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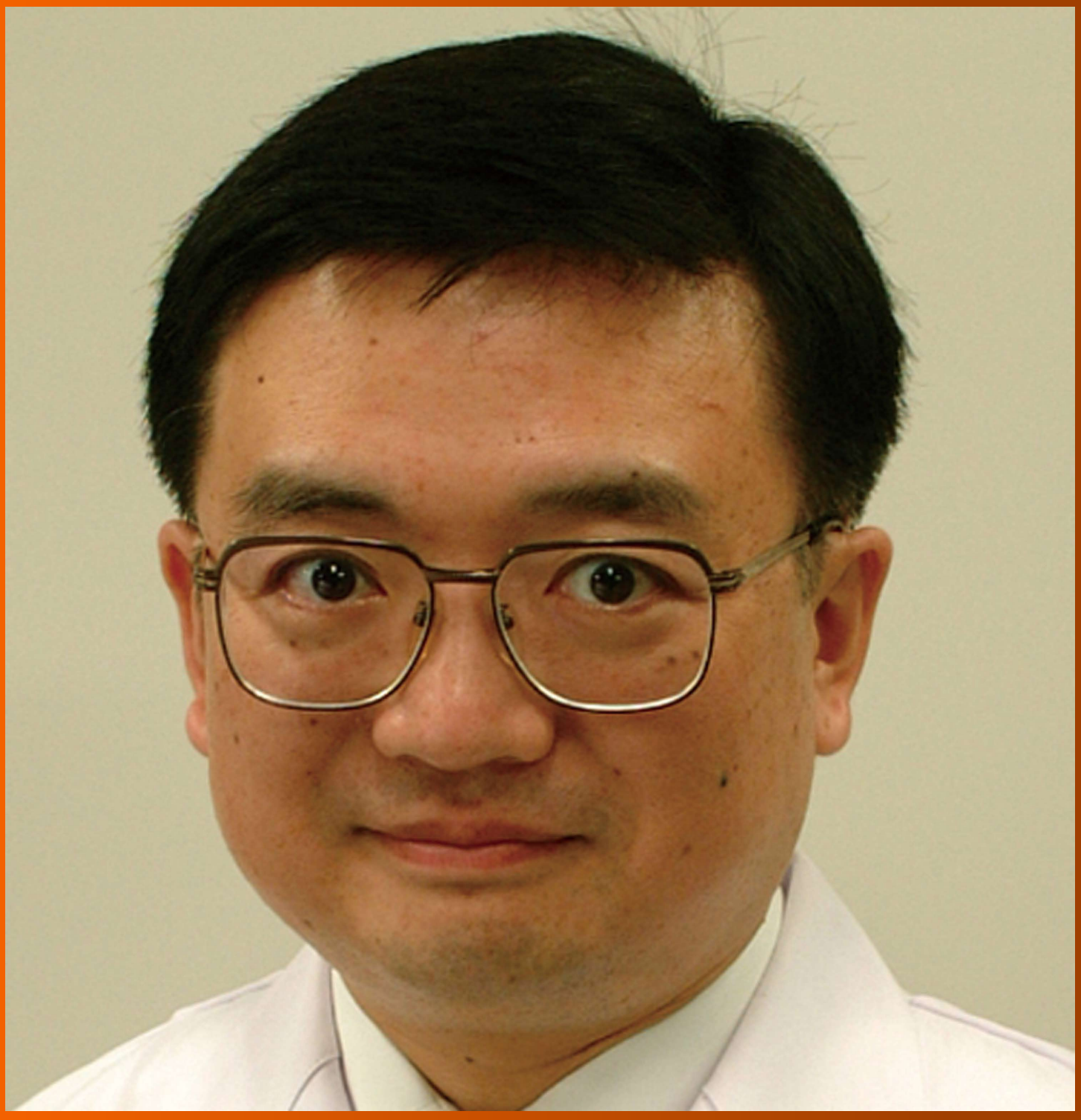

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Contents

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ORIGINAL ARTICLE

Retrospective Cohort Study

Hepatitis B surface antigen clearance in inactive hepatitis B surface antigen carriers treated with peginterferon alfa-2a

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Author contributions: Li MH and Xie Y conceived the study, participated in the study design, and drafted the manuscript; Zhang L, Lu Y, Shen G, Wu SL, Chang M, Mu CQ and Hu LP supervised all aspects of the study implementation; the remaining authors coordinated testing and helped to draft the manuscript.

Institutional review board statement: The study was reviewed and approved by the Beijing Ditan Hospital Institutional Review Board.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There was no conflict of interest and this study was carried out as a part of our routine work.

Data sharing statement: No additional data are available.

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Abstract

AIM: To examine the association between interferon (IFN) therapy and loss of hepatitis B surface antigen (HBsAg) in inactive HBsAg carriers.

METHODS: This was a retrospective cohort study in inactive HBsAg carriers, who were treatment-naive, with a serum HBsAg level < 100 IU/mL and an undetectable hepatitis B virus (HBV) DNA level (< 100 IU/mL). All the 20 treated patients received subcutaneous PEG-IFN alfa-2a 180 μg/wk for 72 wk and were then followed for 24 wk. There were 40 untreated controls matched with 96 wk of observation. Serum HBsAg, HBV DNA, and alanine aminotransferases were monitored every 3 mo in the treatment group and every 3-6 mo in the control group.

RESULTS: Thirteen (65.0%) of 20 treated patients achieved HBsAg loss, 12 of whom achieved HBsAg seroconversion. Mean HBsAg level in treated patients decreased to 6.69 ± 13.04 IU/mL after 24 wk of treatment from a baseline level of 26.22 ± 33.00 IU/mL. Serum HBV DNA level remained undetectable (< 100 IU/mL) in all treated patients during the study. HBsAg level of the control group decreased from 25.72 ± 25.58 IU/mL at baseline to 17.11 ± 21.62 IU/mL at

week 96 (P = 0.108). In the control group, no patient experienced HBsAg loss/seroconversion, and two (5.0%) developed HBV reactivation.

CONCLUSION: IFN treatment results in HBsAg loss and seroconversion in a considerable proportion of inactive HBsAg carriers with low HBsAg concentrations.

Key words: Chronic hepatitis B surface antigen carriers; Inactive hepatitis B surface antigen carriers; Interferon; Peginterferon alfa-2a; Hepatitis B surface antigen loss/seroconversion

Core tip: This study examined the association between interferon (IFN) therapy and loss of hepatitis B surface antigen (HBsAg) in inactive HBsAg carriers. This was a retrospective cohort study in inactive HBsAg carriers with a serum HBsAg level < 100 IU/mL and a persistently undetectable hepatitis B virus (HBV) DNA level (< 100 IU/mL). All the 20 treated patients received subcutaneous PEG-IFN alfa-2a 180 μg/wk for 72 wk and were then followed for 24 wk. IFN treatment resulted in HBsAg loss (65.0%) and seroconversion in a considerable proportion of inactive HBsAg carriers with low HBsAg concentrations. In the control group, no patient experienced HBsAg loss/seroconversion, and 2 (5.0%) developed HBV reactivation.

Li MH, Xie Y, Zhang L, Lu Y, Shen G, Wu SL, Chang M, Mu CQ, Hu LP, Hua WH, Song SJ, Zhang SF, Cheng J, Xu DZ. Hepatitis B surface antigen clearance in inactive hepatitis B surface antigen carriers treated with peginterferon alfa-2a. *World J Hepatol* 2016; 8(15): 637-643 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i15/637.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i15.637

INTRODUCTION

Chronic hepatitis B virus (HBV) infection is the leading cause of end-stage liver disease or hepatocellular carcinoma (HCC) throughout the world. In the nature history of chronic HBV infection, inactive hepatitis B surface antigen (HBsAg) carriers, defined as HBsAg positive, hepatitis B envelope antigen (HBeAg)-negative/antiHBe-positive, undetectable HBV DNA level and normal alanine aminotransferases (ALT) levels, frequently have good long-term clinical outcomes and thus are not recommended for antiviral treatment[1-3]. However, this inactive carrier status was not always sustained. Fourteen percent to 24% of inactive carriers have reactivation after years of quiescent disease, and 4.2% to 20% of them reverse back to HBeAg positivity[4-7], with increased cumulative probabilities of reactivation of hepatitis B after years of follow-up[8]. Compared to a control subcohort (negative for HBsAg), inactive HBsAg carriers have higher risks of hepatocellular carcinoma and liver-related death[9], especially in countries with a high prevalence of HBV infection[8,9]. In contrast, 100% and 90% of patients had improvement and stable liver inflammation and liver fibrosis[10], respectively, and no HCC occurred in patients with HBsAg clearance after interferon (IFN) treatment[11]. Nevertheless, spontaneous HBsAg loss occurred in inactive carriers only at rates from 1% to 1.5% per year observed in Caucasians[12] and Asians[13]. HBsAg clearance usually indicates recovery from HBV infection, and has been an aim of antiviral therapy[2]. In the real life, HBsAg positive people were restricted in many aspects such as work, diet, and cosmetic surgery, in China, and many of them hope to obtain HBsAg loss through effective methods.

IFN treatment exerts direct antiviral as well as immunoregulatory effects[14], and can induce specific and nonhepatotoxic degradation of nuclear HBV covalently closed circular DNA (cccDNA)[15], and increased HBV-specific T-cell responses in chronic HBV infected patients with undetectable levels of serum HBV DNA[16]. This retrospective cohort study was conducted to evaluate the efficacy of PEG-IFN alfa-2a treatment in chronic inactive carriers with a low HBsAg level.

MATERIALS AND METHODS

Selection of patients

A retrospective cohort study including inactive HBsAg carriers attending the department of hepatology, Beijing Ditan Hospital, Capital Medical University between May 2008 and August 2012 was conducted. We diagnosed inactive HBsAg carriers based on their history of HBV infection, HBV DNA level, serological markers, and liver function. Patients with cirrhosis, which was diagnosed as liver stiffness > 9 kPa or presence of portal hypertension (spleen enlargement with a reduction in platelet count) by FibroScan and ultrasonic examinations, were excluded. Patients who were treatment-naive, HBsAg positive, anti-HBs-negative and HBeAg negative for more than 6 mo, had a persistently undetectable HBV DNA level (< 100 IU/mL) and normal ALT levels (< 19 IU/mL for females and < 30 IU/mL for males, measured every 3-6 mo) during the preceding 2 years, and serum HBsAg < 100 IU/mL on two occasions during the month prior to enrollment were included in the study. Patients with other liver diseases or co-infection of hepatitis C virus, hepatitis D virus, and human immunodeficiency virus, as well as those who had a history of immunosuppressive or antiviral drug usage were excluded. HBV genotyping cannot be performed due to an undetectable HBV DNA level in the subjects; however, epidemiological studies showed the HBV genotypes in China were mainly genotypes B and C[17,18].

Participants in the treatment group contained all the patients who were willing to receive IFN treatment for achieve HBsAg clearance and had completed 72 wk of treatment with PEG-IFN alfa-2a and 24 wk of follow-up after completing the treatment. There were

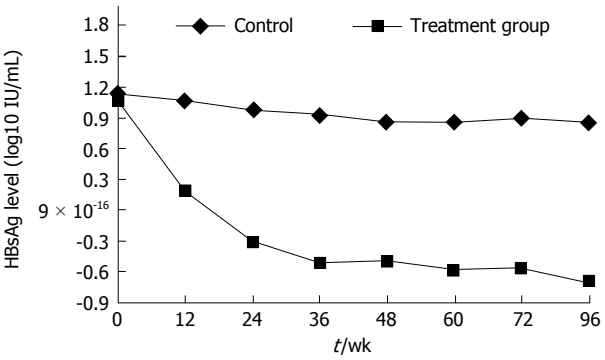

Figure 1 Mean hepatitis B surface antigen level decreased in a time-dependent manner in treated patients and was significantly lower at week 24 than at baseline. HBsAg: Hepatitis B surface antigen.

40 controls matched for age, sex, and HBsAg level, and undetectable HBV DNA with persistently normal ALT levels, and they were selected from 284 untreated patients who attended the clinic and completed 96 wk of observation during the same period as treated patients.

Ethics approval

The study adhered to the Declaration of Helsinki and ethics approval was obtained from the Beijing Ditan Hospital of Capital Medical University Institutional Review Board. Written informed consent was obtained from all subjects before enrolment.

Treatment and follow-up

The treated cohort comprised 20 patients who had received subcutaneous PEG-IFN alfa-2a at a dose of 180 μg/wk for 72 wk and had been followed for 24 wk after completing the treatment, while the control cohort comprised 40 matched patients who had finished 96 wk of observation.

None of the participants received immunosuppressive or oral antiviral drugs during the study period. In the treated patients, serum HBsAg, anti-HBs and HBV DNA levels were measured once every 3 mo, and peripheral blood neutrophil and platelet counts, and liver and kidney function tests were performed once every 1-3 mo. These biomarkers were measured once every 3-6 mo in controls.

Safety and efficacy assessments

Kidney and liver function biomarkers, including serum creatinine, blood urea nitrogen, ALT, aspartate aminotransferase, albumin and total bilirubin (Tbil), were measured with an automated biochemical analyzer. Peripheral blood neutrophil and platelet counts were measured with an automatic blood cell analyzer.

HBV DNA was measured with a commercially available real-time fluorescence PCR kit with a detection limit of 100 IU/mL (Piji Company, Shenzhen City, China). HBsAg concentrations were quantified by an automated chemoluminescent microparticle immunoassay (Architect i2000 HBsAg quantitative assay, Abbott Laboratories, Abbott Park, IL, United States, sensitivity < 0.05 IU/mL; dynamic range 0.05-250 IU/mL). HBsAg loss was defined as HBsAg concentration < 0.05 IU/mL. Anti-HBs was measured with an Architect i2000 kit (Abbott Laboratories, dynamic range of 0.00-1000 mIU/mL), with concentrations ⩾ 10 mIU/L being considered positive. The primary efficacy endpoints were HBsAg loss and seroconversion.

Statistical analysis

Unless otherwise stated, clinical and biological outcomes before and after treatment are expressed as mean ± SD or median (range), and were compared using paired Student's *t*-tests, with a *P*-value less than 0.05 being considered statistically significant. Qualitative variables are presented as counts and percentages and were compared using Fisher's exact tests. All statistical analyses were performed using SPSS statistical software version 13.0 (Chicago, IL, United States).

RESULTS

Patients and clinical characteristics

A total of 60 inactive chronic HBsAg carriers were included in the study, 20 of whom were in the treated group and 40 in the control group. There were no significant differences in the baseline characteristics between the treated and control groups (Table 1). However, in the treatment group, the patients who achieved HBsAg loss had a lower baseline HBsAg level of 8.09 (3.81-22.50) IU/mL and were younger (age of 31.46 ± 12.16 years) than patients without HBsAg loss after treatment [baseline HBsAg level of 18.95 (2.85-83.00) IU/mL and age of 38.24 ± 9.25 years], but there was no significant difference.

HBsAg kinetics and clinical outcomes

HBsAg levels decreased with increasing treatment period in the treated group (Figure 1). Among patients treated with PEG-IFN alfa-2a, the mean HBsAg level decreased by 55.98% from baseline to week 12 (from 26.22 ± 33.00 to 11.59 ± 20.83 IU/mL, $P = 0.108$), by 74.59% from baseline to week 24 (to 6.69 ± 13.04 IU/mL, $P = 0.024$ *vs* baseline), and was 0.045 IU/mL (range, 0.02-2.44 IU/mL) at the end of follow-up (week 96). Of the 20 treated patients, 13 achieved HBsAg loss, of whom 12 occurred during treatment and 1 at follow-up time, with a mean of 40.62 ± 22.74 mo after the initiation of treatment, in which 12 achieved HBsAg seroconversion (Table 1). Eighty percent (8/10) of patients with an HBsAg level < 10 IU/mL achieved HBsAg loss after treatment. In the remaining seven treated patients, the mean HBsAg level decreased by 66.93% from baseline to the end of follow-up (from 37.43 ± 38.69 to 8.20 ± 15.69 IU/mL, $P = 0.049$). Serum HBV DNA remained undetectable (< 100 IU/mL) in all treated patients during the treatment and follow-up periods, and no return to HBsAg positivity occurred in all patients during the study course. In contrast,

Table 1 Baseline characteristics and outcomes at the end of treatment and follow-up

Characteristic	Treatment group	Control group	*P*-value
No.	20	40	
Mean age at entry in year ± SD	33.80 ± 11.45	33.85 ± 8.37	0.985
Age > 40 yr, *n* (%)	4 (20.0)	11 (27.5)	0.527
Men:women, *n*	15:5	30:10	1.000
Mean baseline ALT (U/L) ± SD	23.46 ± 8.78	21.24 ± 10.26	0.874
HBsAg level (IU/mL)			
Mean ± SD	26.22 ± 33.00	25.72 ± 5.58	0.949
Median (Q1, Q3)	11.36 (3.52-37.40)	15.81 (4.59-40.15)	0.714
95%CI of patients with 10-100 IU/mL, *n* (%)	(10.77, 41.75), 10 (50.0)	(17.54, 33.90), 22 (55.0)	
Patients with < 10 IU/mL, *n* (%)	10 (50.0)	18 (45.0)	
Mean decline in HBsAg level at EOT (IU/mL) ± SD	22.33 ± 29.45	5.76 ± 17.67	0.009
Median HBsAg level at EOT (IU/mL)	0.04 (0.02, 0.55)	13.21 (2.97, 30.31)	0.003
(Q1, Q3)	95%CI: (-0.68, 8.53)	95%CI: (12.8, 27.12)	
Mean decline in HBsAg level at EOF (IU/mL) ± SD	23.36 ± 29.47	8.61 ± 19.32	0.023
Median HBsAg level at EOF (IU/mL)	0.045 (0.02, 2.44)	5.69 (1.50, 20.88)	0.007
(Q1, Q3)	95%CI: (-1.63, 7.43)	95%CI: (10.20, 24.03)	
HBsAg loss, *n* (%)	13 (65.0)	0 (0)	0.000
HBsAg seroconversion, *n* (%)	12 (60.0)	0 (0)	0.000
HBV DNA reactivation, *n* (%)	0 (0)	2 (5.0)	0.309

ALT: Alanine aminotransferase; EOF: End of follow-up; EOT: End of treatment; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

the mean HBsAg level of the control group remained relatively stable over 96 wk and was 25.72 ± 25.58 IU/mL at baseline and 17.11 ± 21.62 IU/mL at week 96 (P = 0.108; Figure 1). No patients in the control group experienced HBsAg loss/seroconversion, and two (5.0%) experienced HBV reactivation, defined as return of serum HBV DNA to positivity from undetectable level (< 100 IU/mL) (Table 1).

Safety

Among all patients in the treated group, peripheral blood neutrophil count decreased, which was lower than 0.85 × 10^9/L in 13 (65.0%) individuals. The platelet count also decreased, which was lower than 6.0 × 10^{12}/L in eight (40.0%) patients, and dose reductions were not required. Serum creatinine and blood urea nitrogen remained stable during treatment with PEG-IFN alfa-2a. Five patients had a loss of body weight and six patients had mild hair loss during treatment. There were no thyroid dysfunction and neuropsychiatric adverse effects, including depression, delirium, irritability and agitation. All adverse reactions disappeared 3-6 mo after the therapy was discontinued.

ALT levels increased during treatment in 18 of 20 (90.0%) treated patients, and 9 (45.0%) individuals experienced an ALT level > 80 IU/L. However, bilirubin levels remained within normal limits throughout the treatment and follow-up periods in all treated patients. Normalization of ALT levels coincided with HBsAg loss and/or the end of treatment, and was maintained during follow-up.

DISCUSSION

HBsAg level reflects the transcriptional activity of the cccDNA and is used as a proxy measure of HBV infection and for treatment guidance[19-21]. HBsAg declines during treatment and its level at the end of treatment can predict HBeAg seroconversion in HBeAg-positive patients[22-24] and sustained viral response in HBeAg-negative patients[25-27]. Thus, inactive HBsAg carriers were not recommended for antiviral therapy[1-3]. However, this inactive state was not always sustained. A long-term follow-up study showed cumulative probabilities of hepatitis relapse in inactive HBsAg carriers of 10.2%, 17.4%, 19.3%, 20.2% and 20.2% after 5, 10, 15, 20 and 25 years of follow-up, respectively, with an annual rate of 1.55%[28]. Another long-term longitudinal study (up to 23 years) showed that 1%-17% of inactive carriers reverted back to HBeAg-positive chronic hepatitis[4]. Cirrhosis and HCC may still develop in some inactive HBsAg carriers[28-30]. In contrast, no cirrhosis or HCC occurred in patients with HBsAg loss after IFN treatment, indicating that HBsAg clearance is currently the only parameter associated with an excellent long-term prognosis[10], and the strongest factor predicting excellent long-term outcome in HBV infected individuals is HBsAg loss, spontaneously or after treatment[10]. Therefore, it could be speculated that inactive HBsAg carriers can get further improvement in outcomes if HBsAg loss could be achieved after IFN treatment.

This study contained all participants who were inactive carriers with HBsAg < 100 IU/mL and wished to achieve HBsAg clearance by PEG-IFN alfa-2a treatment during the study period. Despite the lack of liver pathology for diagnosis, the patients could be considered as inactive for having undetectable HBV DNA and persistent normal ALT for 2 years, serum HBV DNA < 100 IU/mL and HBsAg < 100 IU/mL at enrollment. It has been reported that HBsAg < 1000 IU/mL with HBV DNA < 2000 IU/mL can distinguish inactive from active carriers with a diagnostic accuracy of 94.3%, sensitivity

of 91.1%, specificity of 95.4%, positive predictive value of 87.9%, and negative predictive value of 96.7%[31]. Although the present study was not a randomized controlled study, all treated inactive carriers with HBsAg < 100 IU/mL and matched controls according to age, sex, and HBsAg and ALT levels were included for eliminating the bias.

Effects, including the probability of HBsAg clearance, can be enhanced by extended therapy with PEG-IFN alfa-2a[32]. In our study the patients were given 72 wk of treatment. After 12 wk of treatment with PEG-IFN alfa-2a, HBsAg levels decreased significantly compared with baseline levels. Furthermore, at the end of study, HBsAg loss occurred in most of treated patients, and HBsAg levels in the remaining seven treated carriers who did not achieve HBsAg loss decreased significantly. In contrast, mean HBsAg level of the control group remained constant during 96 wk of observation and no patients experienced HBsAg loss. These results suggest that inactive HBsAg carriers could benefit from PEG-IFN alfa-2a treatment.

In the present study, all participants had HBsAg < 100 IU/mL and they may have a good long-term clinical outcome, even HBsAg loss, after long-term follow-up. However, it was reported that spontaneous HBsAg loss in patients with HBsAg < 100 IU/mL occurred in a mean period of 86.6 ± 29 mo (range, 26-115) after the baseline visit with an annual rate of 1.6%[33], and in the present study after 72 wk treatment of PEG-IFN alfa-2a, HBsAg clearance occurred in 65% of treated objects. In a study by Tseng *et al*[34], HBsAg level < 10 IU/mL at baseline was the strongest predictor of HBsAg loss. However, the rate of HBsAg loss was only 7.4 per 100 persons per year and it occurred in a mean period of 5.8 ± 4.2 years. Although half of the subjects included in this study had HBsAg < 10 IU/mL and undetectable HBV DNA, 80% (8/10) of them achieved HBsAg loss after 72 wk of IFN treatment, suggesting that PEG-IFN alfa-2a treatment can make inactive carriers achieve HBsAg clearence in a short-term period compared with spontaneous HBsAg loss occurring in the nature history. Although Chen *et al*[35] reported in a case-control study that the positive predictive value of HBsAg level of 200 IU/mL in predicting HBsAg loss occurring within 1 year was 36%, their study design was different from ours. The aim of their study was to observe the difference in HBsAg decrease between 46 patients who underwent spontaneous HBsAg loss and 46 patients who had no HBsAg loss during the same observation course. The aim of our study was to compare the rate of HBsAg clearance in patients treated with PEG-IFN alfa-2a compared with untreated patients, and the result showed that the rate of HBsAg clearance was significantly higher in patients treated with PEG-IFN alfa-2a than in untreated patients. The results of our study suggested that inactive carriers can receive PEG-IFN alfa-2a therapy to increase the probability of HBsAg clearance and shorten the time compared with that occurring spontaneously.

In conclusion, our study demonstrated that treatment with PEG-IFN alfa-2a produced a high rate of HBsAg loss/seroconversion in inactive carriers with low HBsAg levels. However, whether inactive carriers with HBsAg levels more than 100 IU/mL could benefit from PEG-IFN alfa-2a treatment needs further study.

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COMMENTS

Background

Although inactive hepatitis B surface antigen (HBsAg) carriers often have no liver inflammation and are not recommended to undergo treatment, they may develop hepatitis relapse or revert back to HBeAg-positive chronic hepatitis, and cirrhosis and hepatocellular carcinoma (HCC) may still develop in some inactive HBsAg carriers in a long-term follow-up period. In contrast, no cirrhosis or HCC occurred in patients with HBsAg loss after interferon (IFN) treatment. So, HBsAg loss is generally considered to be the ultimate goal of therapy, indicating a complete response to treatment and the resolution of the disease. It was suggested that inactive HBsAg carriers could get benefits from IFN treatment if HBsAg loss was achieved after treatment.

Research frontiers

HBsAg loss is the goal and ideal end-point of treatment in chronic hepatitis B. The spontaneous rate of HBsAg loss in inactive carriers was only 0.5%-2.5% per year, and HBsAg clearance occurred in a mean period of 86.6 ± 29 mo (range, 26-115) after the initial visit. Even in patients with an HBsAg level < 10 IU/mL, a mean period of 5.8 ± 4.2 years is required to achieve HBsAg clearance.

Innovations and breakthroughs

In contrast to chronic hepatitis B, in which a low rate of HBsAg loss is achieved after IFN treatment, inactive HBsAg carriers with HBsAg < 100 IU/mL could obtain a high rate of HBsAg loss after PEG-IFN treatment in a shorter period than that occurring spontaneously.

Applications

Inactive HBsAg carriers will benefit from PEG-IFN treatment, if HBsAg loss can be achieved after a short period of PEG-IFN therapy.

Terminology

Inactive HBsAg carriers are patients who were HBsAg-positive, with low hepatitis B virus (HBV) replication and no liver inflammation. HBsAg loss was defined as an HBsAg concentration < 0.05 IU/mL, and seroconversion defined as an HBsAg concentration < 0.05 IU/mL and an anti-HBs level ⩾ 10 mIU/L. HBsAg loss often indicates recovery from HBV infection.

Peer-review

The manuscript entitled "Hepatitis B surface antigen clearance in inactive hepatitis B surface antigen carriers treated with peginterferon alfa-2a" discusses a possible application of an IFN therapy in inactive HBsAg carriers with a very low HBsAg level. The authors report that in their study the HBsAg disappeared in 65% of treated patients. This result seems to be very good, taking into account that usually HBsAg clearance is rarely observed.

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ORIGINAL ARTICLE

Retrospective Study

Outcome analysis of management of liver trauma: A 10-year experience at a trauma center

Wong Hoi She, Tan To Cheung, Wing Chiu Dai, Simon HY Tsang, Albert CY Chan, Daniel KH Tong, Gilberto KK Leung, Chung Mau Lo

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Author contributions: She WH was responsible for study design, literature search, collection, analysis and interpretation of data, and manuscript drafting; Cheung TT was responsible for study design, analysis and interpretation of data, and writing and critical revision of manuscript; Dai WC, Tsang SHY and Chan ACY were responsible for study design and critical revision of manuscript; Tong DKH, Leung GKK and Lo CM were responsible for study design; Cheung TT is the guarantor.

Institutional review board statement: Review and approval of this particular study by the Institutional Review Board of The University of Hong Kong are not necessary since the Board permits all use of patient data in retrospective studies provided that no individual patients can be identified.

Informed consent statement: Consent by patients was not required for this particular study since this is an overall review of patient data with no individual patients being identified.

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Abstract

AIM: To review the outcomes of liver trauma in patients with hepatic injuries only and in patients with associated injuries outside the liver.

METHODS: Data of liver trauma patients presented to our center from January 2003 to October 2013 were reviewed. The patients were divided into two groups. Group 1 consisted of patients who had hepatic injuries only. Group 2 consisted of patients who also had associated injuries outside the liver.

RESULTS: Seven (30.4%) patients in group 1 and 10 (28.6%) patients in group 2 received non-operative management; the rest underwent operation. Blunt trauma occurred in 82.8% (48/58) of the patients and penetrative trauma in 17.2% (10/58). A higher injury severity score (ISS) was observed in group 2 (median 45 *vs* 25, $P < 0.0001$). More patients in group 1 were hemodynamically stable (65.2% *vs* 37.1%, $P = 0.036$). Other parameters were comparable between groups. Group 1 had better 30-d survival (91.3% *vs* 71.4%, $P = 0.045$). On multivariate analysis using the logistic regression model, ISS was found to be associated with mortality ($P = 0.004$, hazard ratio = 1.035, 95%CI:

1.011-1.060).

CONCLUSION: Liver trauma patients with multiple injuries are relatively unstable on presentation. Despite a higher ISS in group 2, non-operative management was possible for selected patients. Associated injuries outside the liver usually account for morbidity and mortality.

Key words: Non-operative management; Liver trauma; Multiple injuries; Penetrative trauma; Liver laceration; Blunt trauma

Core tip: Liver trauma patients who have not only liver injury but also associated injury outside the liver usually have a high injury severity score (ISS) and a bigger chance of morbidity and death. Management of liver trauma features surgical and nonsurgical approaches. Choice of approach should depend on individual patients' overall clinical condition rather than just ISS or imaging findings. The applicability of nonsurgical approach has extended to penetrative injuries with success.

She WH, Cheung TT, Dai WC, Tsang SHY, Chan ACY, Tong DKH, Leung GKK, Lo CM. Outcome analysis of management of liver trauma: A 10-year experience at a trauma center. *World J Hepatol* 2016; 8(15): 644-648 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i15/644.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i15.644

INTRODUCTION

The liver is well known to be the most frequently injured internal organ in abdominal injury despite its relatively hidden location behind the subcostal region[1]. In liver trauma management, the widespread use of ultrasonography and computed tomography (CT) has facilitated decision-making, and non-operative management (NOM) has been shown to reduce mortality[2]. NOM is now the standard of care for blunt liver injury in hemodynamically stable patients[3-7]. A contrast CT scan of the abdomen can accurately identify the pathology, presence of complication and proper severity grade of injury in hemodynamically stable patients. For hemodynamically unstable patients, operative management (OM) may be necessary. Other considerations should also be taken into account as patients may suffer multiple injuries. Some injuries call for OM. In such cases, the liver injury can be dealt with in the laparotomy required by associated injuries. Treatment outcomes depend on the severity of injuries to organs. This study reviewed the management of liver trauma with or without associated injuries over 10 years at a level-1 trauma center in Hong Kong.

MATERIALS AND METHODS

This is a retrospective study. The period for review is from January 2003 to October 2013. Patients at Department of Surgery, Queen Mary Hospital, the University of Hong Kong, who had liver trauma from blunt or penetrative injuries in the period were reviewed. Data of interest included demographic data, presentation, associated injury, mechanism of injury, grade of liver injury, injury severity score (ISS), and management outcome. The data were retrieved by a dedicated trauma nurse coordinator and then screened and reviewed by the authors.

The patients were divided into two groups. Group 1 consisted of patients who had hepatic injuries only. Group 2 was comprised of patients who also had associated injuries outside the liver. The presence of associated injuries was checked for either during the primary and the secondary surveys according to the Advanced Trauma Life Support principle and then by imaging (X-ray or CT scan) of various regions, or during operation. Patients (with or without initial fluid resuscitation) were regarded as hemodynamically stable if they had a patent airway, satisfactory oxygen saturation of > 95%, good volume pulse, heart rate of < 100 beats/min, and systolic blood pressure of > 90 mmHg.

The patients' grade of liver injury was determined according to the Organ Injury Scaling developed by the Organ Injury Scaling Committee of the American Association for the Surgery of Trauma[8], with grade 1 being the least severe and Grade 6 being unsurvivable. For patients who received NOM, grade of liver injury was determined with a CT scan; for those who received OM, it was determined during operation.

The ISS is an anatomical scoring system that provides an overall score (0-75) for patients with multiple injuries. Calculation of each patient's ISS was based on signs shown upon physical examination, results of investigation, and findings in operation. Each injury in the six body regions (head, face, chest, abdomen, extremities and external) was assigned an Abbreviated Injury Score (AIS) according to the Abbreviated Injury Scale, and only the highest AIS in each body region were used. Each patient's three most severely injured body regions had their AIS squared and added together to produce an ISS for the patient. An AIS of 6 (unsurvivable injury) always entailed an ISS of 75 (fatality)[9].

NOM was adopted for hemodynamically stable patients whose abdominal examination showed no peritoneal signs and whose imaging scans (X-ray, CT or ultrasonography) showed no intraperitoneal, retroperitoneal or extra-abdominal injuries requiring operative intervention. OM was indicated otherwise and when NOM failed.

All patients were closely monitored in the intensive care unit. Reassessment measures included physical examination, daily blood tests, and reassessment CT scan. Reassessment CT scan of the abdomen was performed 3 to 5 d after initial insult. CT scan for other

Table 1 Comparison of perioperative data of the two groups *n* (%)

	Group 1 (*n* = 23)	Group 2 (*n* = 35)	*P* value
Age (yr)	36 (4-79)	36 (5-75)	0.762
Male:female	16:7	23:12	0.760
Health background			0.208
Good past health	15 (65.2)	28 (80.0)	
With comorbidity	8 (34.8)	7 (20.0)	
Type of trauma			1
Blunt	19 (82.6)	29 (82.9)	
Penetrative	4 (17.4)	6 (17.1)	
Mechanism of injury			0.077
Blunt injury	5 (21.7)	2 (5.7)	
Fall from a height	2 (8.7)	6 (17.1)	
Penetrative injury	4 (17.4)	3 (8.6)	
Road traffic accident	9 (39.1)	23 (65.7)	
Slip and fall	3 (13.0)	1 (2.9)	
With initial CT done	17 (73.9)	25 (71.4)	1
Reassessment CT			0.367
Not done	8 (34.8)	15 (42.9)	
Problem resolved	15 (65.2)	18 (51.4)	
Complication seen	0 (0)	2 (5.7)	
Hemodynamics			0.036
Stable	15 (65.2)	13 (37.1)	
Unstable	8 (34.8)	22 (62.9)	
Management			0.879
NOM	7 (30.4)	10 (28.6)	
OM	16 (69.6)	25 (71.4)	
Blood loss in OM (mL)	300 (0-20000)	1250 (0-24000)	0.133
Blood transfusion			0.018
No	14 (60.9)	10 (29.4)	
Yes	9 (39.1)	24 (70.6)	
Packed cells transfused (mL)	0 (0-2390)	1050 (0-10240)	0.001
Radiological intervention			1
No	21 (91.3)	30 (90.9)	
Yes	2 (8.7)	3 (9.1)	
ISS	25 (16-75)	45 (17-75)	< 0.0001
Grade of liver injury[1]			0.354
1	4 (17.4)	3 (8.8)	
2	5 (21.8)	5 (14.7)	
3	11 (47.8)	12 (35.3)	
4	2 (8.7)	8 (23.5)	
5	1 (4.3)	5 (14.7)	
6	0 (0)	1 (2.9)	
With complication	4 (18.2)	4 (11.4)	0.747
Follow-up duration (mo)	6 (0-60)	3 (0-128)	0.339

[1]There is one missing datum in group 2. Data are presented as median with range or number with percentage. ISS: Injury severity score; NOM: Non-operative management; OM: Operative management; CT: Computed tomography.

regions was performed if necessary.

Statistical analysis

At the Department of Surgery, The University of Hong Kong, we have our own statistical staff. The biostatistics in this study was performed by our own statistical staff. The computer software SPSS, version 21.0, from IBM SPSS Statistics was used for statistical analyses. Continuous variables were compared by the Mann-Whitney *U* test and expressed as median with interquartile range. Student's *t*-test and Pearson's χ^2 test were employed. Thirty-day survival was measured. The Kaplan-Meier method was used for survival estimation and the log-rank test was used for survival comparison. Multivariate analysis was performed to identify the risks for mortality. *P* values < 0.05 were considered statistically significant.

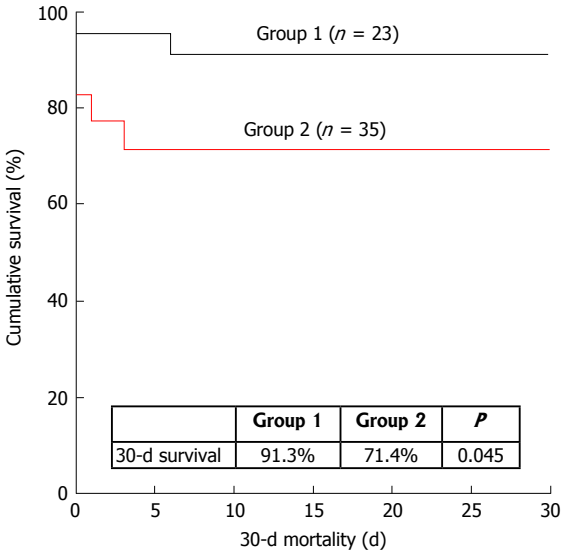


Figure 1 Thirty-day survival in the two groups.

RESULTS

Fifty-eight patients were included in the study, with 23 patients in group 1 and 35 patients in group 2. Seven (30.4%) patients in group 1 and 10 (28.6%) patients in group 2 received NOM. No change in management plan occurred. The median age was 32 years in patients receiving NOM and 39 years in patients receiving OM (*P* = 0.140). Comparison of group 1 and group 2 is shown in Table 1. The amounts of blood loss in patients who received OM were similar in the two groups (300 mL *vs* 1250 mL, *P* = 0.133); the amounts of blood transfused were also similar (2700 mL *vs* 2880 mL, *P* = 0.799). However, significantly more patients in Group 2 required transfusion (70.6% *vs* 39.1%, *P* = 0.018). In the 58 patients, 48 (82.8%) suffered blunt trauma and 10 (17.2%) suffered penetrative trauma. Both group 1 and group 2 had road traffic accident as the commonest cause of injury. ISS (*P* < 0.0001) and hemodynamic stability (*P* = 0.036) were significantly different between the two groups. Group 1 had significantly better 30-d survival (91.3% *vs* 71.4%, *P* = 0.045), as shown in Figure 1. Figure 2 shows 30-d survival stratified by grade of liver injury (*P* = 0.104). On multivariate analysis using the logistic regression model, ISS was found to be associated with mortality (*P* = 0.004, hazard ratio = 1.035, 95%CI: 1.011-1.060) (Table 2).

DISCUSSION

The liver is the most commonly injured abdominal organ despite its well-protected position[1]. Management of liver injury depends on the patient's condition, diagnosis,

Table 2 Multivariate analysis of risk factors for mortality

Dependent factor			
Mortality			
Variables put into the system for model selection			
ISS			
Location of injury (0: Liver only; 1: Liver and outside the liver)			
Hemodynamics (0: Stable; 1: Unstable)			
Variable remaining in the final logistic regression model			
Factor	*P*	Hazard ratio	95%CI
ISS	0.004	1.035	1.011-1.060

ISS: Injury severity score.

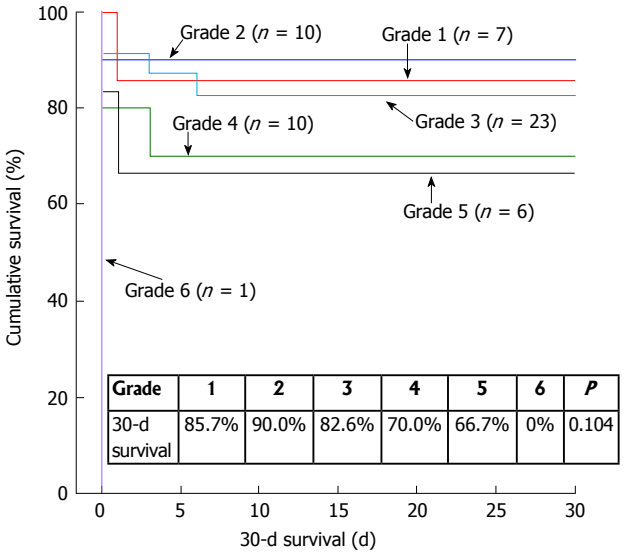
transfusion requirement and complications, as well as facilities for monitoring. NOM of liver injuries has gained wide support; it was adopted for approximately 60% of cases of liver injuries from low grades to high grades[8,10]. Its application has been extended to penetrative injuries[11].

At our center, liver trauma patients (with blunt or penetrative injuries) are subjected to CT for diagnostic purpose if they are hemodynamically stable; otherwise they are resuscitated and stabilized in the Accident and Emergency department, with a brief examination by a Focused Assessment with Sonography for Trauma scan, and then sent to the operation theater. Severity of injuries and presence of associated injuries are checked with CT or during laparotomy.

CT scan of the abdomen is widely used to evaluate intra-abdominal injuries in patients with stable hemodynamics; it should not be used if a patient has unstable hemodynamics since the patient's condition may deteriorate rapidly during scanning. CT scan can present the precise grade of liver injury, thereby allowing formulation of a proper management plan. A high grade (Grade 3-5) represents relatively severe injury. Patients with a high grade of liver injury tend to be more unstable and require OM[12]. But NOM is becoming more applicable to these patients because of improvement in intensive clinical care and increased use of interventional radiology. If NOM is adopted, reassessment CT scan should be performed within 7 to 10 d after the initial CT scan to check if there are any delayed complications[5].

Grade of liver injury can reflect the degree of hepatic parenchymal damage, but it is not indicative of complication development or need for OM[13]. Grade-6 injuries are by definition not salvageable. In our present study, morbidity and mortality tended to worsen with a higher grade of liver injury. However, the presence of associated injuries also mattered; patients in group 2 with a high ISS fared the worst. Our 30-d survival curves by grade of liver injury reflected worsening survival with rising grades in both groups. However, further subgroup analysis showed that grade of liver injury did not make difference in survival (P = 0.104). In fact, if there are associated injuries outside the liver, grade of liver injury cannot reflect the overall severity of injuries.

Multiple injuries, which can be caused by more than one mechanism of injury, often lead to major trauma (or



Grade	1	2	3	4	5	6	*P*
30-d survival	85.7%	90.0%	82.6%	70.0%	66.7%	0%	0.104

Figure 2 Thirty-day survival by grade of liver injury (with 1 missing datum).

multi-trauma) and result in serious physical complications and physiological decompensation. Major trauma is defined as ISS > 15[14]. It is usually caused by a high impact of energy, and the commonest cause is road traffic accident[15]. The higher median ISS in group 2 was due to significant associated injuries outside the liver. And more patients in this group had transfusion need, a reflection of the severity of injury. It is not surprising that group 2 had a lower survival rate[16] as it has been reported that ISS could predict length of intensive care unit stay as well as mortality and survival[17]. Our multivariate analysis also found that patients with a higher ISS were more likely to have shorter survival.

Most of the patients who suffered blunt injuries in group 2 were unstable. At our center, the decision on management approach is based on individual patients' clinical condition rather than ISS. Although ISS is used as an index for quality assurance at most trauma centers, it is not an accurate indicator and it does not reflect multiple injuries in the same body region. Hence, a high ISS should not be an indicator for OM. OM is required if a patient's hemodynamics is unstable; it is also required in the presence of another operative indication (*e.g.,* the need for thoracotomy, neurosurgery, orthopedic operation, repair of viscera, management of pelvic bleeding, *etc*). Decision on initial and subsequent management approaches should be based on clinical condition as well as mechanism and site of injury. Understanding the mechanism of the injury helps to identify potential life-threatening and limb-threatening conditions, which can maximize the chance of salvage and prevent functional deficit.

This study is not rid of the inherent limitations of a single-center retrospective study, and the patients were heterogeneous in terms of premorbid status, mechanism of injury and severity of injury. The use of ISS was to quantify severity of injuries for a more standardized representation.

In conclusion, liver trauma patients with multiple injuries are relatively unstable on presentation. Despite a significantly higher ISS in group 2, NOM was possible for selected patients. Associated injuries outside the liver usually account for morbidity and mortality.

COMMENTS

Background

In liver trauma management, the widespread use of ultrasonography and computed tomography (CT) has facilitated decision-making, and non-operative management (NOM) has been shown to reduce mortality. NOM is now the standard of care for blunt liver injury in hemodynamically stable patients.

Research frontiers

This study reviewed the management of liver trauma with or without associated injuries over 10 years at a level-1 trauma center in Hong Kong.

Innovations and breakthroughs

Liver trauma patients with multiple injuries are relatively unstable on presentation. Despite a significantly higher injury severity score in group 2, NOM was possible for selected patients. Associated injuries outside the liver usually account for morbidity and mortality.

Peer-review

It is well written and documented and discussed paper, it has valuable points to stress the nonoperative management of liver trauma in addition to that on behalf of the scope of your journal this type of articles may increase the impact effect of it since the paper is discussed a huge number of cases even they collected them in 10 years but it is meaningful and it likes a review of liver trauma.

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Observational Study

Hepatitis C virus infection in Argentina: Burden of chronic disease

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Abstract

AIM: To estimate the progression of the hepatitis C virus (HCV) epidemic and measure the burden of HCV-related morbidity and mortality.

METHODS: Age- and gender-defined cohorts were used to follow the viremic population in Argentina and estimate HCV incidence, prevalence, hepatic complications, and mortality. The relative impact of two scenarios on HCV-related outcomes was assessed: (1) increased sustained virologic response (SVR); and (2) increased SVR and treatment.

RESULTS: Under scenario 1, SVR raised to 85%-95% in 2016. Compared to the base case scenario, there was a 0.3% reduction in prevalent cases and liver-related deaths by 2030. Given low treatment rates, cases of hepatocellular carcinoma and decompensated cirrhosis decreased < 1%, in contrast to the base case in 2030. Under scenario 2, the same increases in SVR were modeled, with gradual increases in the annual diagnosed and treated populations. This scenario decreased prevalent infections 45%, liver-related deaths 55%, liver cancer cases 60%, and decompensated cirrhosis 55%, as compared to the base case by 2030.

CONCLUSION: In Argentina, cases of end stage liver disease and liver-related deaths due to HCV are still growing, while its prevalence is decreasing. Increasing in SVR rates is not enough, and increasing in the number of patients diagnosed and candidates for treatment is needed to reduce the HCV disease burden. Based on this scenario, strategies to increase diagnosis and treatment uptake must be developed to reduce HCV burden in Argentina.

Key words: Diagnosis; Disease burden; Epidemiology; Incidence; Mortality; Prevalence; Treatment; Argentina; Hepatitis C

Core tip: This is a study evaluating potential policies to diminish hepatitis C virus (HCV) disease burden. Increasing diagnoses and treated individuals with the high current sustained virologic response rates, will diminish HCV disease burden.

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INTRODUCTION

Chronic hepatitis C virus (HCV) liver disease is a global public health issue, with an estimated prevalence of 170 million infected people. Every year, 3000000 to 4000000 new HCV infections are diagnosed, and a mean global seroprevalence of nearly 3%[1].

In many countries, while HCV prevalence is decreasing, its morbidity and mortality is increasing[2]. Population aging results in a rise in all-cause mortality. This leads to a reduction in the total of infected patients. Progression to advanced HCV related liver disease combined with populace aging, is associated with a rising in mortality due to advanced liver disease[2,3].

In Argentina, the exact HCV prevalence is unknown. According to different studies it varies between 0.17% to 5.6%; in some areas of high endemicity it may vary between 2.2% to 7.3%[4]. Nosocomial transmission appears to be the main route of infection, and genotype 1 is most prevalent in the infected population[5,6]. Precise data for incidence and prevalence estimates are lacking in Argentina. Also, there are no data about the burden of the disease and its impact on public health. Data on the percentage of HCV patients treated and their outcomes are also scarce. It has been estimated that only 0.15% of HCV patients have been treated in the last 15 years in Argentina[7]. These results are comparable to other countries in the region. Our aim was, using a modeling method, to describe HCV-related disease progression at the national level.

A model was also used to evaluate the influence of distinct actions aimed at diminishing the burden of HCV disease (*e.g.,* multiply the percentage of treated patients, improved cure rates and improved case identification). This model has been already validated and used in similar studies in different countries[8-11].

MATERIALS AND METHODS

A systematic review of the literature was done to find studies addressing the proportion of HCV patients who had been diagnosed, received treatment and achieve sustained virologic response (SVR) in Argentina. The review included all studies published between January 1990 and July 2014.

PubMed and EMBASE databases were consulted looking for indexed articles. Non-indexed sources were identified by searching in the National Ministry of Health Website, proceedings of local medical meetings, unpublished data and data from large liver centers.

Also, an expert panel including epidemiologists, hepatologists, infectious disease specialists, public health professionals and virologists, gathered in a person to person meeting to analyze all the retrieved information.

Data from countries with similar healthcare practices and/or risk factors, or expert consensus were used there was no input data available. Some of these data were included in a previous global report[2,3]. To populate a disease progression model and to assess the magnitude of the HCV-infected populace according to liver fibrosis stages (METAVIR score F0-F4), country-specific inputs from 2013-2030 were loaded in Microsoft Excel® database (Microsoft Corp., Redmond, WA) (Figure 1). Crystal Ball, an Excel add-in by Oracle, was utilized for uncertainty and sensitivity analyses. For the uncertainty model, beta-PERT distributions were utilized associated with all inputs. To analyze the incertitudes that had the biggest repercussion on in 2030 HCV prevalence, a sensitivity analysis was utilized.

Populace information were arranged by sex, five-year age groups, and year (1950-2100) and obtained from the United Nations population database[12]. Based on expert inputs, in adults (persons aged ⩾ 20 years) HCV viremia prevalence in Argentina in 2013, was estimated at 1.5%. The HCV viremic rate in Argentina is

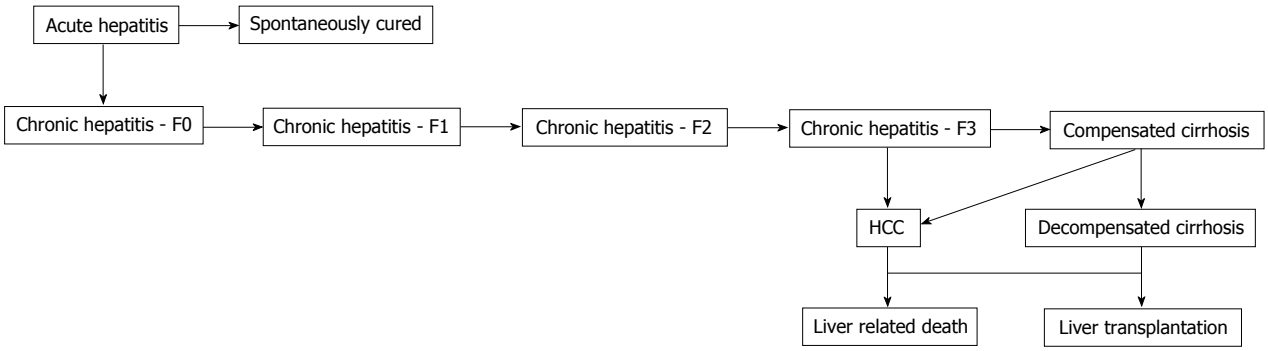


Figure 1 The flow of the hepatitis C virus disease progression model. HCC: Hepatocellular carcinoma.

80%, as previously reported[13].

Using a 0.83% viremic prevalence, it was calculated that 342000 persons had HCV RNA detectable in 2013.

A hybrid distribution was constructed to calculate age and gender specific HCV diagnosis rates by five-year age group using notification inputs for HCV infection for persons aged 0 to 59 years[14], and transplant inputs classified by age and gender for persons aged ⩾ 60 years[15]. The notified and transplanted people were weighted to the national estimate for total prevalence and aged to the year 2013, accounting for mortality and cured patients.

To estimate HCV genotype distribution, data from over 200 treated patients was used[16]. Genotype 1 (G1) subtypes distribution was calculated using data from another study[5]. The genotype distribution applied in the model was G1/other = 63%, G2 = 25%, G3 = 11%, G4 = 1%.

As outlined in a previous work, annual patients progress through each disease state were include in the model using age and gender specific transition probabilities[2,3].

Changes in historical HCV incidence were estimated according to expert opinion. Changes in historical HCV incidence were estimated according to expert opinion. After an estimated peak incidence in 1989, it has markedly decrease with the introduction of antiHCV screening in blood donors. In Argentina, it was estimated that 1850 new infections were diagnosed in 2013.

It was estimated that 350 and 200 patients receive treatment in 2014 and 2015, respectively, based on expert consensus and IMS data for pegylated-interferon (IFN) units sold in Argentina[17]. A multiplier was used to account for under-reporting in IMS data. The Argentinean genotype distribution was used to estimate the average number of weeks of treatment per patient with 85% compliance/persistence.

In 2013, 74 of 329 (22.4%) patients receiving a liver transplant were related to HCV end stage liver disease. Data from the national organ registry for the years 1999 to 2013 showed that the percentage of liver transplant in HCV patients was 22.0% before adoption of model for end stage liver disease (MELD) based allocation and 22.4% after MELD implementation[15,16].

Database from the Pan American Health Organization allow us to estimate the diagnosed population based upon data for HCV positive blood donors[7]. The annual number of confirmed cases was balanced to account for diagnosis in other settings. It was assumed that 118800 persons were previously diagnosed and 6560 new cases were confirmed in 2010. The Berkeley Human Mortality database was used to estimate mortality rate by year, age group and gender[18] (Table 1).

Using estimates of 65000 active injection drug users (IDU) and a 54.6% HCV prevalence in Argentina, it was calculated that in 2001, 9.3% of the HCV population were IDU[19,20].

Using a standard mortality ratio (SMR) of 10.0 for persons between 15 and 44 years old, a raised mortality was estimated among active IDU[21-26].

It was estimated that 20.8% of the HCV patients were related blood transfusions in 2005, according to data from a national study[6]. In this subgroup of patients, a SMR of 1.5 was applied for all age groups[27].

Scenarios

Base scenario: Patients aged 15-69 years were considered for treatment and 60% of potential patients in Argentina were considered candidates for antiHCV therapy. It was considered that median SVR rates were 60% (G1), 75% (G2/4), and 65% (G3). Treated populations of 350 patients in 2014 and 200 patients annually during 2015-2030 were modeled, was and were restricted to patients with fibrosis stages ⩾ F3 (G1) and ⩾ F2 (G2/3/4).

It was considered that until 2016 patients with severe liver disease such as decompensated cirrhosis or eligible for transplantation, or those with hepatocellular carcinoma (HCC), were not candidates for treatment.

Scenario 1: Increased efficacy: It was assumed that by 2016, treatment eligibility raised to 95% for all genotypes and SVR rates steadily raised to 90% (G1/4), 95% (G2), and 85% (G3). The number of patients treated and newly diagnosed every year remained constant, while treatment was extended to fibrosis stages ⩾ F2 in all genotypes (Figure 2).

Scenario 2: Increased efficacy and treatment: SVR, treatment eligibility, and fibrosis restriction increases

Table 1 Model inputs and 2013 estimates

	Historical	Year	2013 (Est.)
HCV infected cases	427890 (132720-829480)	2013	428260
AntiHCV prevalence	1.0% (0.3%-2.0%)		1.0%
Total viremic cases	342310 (106170-663580)	2013	342310
Viremic prevalence	0.8% (0.3%-1.6%)		0.8%
Viremic rate	80.0%		80.0%
HCV diagnosed (viremic)	112270	2010	117250
Viremic diagnosis rate	32.8%		34.2%
Annual newly diagnosed	4920	2010	4920
New infections			1950
New infection rate (per 100K)			4.7
Treated			
Number treated			650
Annual treatment rate			0.2%
Risk factors			
Number of active IDU with HCV			31950
Percent active IDU			9.3%
Previous blood transfusion			48420
Percent previous blood transfusion			14.1%

HCV: Hepatitis C virus; IDU: Injection drug users.

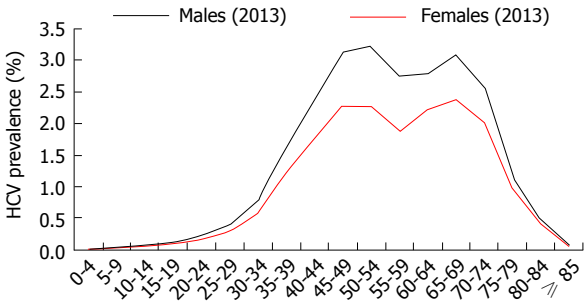


Figure 2 Age and gender distribution of anti-hepatitis C virus prevalence, Argentina, 2013. HCV: Hepatitis C virus.

were the same as in scenario 1. The number of patients newly diagnosed every year progressively escalated to 14770 in 2016, while the number of patients treated every year progressively escalated to 12000 by 2020 (Figure 3).

RESULTS

Prevalence of chronic hepatitis C and complications

According to the model, the HCV prevalence in Argentina peaked in 2002 at 376000 viremic individuals. In 2013, there were an estimated 342000 (95%CI: 146000-517000) infected individuals, a 10% decline from 2002. In the base scenario, viremic cases are estimated at 241000 in 2030, a decline of 30% from 2014 (Figure 4). The incidence of HCV in Argentina peaked in 1989 with an estimated 21340 new infections, and declined by 90% in 2013 with an estimated 1850 cases new infections.

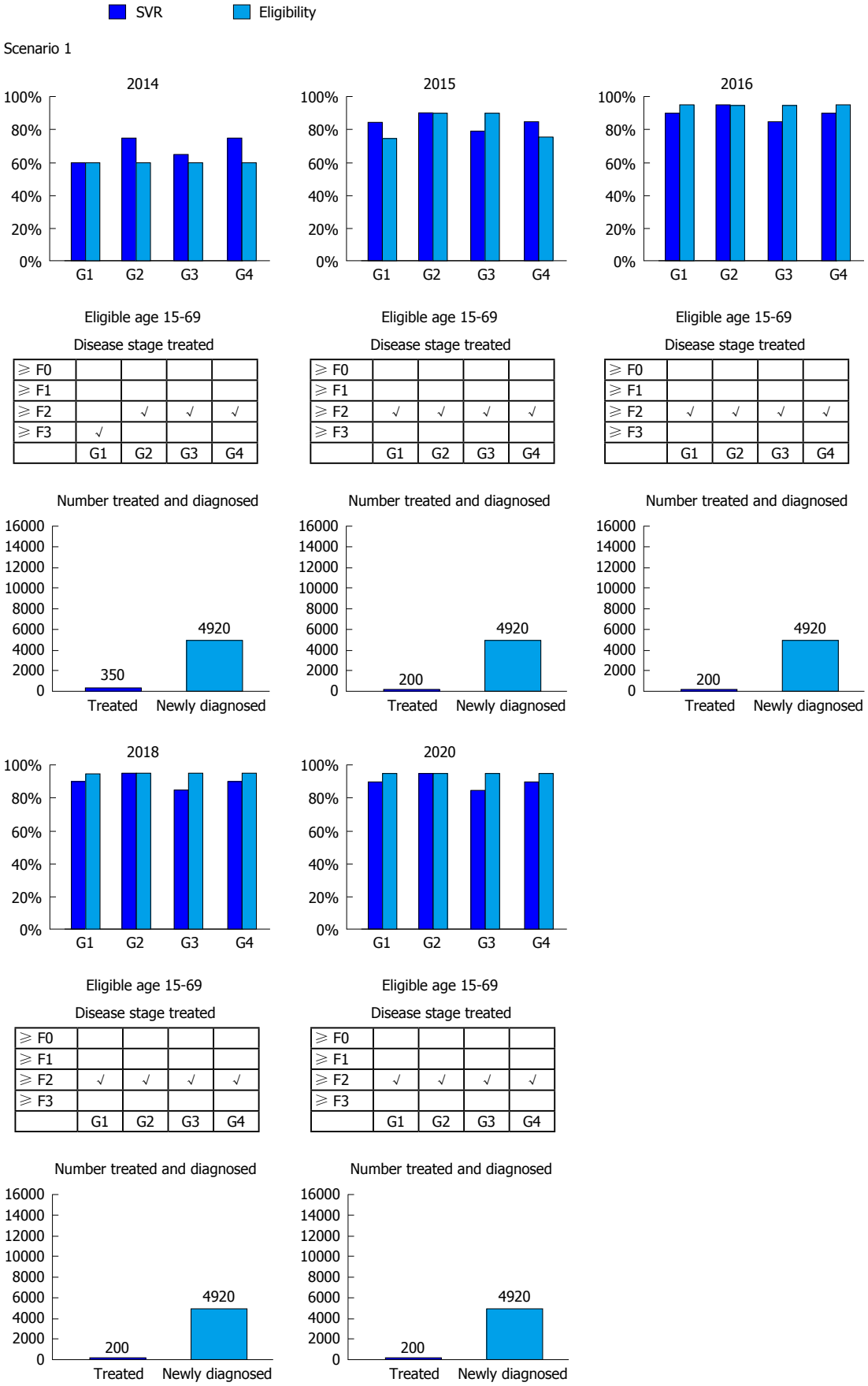
There were 42910 compensated cirrhotic patients in 2013 and it was calculated that there will be 69600 by 2030. Also by 2030 there will be 2500 new cases of HCC 7830 patients will develop decompensated cirrhosis. By 2030, 2890 patients will die from HCV related liver disease in contrast to 1520 patients who died in 2013. The proportion of viremic patients who have compensated cirrhosis or decompensated cirrhosis or HCC will increase to 34% in 2030, as compared with 14% in 2013 (Figures 5 and 6).

New HCV treatment strategies imply an increase in SVR rates. Based on recent results SVR rates will increase to at least 90% (G1/4), 95% (G2), and 85% (G3) by 2016. In the same period, treatment eligibility will increase to 95% for all genotypes. According to the model, increasing treatment efficacy but keeping the same low number of treated patients (scenario 1) will result in 660 fewer viremic patients in 2030, a 0.3% reduction as compared to the base case.

Compared with the base case, by 2030 it was estimated a 0.3% decrease in the number of HCC cases (2490 cases), a 0.3% decrease in liver related deaths (2880 cases), a 0.2% decrease in decompensated and 0.3% in compensated cirrhosis new cases (7800 and 69380 cases, respectively) (Figure 7).

Increased treatment efficacy alone seems to have little impact in decreasing HCV burden, so another scenario was developed with the same SVR rates but increasing numbers of patients diagnosed and treated (scenario 2).

If the number of diagnosed and treated patients is markedly increased, a 45% reduction in the number of viremic patients can be obtained by 2030, meaning 107000 fewer infected patients. A 60% reduction in HCC cases is expected, with 1000 new HCC cases diagnosed by 2030. It is expected that the number of liver related deaths will also decrease with 1260 by 2030, meaning a 55% reduction when compared to the base case. New cirrhosis cases will decrease by 55% in decompensated and by 60% in compensated cases by 2030 (3390 and 29210, respectively) (Figure 7).


SVR
Eligibility
Scenario 1
2014
2015
2016
100%
80%
60%
40%
20%
0%
G1
G2
G3
G4
Eligible age 15-69
Disease stage treated
≥ F0
≥ F1
≥ F2
≥ F3
√
Number treated and diagnosed
16000
14000
12000
10000
8000
6000
4000
2000
0
350
200
4920
Treated
Newly diagnosed
2018
2020

Scenario 2

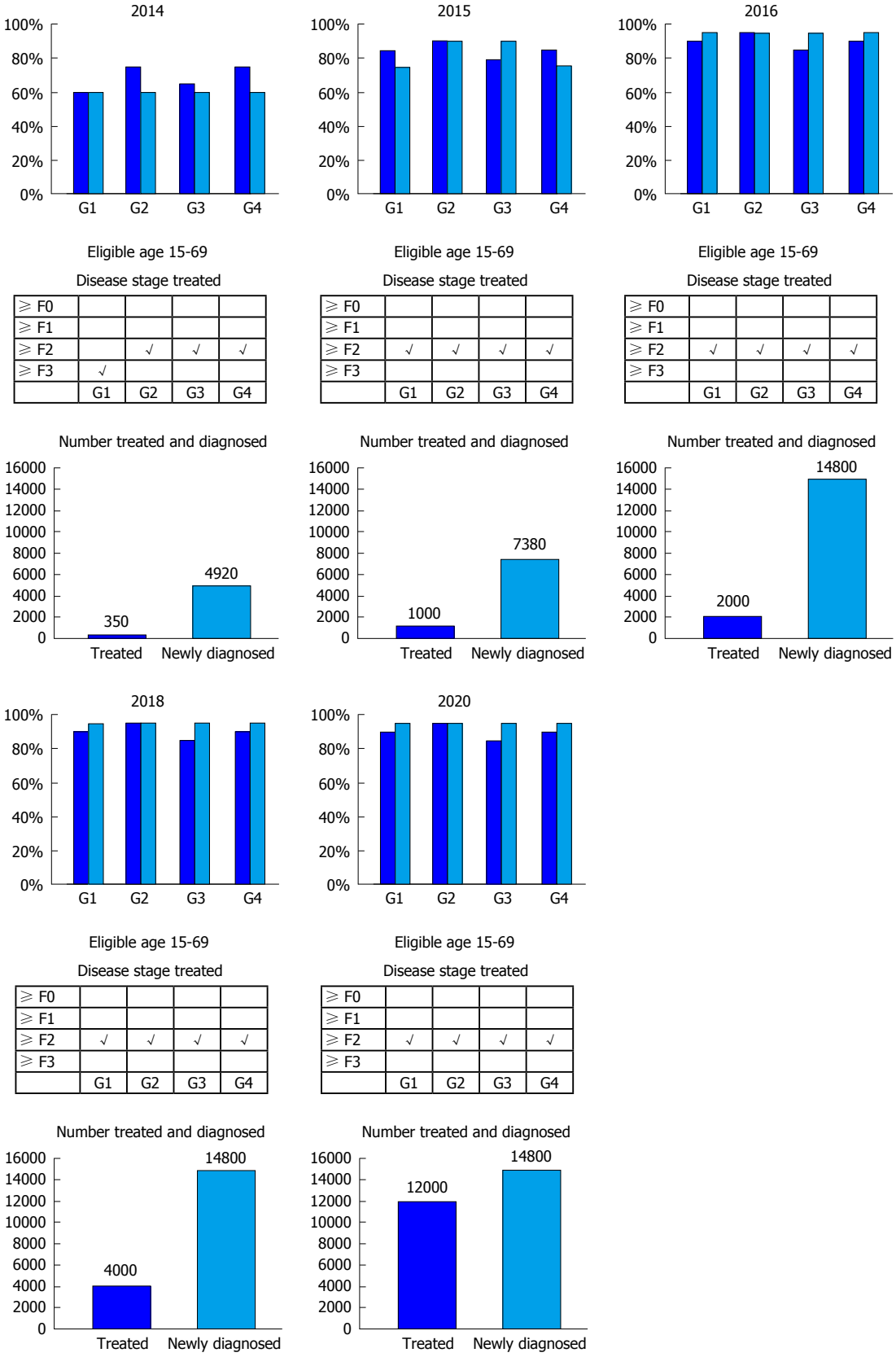


Figure 3 Model inputs for scenarios 1 and 2. SVR: Sustained virologic response; G1: Genotype 1.

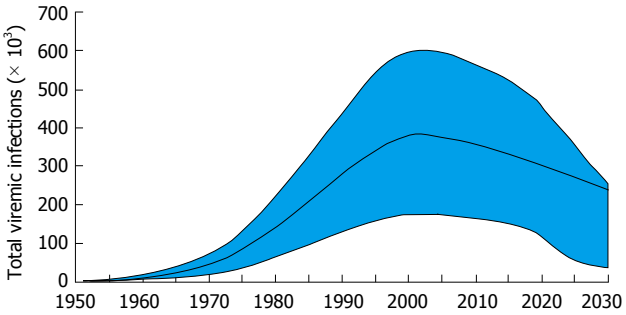


Figure 4 Total number of viremic hepatitis C virus cases (with uncertainty intervals) according to year, 1950 to 2030.

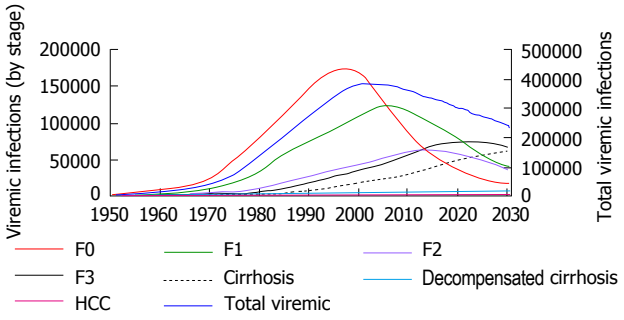


Figure 5 Number of viremic hepatitis C virus cases, in total and according to disease stage. F: Fibrosis stage; HCC: Hepatocellular carcinoma.

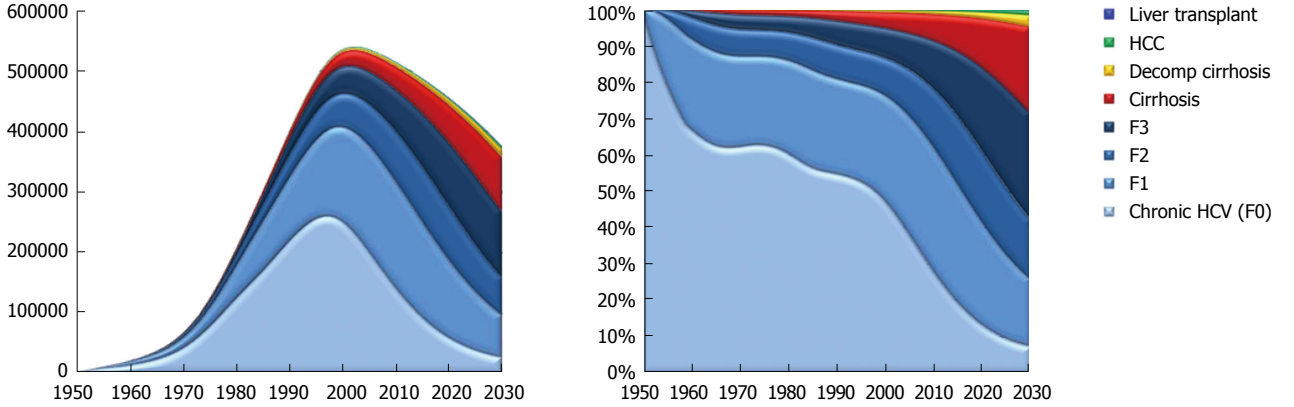


Figure 6 Proportion of all viremic hepatitis C virus cases according to disease stage, 1950 to 2030. Decomp: Decompensated; F: Fibrosis stage; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus.

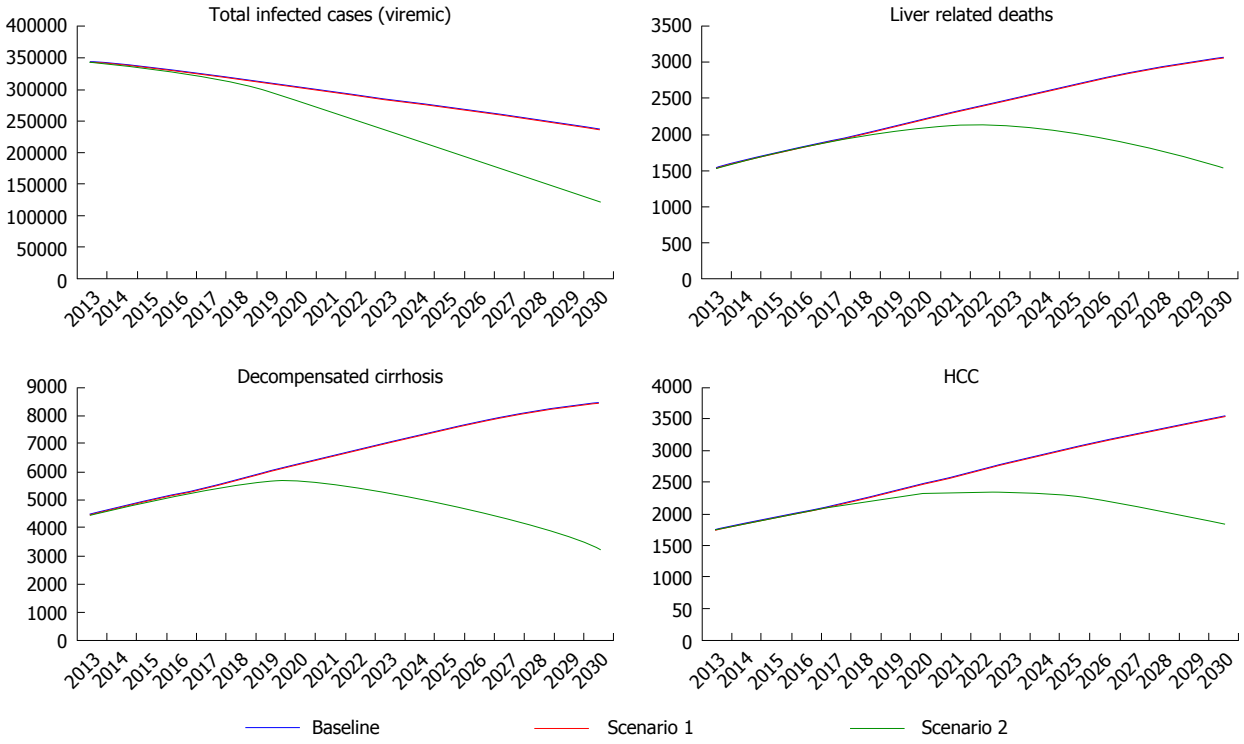


Figure 7 Selected hepatitis C virus-related outcomes by scenario - Argentina, 2013-2030. Scenario 1: Increased treatment efficacy; Scenario 2: Increased treatment efficacy and increased annual diagnosed/treated populations; HCC: Hepatocellular carcinoma.

DISCUSSION

Increasing access to HCV diagnosis and treatment are pending actions in Argentina and in Latin-America. It is estimated that less than 20%-30% of patients are diagnosed and only 1%-2% of those diagnosed have been treated[7]. Approval of new HCV treatments in the region is delayed compared with Europe or the United States. In the last months of 2015, three novel regimens were approved in Argentina. Upcoming IFN and ribavirin free regimens are safe and effective, offering SVR rates over 90%-95% for most genotypes. To impact the burden of disease, patients must be diagnosed and treatment availability must increase.

Our study shows important results for our country. The greatest burden of HCV-related advanced liver disease will come in the next 5 to 15 years. HCV burden will increase if no action is taken. Our model showed that the only way to significantly reduce HCV burden is to increase diagnosed and treated patients 10 times the current number of treated persons. Similar results have been reported in many countries around the world, including some in Latin-America, including Brazil and Mexico[2,3].

The main challenge in the region is to develop strategies to increase diagnosis. Strategies must be country specific since epidemiology and risk factors for HCV infection vary between countries. For example, the United States Centers for Disease Control and Prevention has recommended a birth-year based screening strategy: Persons born during 1945-1965 in the United States have an increased rate of HCV infection and focused screening of this cohort is an efficient use of resources[28]. But this strategy might not be effective in Argentina, since in 2013 the majority of HCV patients are estimated to be 40 to 75 years old (Figure 2), meaning that they were born between 1938 and 1973. The same was shown in Brazil where most patients were born between 1950 and 1980[29]. Country specific screening campaigns must be developed to achieve this goal.

Another pending issue is adequate access to care and treatment. This means that all people involved in HCV management must make an effort to achieve this goal. Patients need greater access to new therapies, but the main restriction is treatment cost. In resource constrained countries, treating all patients with current drug costs is unaffordable. There must be strategies to reduce HCV treatment costs and at the beginning, prioritization of treatment may be necessary. For example, the sickest patients will be treated first with the safest and more effective drugs. Then earlier stage patients will be treated later to reduce the impact of the disease.

This is the first study evaluating HCV burden in Argentina. These results might help public health authorities take action to reduce its impact. But it has to be mentioned that our results have some limitations.

First, each input may have its limitations, but to our knowledge the best data from published and unpublished studies available in Argentina were applied in our model. Second, some patients may have progressive liver disease despite achieving SVR; progression of cured patients was not evaluated in this model[30]. And finally, we did not include extrahepatic manifestations of HCV infection in the model, which may had contribute to all-cause mortality and may lead to underestimation in mortality among viremic patients[9].

In conclusion, the present analysis, with the available data, showed that HCV prevalence is decreasing in Argentina, but advanced liver disease prevalence is expected to raise as HCV infected patients get older. There is an urgent need to enhance diagnosis and treatment rates to reduce the future disease burden and its impact on Argentina's public health.

COMMENTS

Background

Chronic hepatitis C virus (HCV) infection is one of the main causes of end stage liver disease, liver transplantation, hepatocellular carcinoma (HCC) and liver-related mortality in Argentina. Burden of HCV disease is unknown, and strategies to reduce it are not yet developed.

Research frontiers

An epidemiological model has been developed to estimate HCV disease burden and to evaluate different diagnostic and therapeutic strategies that may impact in HCV natural history.

Innovations and breakthroughs

This model allows them for the first time to evaluate HCV burden in Argentina. This estimated data can help health authorities to develop a national plan to manage HCV disease. Also, it permits the authors to estimate the number of persons needing treatment to reduce HCV burden in the next 15 years.

Applications

This study shows that HCV treatment impacts in its disease burden and that a major work has to be done in improving its diagnosis and access to treatment.

Terminology

HCV disease burden implies the development of liver related disease: Cirrhosis, HCC, liver failure, liver transplantation and death.

Peer-review

In this study the authors have used a modeling approach to describe HCV-related disease progression in Argentina. The methods are well designed and are exposed very clearly for the reader. In general, it is a good manuscript.

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CASE REPORT

Host factors are dominant in the development of post-liver transplant non-alcoholic steatohepatitis

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Author contributions: Boga S and Munoz-Abraham AS collected the data from patients' file, reviewed literature and drafted manuscript; Jain D evaluated the biopsy specimens from pathologic points of view, prepared demonstrative pathology pictures; Rodriguez-Davalos MI, Emre SH and Schilsky ML supervised in designing and drafting the manuscript, revised the manuscript critically for important intellectual content; Emre SH and Schilsky ML presented patients' clinical data, constituted the final form of manuscript; all authors read and approved the final manuscript.

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a recognized problem in patients after orthotopic liver transplantation and may lead to recurrent graft injury. As the increased demand for liver allografts fail to match the available supply of donor organs, split liver transplantation (SLT) has emerged as an important technique to increase the supply of liver grafts. SLT allows two transplants to occur from one donor organ, and provides a unique model for observing the pathogenesis of NAFLD with respect to the role of recipient environmental and genetic factors. Here we report on two recipients of a SLT from the same deceased donor where only one developed non-alcoholic steatohepatitis (NASH), suggesting that host factors are critical for the development of NASH.

Key words: Liver; Split graft; Steatohepatitis; Host factors; Transplant

Core tip: Split liver transplantation provides a unique model of the pathogenesis of non-alcoholic fatty liver disease with respect to the role of recipient environmental risk factors and genetic background because the same donor graft is shared by two distinct recipients. Here we present two recipients of a split liver transplantation from same deceased donor, with one developing nonalcoholic steatohepatitis and the other without any evidence of hepatic steatosis three years after they were transplanted. These cases provide a unique natural experiment to explore host factors that contributed to the development of nonalcoholic steatohepatitis after liver transplantation.

Boga S, Munoz-Abraham AS, Rodriguez-Davalos MI, Emre SH, Jain D, Schilsky ML. Host factors are dominant in the development of post-liver transplant non-alcoholic steatohepatitis. *World J Hepatol* 2016; 8(15): 659-664 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i15/659.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i15.659

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) affects around one third of the western population with an incidence that continues to grow in other parts of the world[1]. Histopathological findings of NAFLD in the liver range from simple steatosis to non-alcoholic steatohepatitis (NASH), and can eventually progress to cirrhosis and liver cancer[2]. NAFLD is recognized as a potential complication following LT and studies are being conducted to determine the prevalence and risk factors for development of NAFLD in LT recipients[3,4].

Split liver transplantation (SLT) has emerged as an important strategy to increase the supply of liver grafts by allowing two transplants to occur from one donor organ, and provide a unique opportunity to observe the role of host factors in the development of NAFLD. The technique of SLT is continuously evolving with reduced ischemia times and reduced vascular and biliary complications,and when performed *in situ*, SLT has yielded excellent outcomes[5]. However, SLT still involves significant complexity and short and long term complications of the split grafts need to be continually analyzed. Here we present data on the clinical course and outcomes of two recipients of a SLT from the same deceased donor where only one developed NASH, suggesting that extrahepatic host factors are critical for the development of NASH.

CASE REPORT

Case 1

A female infant with a diagnosis of Crigler Najjar syndrome underwent a SLT at age 15 mo old, receiving a left lateral liver segment from a deceased donor who was exitus because of head trauma at age 16 years without any history of obesity, diabetes, hyperlipidemia or hypertension. The explanted liver did not reveal any significant histopathological abnormality and the donor pre-reperfusion biopsy was also negative for any significant pathologic findings, including inflammation, fibrosis, necrosis and steatosis (Figure 1). During the first year following transplantation, several episodes of liver test elevations were noted. Histology of the liver biopsy performed 19 mo post-SLT was not consistent with acute cellular rejection but showed minimal lobular inflammation, mild periportal edema and mild fibrosis (stage 1-2/4) without significant ductular reaction. No steatosis was present. A second biopsy performed 25 mo post-transplant due to continued liver test abnormalities revealed no histologic evidence of steatosis or progression of fibrosis (Figure 2). At this time the liver biopsy showed minimal portal fibrosis and no evidence of rejection, duct injury or duct loss. Subsequently magnetic resonance cholangiopancreatography was performed and an anatomic biliary stricture and dilated intrahepatic biliary ducts were identified. The patient underwent biliary reconstruction and a Roux-en-Y hepatojejunostomy and biliary stenting with internal-external drain placement at age 4 years. Three years following transplantation and two months after the biliary repair, liver tests improved [alanine aminotransferase (ALT): 29 U/L, aspartate aminotransferase (AST): 39 U/L, T/D Bil: 0.34/0.10 mg/dL, international normalized ratio (INR): 0.93]. Growth was in the normal range with a body mass index (BMI): 17.58 kg/m^2. She was maintained on tacrolimus, mycophenolate mofetil and ursodeoxycholic acid treatment with routine biliary drain checks and close follow-up.

Case 2

A 69-year-old male patient with a history of heterozygocity for genetic hemochromatosis (single copy of C282Y for the *HFE* gene) and alcoholic cirrhosis complicated by development of hepatocellular carcinoma (HCC) within Milan criteria (a 2.6 cm in segment Ⅲ, and 1.5 and 1.1 cm lesions in segment Ⅵ). He was treated with chemoembolization and 8 mo later underwent an extended right lobe LT (segments Ⅰ-Ⅳ-Ⅷ) from the same deceased donor. The explanted liver revealed cirrhosis with residual viable nodules of moderately differentiated hepatocellular carcinoma without any vascular invasion, mild steatosis with steatohepatitis and increased hepatocellular siderosis. His past medical history was remarkable for hypertension, hyperlipidemia and diabetes mellitus. Initial immunosuppression was with steroid and tacrolimus, and he was changed to sirolimus and a lower dosage of tacrolimus at eight weeks post-transplant to try to reduce the risk of recurrent HCC. Although his postoperative course was uncomplicated but he remained on insulin for glycemic control. Twenty-four months after SLT, he had HCC

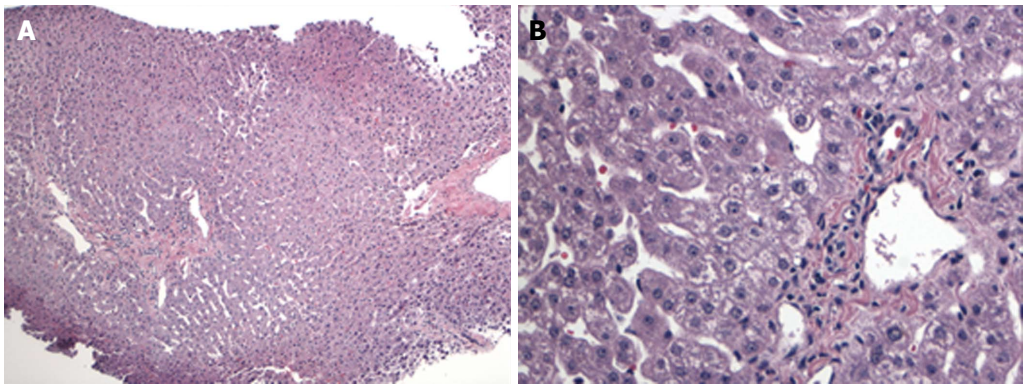

Figure 1 Biopsy of the donor liver showing a lack of obvious pathologic changes. Specifically there is no steatosis, fibrosis or inflammation (H and E stain). A: Low magnification (× 100); B: Higher magnification (× 200) of the biopsy.

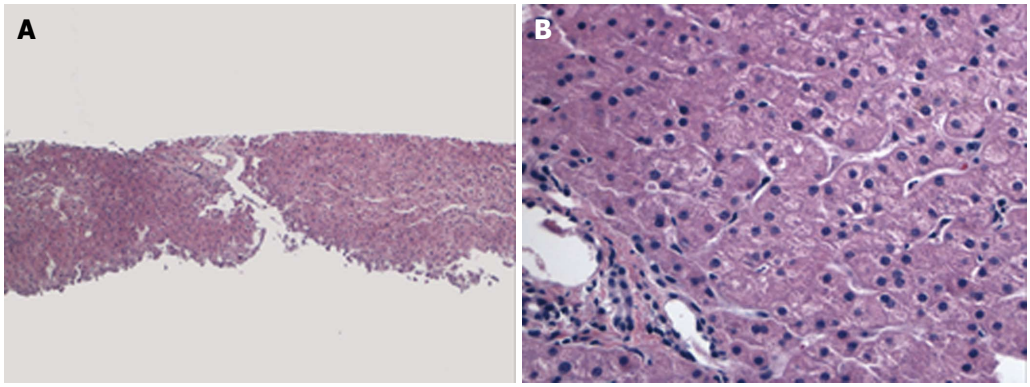

Figure 2 Biopsy of liver graft from case 1 performed 25 mo later showing a lack of significant pathologic changes. Specifically, no steatosis is noted (H and E stain). A: Low magnification (× 100); B: Higher magnification (× 200) of the biopsy.

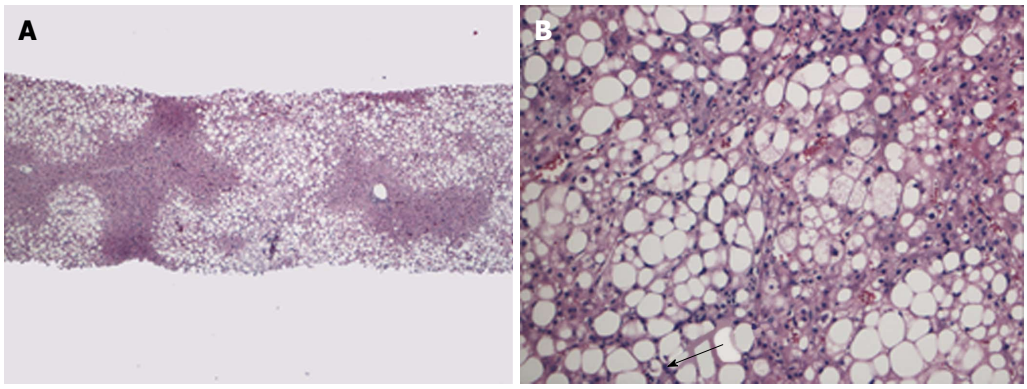

Figure 3 Biopsy of the liver graft from case 2 about 3 years post split liver transplantation showing marked macrovesicular steatosis (H and E stain). A: Low magnification (× 100); B: Higher magnification showing rare Mallory Denk bodies (arrow), ballooned hepatocytes and mild lobular inflammation (× 200). Trichrome stain revealed mild sinusoidal fibrosis (not shown here).

recurrence with a solitary 1.5 cm nodule in segment Ⅷ found on surveillance imaging. The tumor was treated by selective chemoembolization and he is without recurrence on follow up magnetic resonance images; the most recent being 34 mo post-transplant. Three years after transplantation, his liver function tests were found to be elevated on routine testing, and increased cholesterol and triglyceride levels were noted (ALT: 154 U/L, AST: 125 U/L, T/D Bil: 0.85/0.20 mg/dL, INR: 1.1, total cholesterol: 218 mg/dL, HDL cholesterol: 34 mg/dL, triglyceride: 501 mg/dL). At the same time, his weight had increased by 12% (had BMI increased from 30.5 kg/m^2 to 34 kg/m^2). He denied drinking alcohol. A liver biopsy was performed and showed no evidence of acute or chronic cellular rejection but was notable for marked macrovesicular steatosis involving about 70% of liver parenchyma, steatohepatitis and perisinusoidal fibrosis (grade 1 of 3, stage 1 of 4, Brunt system) (Figure

3).

DISCUSSION

LT is the accepted treatment of end-stage liver disease. The establishment of standard transplantation techniques, development of better immunosuppressive medications and accumulated experience in their safe use, improvement of intensive care and anesthesia all have played a major role in improving current 1-year survival after LT to 90%. Long-term outcomes, however, are still compromised by recurrent liver disease, increased risk of cancer, adverse effects of immunosuppressive drugs and possible metabolic complications[6,7]. One of the possible metabolic complications is the development of NASH/NAFLD.

SLT has developed as an alternative to increase the donor pool of organ for LT. The concept of splitting a liver allograft between two recipients was reported almost simultaneously by Pichlmayr *et al*[8] and Bismuth *et al*[9]. Recipients of SLT in the mid 1990s[10,11] were primarily one child who received the left-lateral segments and one adult who received the extended right lobe. SLT provides a unique model of the pathogenesis of NAFLD with respect to the role of recipient environmental risk factors and genetic background because the same donor graft is shared by two distinct recipients. Here we present two recipients of a SLT from same deceased donor, with one developing NASH and the other without any evidence of hepatic steatosis three years after they were transplanted. These cases provide a unique natural experiment to explore host factors that contributed to the development of NASH after LT.

LT recipients have several risk factors that put them at risk for NAFLD. Age and rapid weight gain causing obesity and long-term exposure to immunosuppressive medications can in part be responsible for NAFLD. Hyperlipidemia ocurrs frequently following solid-organ transplantation. Between 16% and 43% of adult LT recipients can have increased plasma cholesterol levels[7,12,13]. Furthermore corticosteroids and calcineurin inhibitors promote hypertension and hyper-cholesterolemia, prednisone, tacrolimus, and cyclosporine A are diabetogenic, and sirolimus induces hyperlipidemia. Although both of our recipients were placed on tacrolimus, the older patient was also treated with sirolimus. In our adult recipient, use of tacrolimus and the aberrant gain in weight likely increased his already present insulin resistance and contributed to further deterioration of glucose regulation, causing an increase in hepatic fatty infiltration and inflammation that ended with steatohepatitis.

In the first few months after liver LT, weight gain may be regarded as one of the positive effects of transplantation, especially in patients with advanced liver disease and pre-transplant cachexia. However, within two years of transplantation, an excess body weight is recorded in up to 60% to 70% of patients and 20% of previously non-obese transplant recipients become obese[14,15]. The recipient with steatohepatitis showed an increase in BMI from 30.5 kg/m^2 at time of transplant to 34 kg/m^2, corresponding to a 12% increase in weight over 3 years time. NAFLD is strongly linked to obesity, (BMI > 30 kg/m^2) with a reported prevalence as high as 80% in obese patients and only 16% in individuals with a normal BMI[16]. Although the exact mechanisms leading to excessive weight gain in post-LT patients are uncertain, a major role is attributed to the development of post-LT insulin resistance, diabetes mellitus, arterial hypertension, hyperlipidemia and the metabolic effects of immunosuppressive medications (corticosteroids, mTOR inhibitors and calcineurin inhibitors).

There are other factors in our steatohepatitic recipient that may have increased hepatic fatty infiltration. The patient had a history of alcoholic cirrhosis, and some patients transplanted for alcoholic disease have a significantly higher risk of post-LT NAFLD even in the absence of recurrent alcoholic intoxication. Kim *et al*[4], reported that even though in 156 patients who had stopped drinking or had a limited amount of alcohol after LT, pre-LT alcoholic liver cirrhosis was a significant factor for their development of post-LT NAFLD. Similarly Dumortier *et al*[17] suggested that many patients with post-LT NAFLD have an unrecognized combination of alcoholic and non-alcoholic steatohepatitis that put them at risk of secondary liver failure because of persistent metabolic abnormalities. Recently Hejlova *et al*[18] examined 2360 post-transplant biopsies of 548 LT recipients to identify risk factors for the development of significant steatosis and found alcohol induced cirrhosis as a pre-transplant factor that is associated with significant post-transplant steatosis. It is likely patients with this combination of alcoholic and non-alcoholic steatohepatitis pre-transplanthave an increased risk of persistence of metabolic abnormalities post-LT due to newly *de-novo* or aggravated insulin resistance.

Though the adult recipient had a pre-transplant diagnosis of iron overload disorder, genetic hemochromatosis is cured by liver transplantation[19]. There are instances where recipients received organs from patients with hemochromatosis and iron accumulation has occured[20]. In the adult recipient, we did not find iron accumulation in his liver biopsy, suggesting iron did not play any additional role in the genesis of his steatohepatitis. Of the factors mentioned above; age, genetic background and even pretransplant history of alcoholic cirrhosis may be considered as unchangeable host factors where as post-transplant life style changes, diet, glycemic control by anti-diabetic medications, control of weight gain, hyperlipidemia therapy and immunesuppressive medications are changeable host factors that can affect the presence and progression of post-LT NASH.

In conclusion, this SLT provided a unique opportunity to observe the pathogenesis of NAFLD in the post-transplant setting. Although we can not exclude an interaction of donor and host factors, our data suggest host factors may be dominant for the development of

post-LT NASH.

Because we can not change the genetic background of the donor organ, careful attention to potentially alterable host factors or treatments like diet, life style changes, hyperlipidemia therapy and immunesuppressive medications can result in improved long term outcomes for recipients.

COMMENTS

Case characteristics

A female infant with a diagnosis of Crigler Najjar syndrome and a 69-year-old male patient with cirrhosis complicated by development of hepatocellular carcinoma (HCC) underwent split liver transplantation (SLT).

Clinical diagnosis

Infant had jaundice and the elderly patient had signs of cirrhosis such as jaundice, ascites and spider angioma.

Differential diagnosis

Inherited disorders of bilirubin metabolism for the first patient and primary and metastatic malignities of the liver for the second patient.

Laboratory diagnosis

The first patient had elevated bilirubin levels (total bilirubin: 21 mg/dL, direct bilirubin: 0.25 mg/dL) and the second patient had an alpha fetoprotein of 109 ng/mL.

Imaging diagnosis

The adult patient had a 2.6 cm HCC lesion in segment Ⅲ, and 1.5 and 1.1 cm HCC lesions in segment Ⅵ on magnetic resonance scan.

Pathological diagnosis

While the explanted liver did not reveal any significant histopathological abnormality in the first patient and revealed cirrhosis with residual viable nodules of HCC in the second patient; post-transplant liver biopsies showed minimal portal fibrosis and no histologic evidence of steatosis in the first patient and showed macrovesicular steatosis, steatohepatitis and perisinusoidal fibrosis in the second patient.

Treatment

First patient underwent biliary reconstruction, a Roux-en-Y hepatojejunostomy and biliary stenting with internal-external drain placement and was maintained on tacrolimus, mycophenolate mofetil and ursodeoxycholic acid treatment and the second patient had an initial immunosuppression with steroid and tacrolimus, and then was changed to sirolimus and a lower dosage of tacrolimus at eight weeks post-transplant and had selective chemoembolization for recurrent HCC.

Related reports

Even though emerging literature puts non-alcoholic fatty liver disease (NAFLD) forward as a potential complication following liver transplantation, SLT presented in this report provided a unique model of the pathogenesis of NAFLD with respect to the role of recipient environmental risk factors and genetic background because the same donor graft was shared by two distinct recipients.

Term explanation

Crigler-Najjar syndrome is a rare hereditary disorder of bilirubin metabolism characterized by unconjugated hyperbilirubinemia due to deficiency of the enzymatic activity of glucuronosyltransferase.

Experiences and lessons

This SLT provided a unique opportunity to observe the pathogenesis of NAFLD in the post-transplant setting. The data suggest host factors may be dominant for the development of post-LT non-alcoholic steatohepatitis (NASH). The authors recommend paying careful attention to potentially alterable host factors or treatments like diet, life style changes, hyperlipidemia therapy and immunesuppressive medications to improve the long term outcomes for recipients.

Peer-review

This is an interesting case report about post transplant NASH comparing two different scenarios (two different hosts) for a unique donor from a split liver transplant.

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