan 19. pii: AAC.02427-15.

Antiviral activity of different interferon (sub-) types against hepatitis E virus replication.

Todt D[1], François C[2], Anggakusuma[1], Behrendt P[3], Engelmann M[1], Knegendorf L[1], Vieyres G[1], Wedemeyer H[4], Hartmann R[5], Pietschmann T[1], Duverlie G[2], Steinmann E[6].

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Abstract

Hepatitis E virus (HEV) is the causative agent of hepatitis E in humans and a member of the genus Orthohepevirus in the family Hepeviridae. HEV infections are the common cause of acute hepatitis but can also take chronic courses. Ribavirin is the treatment of choice for most patients and type I interferon (IFN) has been evaluated in a few infected transplantation patients in vivo. In this study, the antiviral effects of different exogenously administered interferons were investigated by using state-of-the-art subgenomic replicon and full-length HEV genome cell culture models. Hepatitis C virus (HCV) subgenomic replicons based on the genotype 2a JFH1 isolate served as reference. The experiments revealed that HEV RNA replication could be inhibited by the application of all types of IFN including IFN-α (type-I), -γ (type-II), and -λ3 (type-III), but to a far lesser extent as compared to HCV. Simultaneous determination of interferon stimulated genes (ISGs) expression levels for all IFN types demonstrated an efficient down-regulation by HEV. Furthermore, different IFN-α subtypes were able to block viral replication also in combination with ribavirin. The IFN-α subtypes 2a and 2b exerted the strongest antiviral activity against HEV. In conclusion, these data demonstrates for the first time moderate anti-HEV activities of type -II and -III IFNs and different IFN-α subtypes. As HEV employed a potent anti-interferon mechanism by restricting ISG expression, exogenous application of IFNs as immunotherapy should be carefully assessed.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ribavirin for Chronic Hepatitis E Virus Infection in Transplant Recipients

Nassim Kamar, M.D., Ph.D., Jacques Izopet, Pharm.D., Ph.D., Simona Tripon, M.D., Michael Bismuth, M.D., Sophie Hillaire, M.D., Jérôme Dumortier, M.D., Ph.D., Sylvie Radenne, M.D., Audrey Coilly, M.D., Valérie Garrigue, M.D., Louis D'Alteroche, M.D., Matthias Buchler, M.D., Ph.D., Lionel Couzi, M.D., Ph.D., Pascal Lebray, M.D., Sebastien Dharancy, M.D., Ph.D., Anne Minello, M.D., Maryvonne Hourmant, M.D., Ph.D., Anne-Marie Roque-Afonso, M.D., Ph.D., Florence Abravanel, Pharm.D., Ph.D., Stanislas Pol, M.D., Ph.D., Lionel Rostaing, M.D., Ph.D., and Vincent Mallet, M.D., Ph.D.

N Engl J Med 2014;370:1111-20.
DOI: 10.1056/NEJMoa1215246

BACKGROUND

There is no established therapy for hepatitis E virus (HEV) infection. The aim of this retrospective, multicenter case series was to assess the effects of ribavirin as monotherapy for solid-organ transplant recipients with prolonged HEV viremia.

METHODS

We examined the records of 59 patients who had received a solid-organ transplant (37 kidney-transplant recipients, 10 liver-transplant recipients, 5 heart-transplant recipients, 5 kidney and pancreas–transplant recipients, and 2 lung-transplant recipients). Ribavirin therapy was initiated a median of 9 months (range, 1 to 82) after the diagnosis of HEV infection at a median dose of 600 mg per day (range, 29 to 1200), which was equivalent to 8.1 mg per kilogram of body weight per day (range, 0.6 to 16.3). Patients received ribavirin for a median of 3 months (range, 1 to 18); 66% of the patients received ribavirin for 3 months or less.

RESULTS

All the patients had HEV viremia when ribavirin was initiated (all 54 in whom genotyping was performed had HEV genotype 3). At the end of therapy, HEV clearance was observed in 95% of the patients. A recurrence of HEV replication occurred in 10 patients after ribavirin was stopped. A sustained virologic response, defined as an undetectable serum HEV RNA level at least 6 months after cessation of ribavirin therapy, occurred in 46 of the 59 patients (78%). A sustained virologic response was also observed in 4 patients who had a recurrence and were re-treated for a longer period. A higher lymphocyte count when ribavirin therapy was initiated was associated with a greater likelihood of a sustained virologic response. Anemia was the main identified side effect and required a reduction in ribavirin dose in 29% of the patients, the use of erythropoietin in 54%, and blood transfusions in 12%.

CONCLUSIONS

This retrospective, multicenter study showed that ribavirin as monotherapy may be effective in the treatment of chronic HEV infection; a 3-month course seemed to be an appropriate duration of therapy for most patients.

Sofosbuvir Inhibits Hepatitis E Virus Replication In Vitro and Results in an Additive Effect When Combined With Ribavirin

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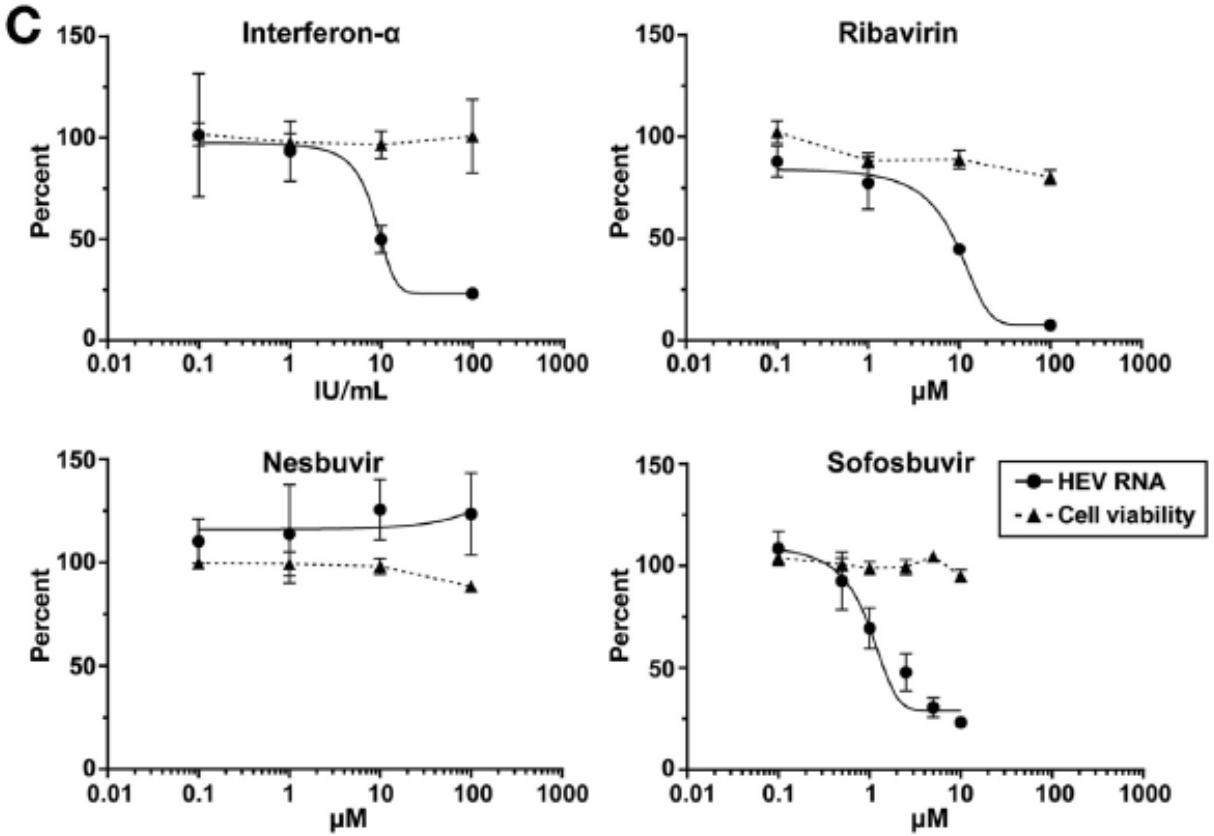
Gastroenterology 2016;150:82–85

Infection with hepatitis E virus genotype 3 may result in chronic hepatitis in immunocompromised patients. Reduction of immunosuppression or treatment with ribavirin or pegylated interferon-α can result in viral clearance. However, safer and more effective treatment options are needed. Here, we show that sofosbuvir inhibits the replication of hepatitis E virus genotype 3 both in subgenomic replicon systems as well as a full-length infectious clone. Moreover, the combination of sofosbuvir and ribavirin results in an additive antiviral effect. Sofosbuvir may be considered as an add-on therapy to ribavirin for the treatment of chronic hepatitis E in immunocompromised patients.



An Early Viral Response Predicts the Virological Response to Ribavirin in Hepatitis E Virus Organ Transplant Patients

Nassim Kamar, MD, PhD,[1,2,3] Sebastien Lhomme, PhD, PharmD,[2,3,4] Florence Abravanel, PhD, PharmD,[2,3,4] Olivier Cointault, MD,[1] Laure Esposito, MD,[1] Isabelle Cardeau-Desangles, MD,[1] Arnaud Del Bello, MD,[1,3] Gaëlle Dörr, MD,[1,3] Laurence Lavayssière, MD,[1] Marie Béatrice Nogier, MD,[1] Joelle Guitard, MD,[1] David Ribes, MD,[1] Anne Laure Goin, MD,[5] Pierre Broué, MD,[6] David Metsu, MD,[7] Karine Sauné, PhD, PharmD,[2,3,4] Lionel Rostaing, MD, PhD,[1,2,3] and Jacques Izopet, PhD, PharmD[2,3,4]

Background. Ribavirin is efficient at treating chronic hepatitis E virus infection in solid-organ transplant patients. However, the early kinetics of viral replication under therapy and the impact of immunosuppressant regimens on viral replication are unknown: thus, determining the aim of our study. **Methods.** Thirty-five patients with a solid-organ transplant and chronic hepatitis E virus infection were given ribavirin for 3 months. The hepatitis E virus (HEV) RNA concentrations were determined before treatment, at days 7, 15, and 21 and at months 1, 2, and 3 during therapy and after ribavirin cessation. **Results.** A sustained virological response (SVR) occurred in 63%. Decreased viral concentration within the first week post-ribavirin therapy was an independent predictive factor for SVR, and a decreased HEV concentration of 0.5 log copies/mL or greater had an 88% positive predictive value. No correlation between ribavirin trough level on day 7 or at month 2 with a virological response or an SVR was observed. Before therapy, HEV RNA concentration was significantly greater in patients receiving mechanistic target of rapamycin inhibitor-based immunosuppression compared to patients given calcineurin inhibitors. The use of mycophenolic acid did not impact on the response to ribavirin. **Conclusion.** An early response to ribavirin can be used to define the optimal duration of therapy in the setting of HEV infection.

(*Transplantation* 2015;99: 2124–2131)

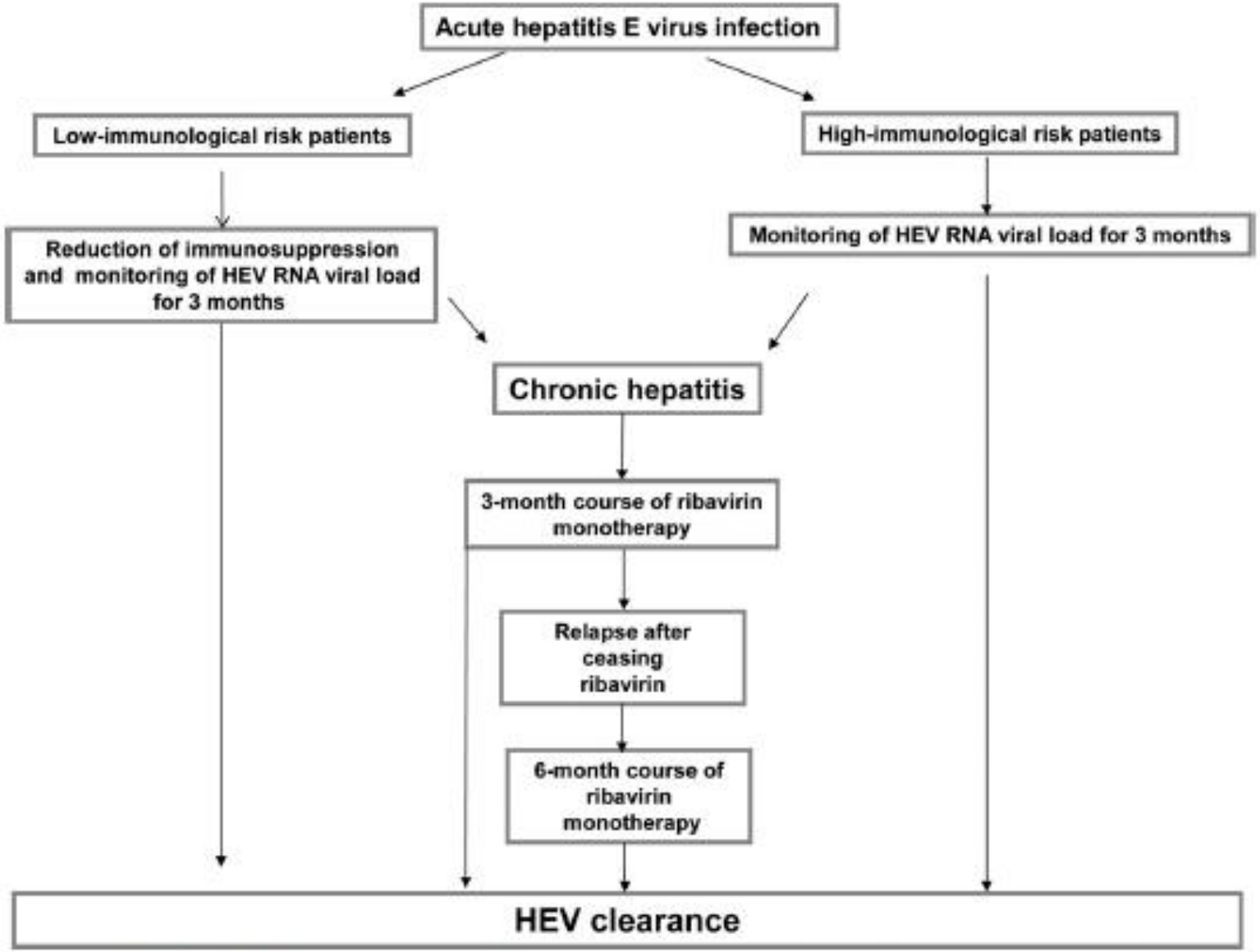


FIGURE 3. Management of hepatitis E virus infection in solid-organ transplant patients.

Relevance of chronic hepatitis E in liver transplant recipients: a real-life setting

A. Galante, S. Pischke, S. Polywka, M. Luetgehethmann, P.V. Suneetha, A. Gisa, J. Hiller, H.P. Dienes, B. Nashan, A.W. Lohse, M. Sterneck. Relevance of chronic hepatitis E in liver transplant recipients: a real-life setting.
Transpl Infect Dis 2015: **17**: 617–622.

A. Galante[1,*], S. Pischke[1,2,*], S. Polywka[3], M. Luetgehethmann[3], P.V. Suneetha[4], A. Gisa[4], J. Hiller[5], H.P. Dienes[6], B. Nashan[7], A.W. Lohse[1], M. Sterneck[1,2]

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Characteristics of the 4 chronically hepatitis E virus (HEV)-infected patients

	Patient 1	Patient 2	Patient 3	Patient 4
Age in years	60	43	57	27
Immunosuppression	Cyclosporine, mycophenolate mofetil	Cyclosporine, mycophenolate mofetil	Cyclosporine, everolimus	Cyclosporine, azathioprine, steroids
Time between transplantation and infection, months (retrospective)	14	107	36	2
Time between transplantation and diagnosis, months	23	110	43	6
Peak ALT, U/L	75	646	271	307
Peak AST, U/L	68	317	191	149
Lowest GFR, mL/min	43.9	50.6	41.5	59.9
ALT at last follow up, U/L	6	15	15	35
AST at last follow up, U/L	11	16	19	32
GFR at last follow up	50.7	54.4	44.3	60.3
Ribavirin dose, mg/day	400/200	400	800/600	800/600
Histology	Not performed	Signs of chronic hepatitis with mild-to-moderate necro-inflammatory activity without fibrosis	Signs of chronic hepatitis with moderate inflammatory activity	Signs of mild to moderated portal inflammation, consistent with hepatitis
HEV viral load blood peak, copies/mL	500,000	100,000	200,000,000	36,000,000
HEV viral load stool peak, copies/mL	15,000,000	30,000,000	100,000,000	13,000,000

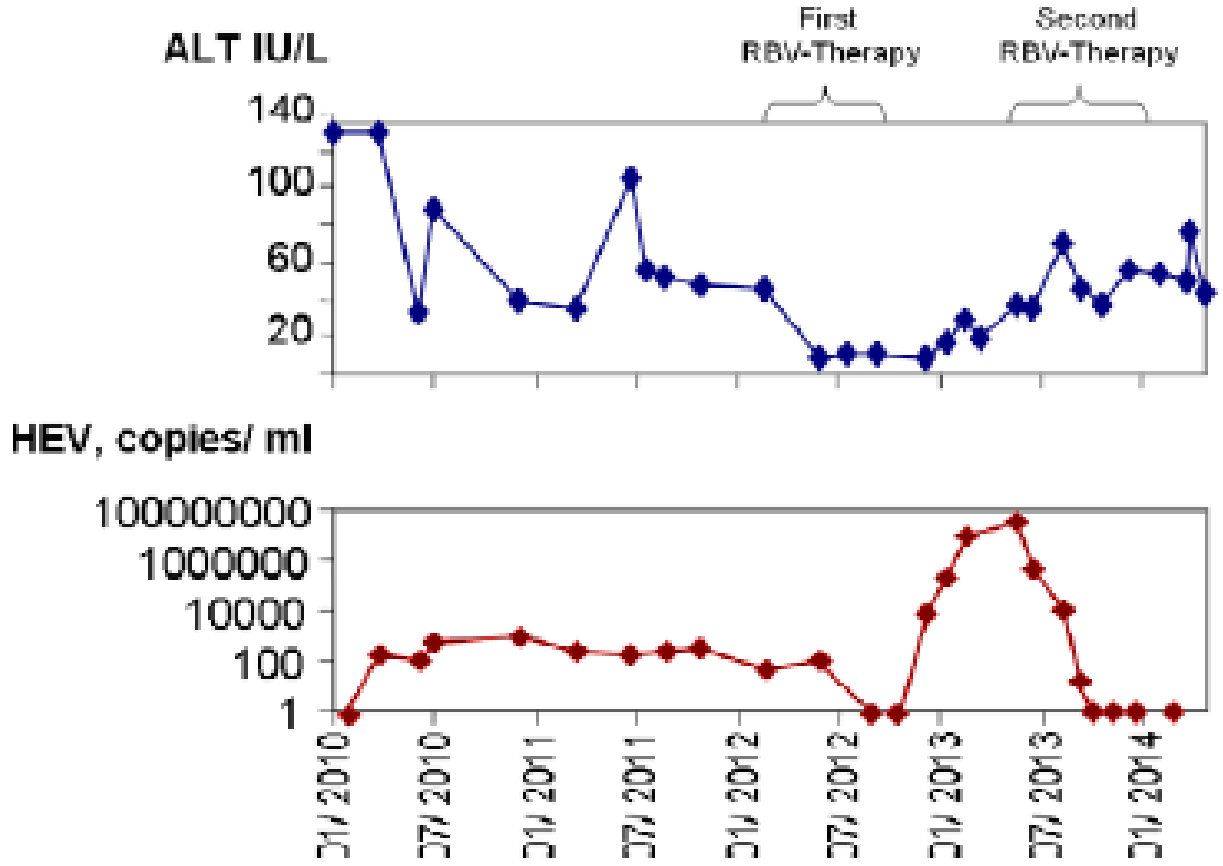
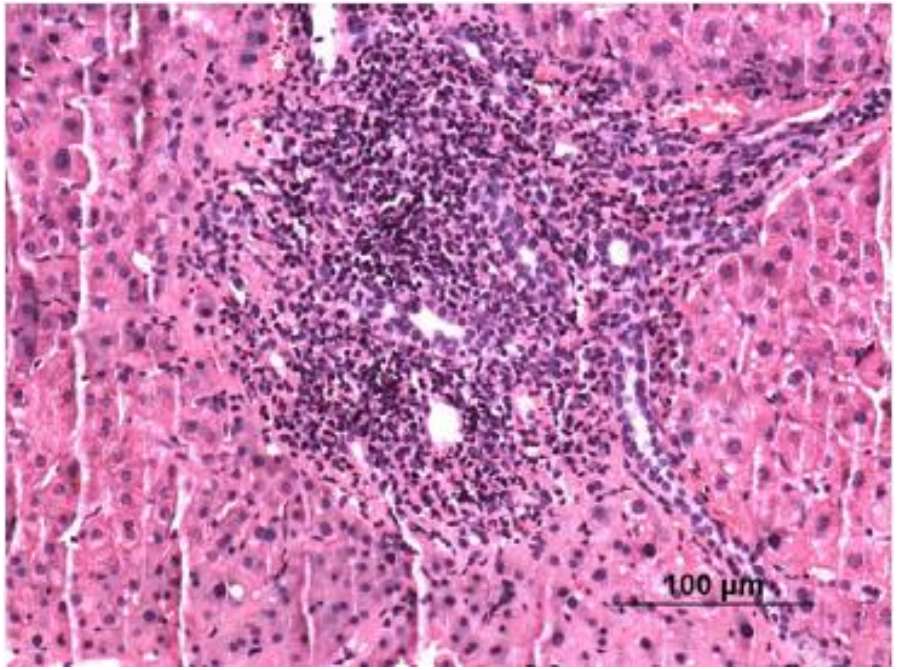


Fig. 2. The course of alanine transaminase (ALT) and hepatitis E virus (HEV) viral load in orthotopic liver transplant Patient 4. RBV, ribavirin.



HEPATİT D

Antivir Ther. 2015;20(5):529-33. doi: 10.3851/IMP2943. Epub 2015 Feb 10.

Interferon lambda-3 polymorphism and response to pegylated interferon in patients with hepatitis D.

Abbas Z[1], Yakoob J, Umer MA, Abbas M, Hamid S.

Author information

Abstract

BACKGROUND: Specific single nucleotide polymorphisms (SNPs) near the interferon lambda-3 (IFNλ3) gene (formerly interleukin 28B) influence the response to treatment with interferon in hepatitis C patients. We aimed to investigate such an influence in hepatitis D patients.

METHODS: The study population consisted of hepatitis D patients who were previously treated with pegylated interferon for one year and who were spontaneous clearers of the virus post recent superinfection. The SNP of IFNλ3, rs12979860, was determined by polymerase chain reaction-restriction fragment length polymorphism protocol.

RESULTS: The total number of patients was 64; median age was 30.5 years and 53 were male. The number of patients with sustained virological response 1 year post-treatment was 17, non-responders 29, relapsers 11 and spontaneous clearers post superinfection 7. Cirrhosis was present in 28 (44%). IFNλ3, rs12979860 genotype CC, was present in 41 (64.1%), CT in 21 (32.8%) and TT in 2 (3.1%). There was no difference in the body mass index, baseline alanine aminotransferase, hepatitis B e antigen and HBV DNA status among patients with sustained response and response failure (no response or relapse). The median age of response failures was 33.5 years compared to 26 in responders (P=0.024). They had higher gamma glutamyl transferase levels (P=0.030) and cirrhosis (P=0.003). Genotype CC was present in 29/40 of response failures compared to 9/17 of the responders (P=0.152). Logistic regression analysis showed that cirrhosis was the independent risk factor for failure to have a response (P=0.001). 4/7 patients with spontaneous clearance had genotype CC.

CONCLUSIONS: IFNλ3 rs12979860 SNP does not have any significant influence on long-term hepatitis D clearance. Presence of cirrhosis may influence the response.

Oral prenylation inhibition with lonafarnib in chronic hepatitis D infection: a proof-of-concept randomised, double-blind, placebo-controlled phase 2A trial

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Lancet Infect Dis 2015; 15: 1167–74

Summary

Background Therapies for chronic hepatitis delta virus (HDV) infection are unsatisfactory. Prenylation is essential for HDV and inhibition abrogates HDV production in experimental models. In a proof-of-concept study, we aimed to assess the effect on HDV RNA levels, safety, and tolerability of the prenylation inhibitor lonafarnib in patients with chronic delta hepatitis.

Methods In this phase 2A double-blind, randomised, placebo-controlled study, patients aged 18 years or older with chronic HDV infection were randomly assigned (3:1 in group 1 and 2:1 in group 2) to receive lonafarnib 100 mg (group 1) or lonafarnib 200 mg (group 2) twice daily for 28 days with 6 months' follow-up. Participants were randomised by random-number tables blocked in groups of four without stratification. Both groups enrolled six treatment participants and two placebo participants. Group 1 placebo patients received open-label lonafarnib as group 2 participants. The primary therapeutic endpoint was a decrease in HDV RNA viral titre in serum and the primary safety endpoint was the ability to tolerate the drug at the prescribed dose for the full 4-week duration, defined as drug discontinuation due to intolerance or grade 3/4 adverse events. This trial is registered with ClinicalTrials.gov, number NCT01495585.

Findings Between Jan 19, 2012, and April 28, 2014, 14 patients were enrolled, of whom eight were assigned to group 1 and six were assigned to group 2. At day 28, compared with placebo, mean log HDV RNA declines from baseline were −0·73 log IU/mL in group 1 (95% CI 0·17–1·31; p=0·03) and −1·54 log IU/mL in group 2 (1·21–1·93; p<0·0001). Lonafarnib serum concentrations correlated with HDV RNA change (r^2=0·78, p<0·0001). Model fits show that hepatitis B surface antigen (HBsAg) remained stable after a short pharmacological delay (0·75 days [SE 0·24]), lonafarnib effectiveness in blocking HDV production was greater in group 2 than in group 1 (0·952 [SE 0·06] *vs* 0·739 [0·05], p<0·001), and the HDV half-life was 1·62 days (0·07). There was no evidence of virological resistance. Adverse events were mainly mild to moderate with group 1 patients experiencing diarrhoea in three patients (50%) and nausea in two patients (33%) and in group 2 with all patients (100%) experiencing nausea, diarrhoea, abdominal bloating, and weight loss greater than 2 kg (mean of 4 kg). No treatment discontinuations occurred in any treatment groups.

Interpretation Treatment of chronic HDV with lonafarnib significantly reduces virus levels. The decline in virus levels significantly correlated with serum drug levels, providing further evidence for the efficacy of prenylation inhibition in chronic HDV.

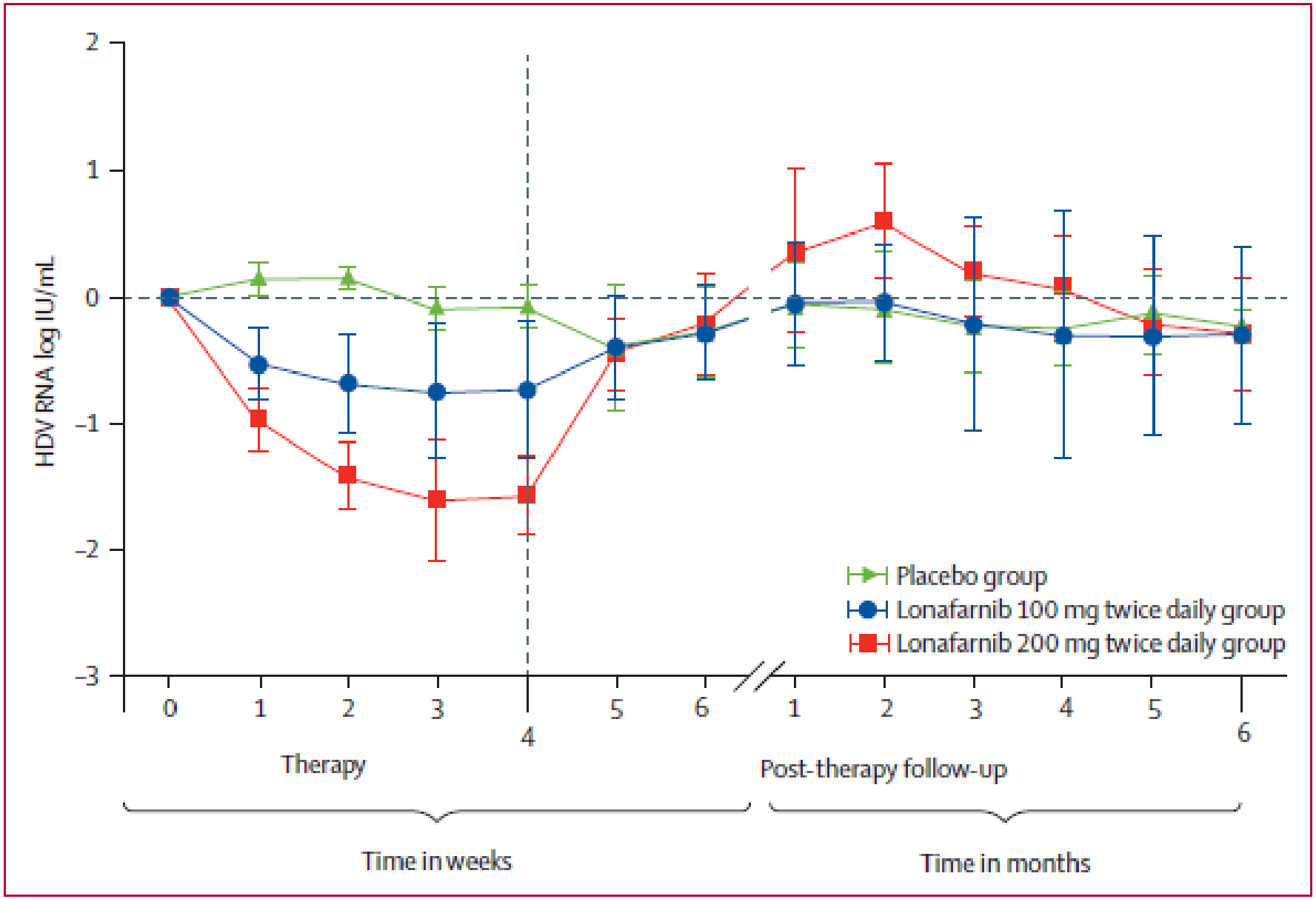

Figure 2: **Mean serum hepatitis delta virus RNA (SD) change during therapy with lonafarnib**

Association Between Level of Hepatitis D Virus RNA at Week 24 of Pegylated Interferon Therapy and Outcome

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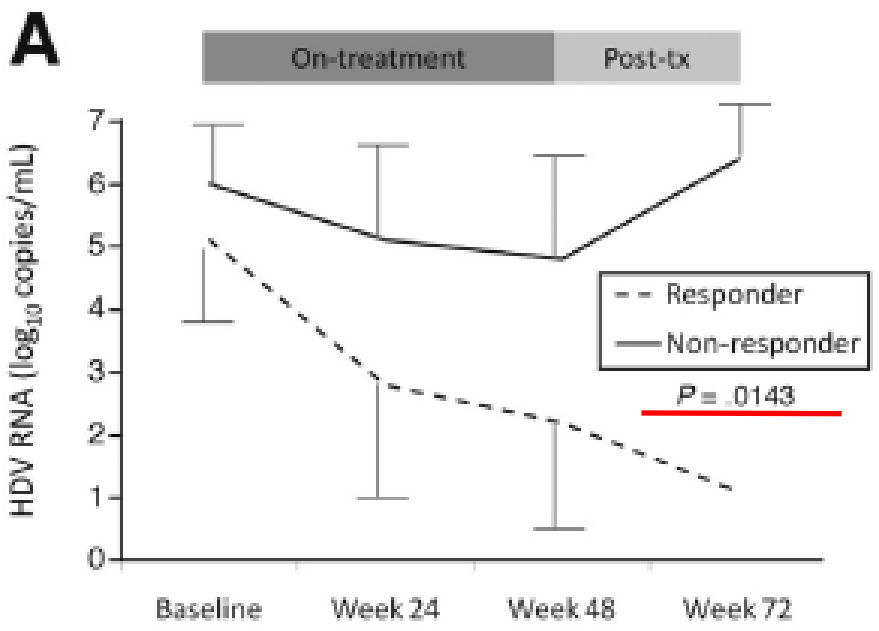
Clinical Gastroenterology and Hepatology 2015;13:2342–2349

BACKGROUND & AIMS: Interferon is the only effective treatment for chronic hepatitis D virus (HDV) infection. No rules have been set for stopping treatment based on viral kinetics. We analyzed data from an international study of hepatitis D treatment to identify factors associated with outcomes of pegylated interferon treatment, with and without adefovir.

METHODS: We analyzed data from the Hep-Net-International Delta Hepatitis Intervention Trial on 50 patients with compensated liver disease who tested positive for anti-HDV and HDV RNA. Subjects received pegylated interferon α 2a, with adefovir or placebo, or only adefovir, for 48 weeks. Twenty-four weeks after treatment ended, 41 patients were evaluated for levels of HDV RNA and DNA, liver enzymes, and hepatitis B surface antigen (HBsAg); liver biopsy specimens were analyzed for fibrosis. Response to therapy was defined as end-of-treatment response or post-treatment week 24 virologic response. In both cases virologic response was associated with undetectable HDV RNA levels. Patients with less than a 1 log decrease in HDV RNA at the end of treatment were considered null responders.

RESULTS: Based on univariate and multivariate analysis, the level of HDV RNA at week 24 of treatment was associated more strongly with response to therapy than other factors analyzed. The level of HBsAg at week 24 of treatment was associated with a response to therapy only in univariate analysis. Lack of HDV RNA at week 24 of treatment, or end of treatment, identified responders with positive predicted values of 71% and 100%, respectively. At 24 weeks after treatment, a decrease in HDV RNA level of less than 1 log, combined with no decrease in HBsAg level, identified null responders with a positive predictive value of 83%. A decrease in HDV RNA level of more than 2 log at week 24 of treatment identified null responders with a negative predictive value of 95%.

CONCLUSIONS: Based on an analysis of data from a large clinical trial, the level of HDV RNA at week 24 of treatment with pegylated interferon, with or without adefovir for 48 weeks, can identify patients who will test negative for HDV RNA 24 weeks after the end of treatment. This information can be used to help physicians manage patients receiving therapy for chronic hepatitis D.



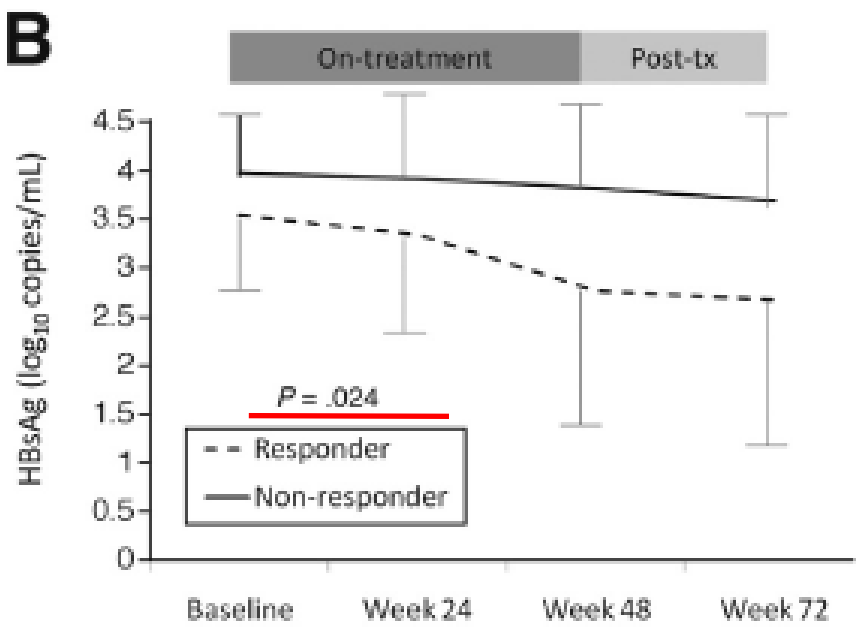


Figure 1. A significant difference was observed in (*A*) HDV RNA and (*B*) quantitative HBsAg levels throughout the treatment and post-treatment follow-up period between post-treatment week 24 virologic responders vs non-responders to pegylated interferon treatment. tx, treatment.