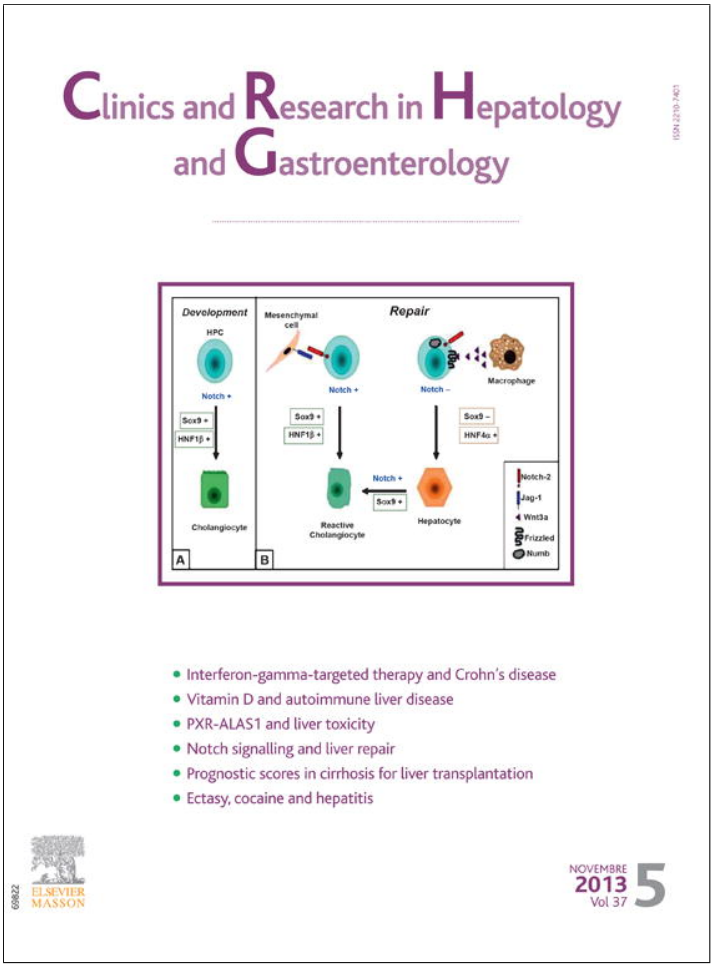

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ORIGINAL ARTICLE

Hepatitis C genotype 4 with normal transaminases: Correlation with fibrosis and response to treatment, a cohort Egyptian study of 4277 patients

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Summary

Background and objective: Chronic hepatitis C virus (HCV) patients with persistently normal transaminases represent a subgroup of patients with mild, slowly progressive disease, natural history, and optimal management of these patients needs to be investigated in Egypt. Our aim is to assess the severity of hepatic fibrosis and response to therapy in a cohort of Egyptian HCV patients with normal transaminases.

Patients and methods: Retrospective demographics, laboratory, histological features and treatment outcome of patients included in the national program for the control of viral hepatitis in Egypt since 2007 were collected. Combined pegylated IFN/ribavirin therapy was given for patients with fibrosis stage ≥ F1 and elevated transaminases while those with normal transaminase; therapy was initiated only in patients with fibrosis stage ≥ F2.

Results: Normal ALT and AST were detected in 1308/4277 (30.6%) and 1662/4277 (38.9%) patients, respectively, while both enzymes were normal in 943 patients (22%). Multivariate regression analysis showed that lower AFP and higher platelets count (compared with elevated transaminases group) were significantly correlated with normal transaminases ($P < 0.01$), however, HCV-RNA levels did not show such significance. The number of patients with HAI score ≥ A1 was significantly lower in normal than elevated transaminases (36.5% vs 40.9%, respectively, $P < 0.01$) and patients with fibrosis ≥ F2 was significantly lower in normal than elevated transaminases (36.4%) and (43%), respectively ($P < 0.01$). There was no significant correlation between baseline transaminases levels and response to treatment.

Conclusion: Normal transaminases are frequently encountered in chronic HCV Egyptian patients (22%). They show low AFP level, mild degree of activity and stage of fibrosis with no correlation with response to therapy.

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Introduction

Approximately 3% of people worldwide are infected with hepatitis C virus (HCV) [1]. More than 80% of the infected patients will develop chronic infection [2]. Around 25—30% of chronically HCV infected patients have repeatedly normal levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [3,4]. The definition of normal transaminases levels has changed over time. Reference ranges for serum ALT and AST levels vary widely between different laboratories, usually considering ''upper normal limits'', when levels are up to 40 U/L, making slight differences for women. Recent data has shown that when considering ''healthy'' population the upper limit of normal ALT should be around 30 U/L for males and 19 U/L for females [5]. For clinical purposes, most studies evaluating the management and treatment of patients of chronic HCV with normal ALT, have considered the historical definition by local laboratories [6].

Most studies have shown that in patients with chronic HCV with normal transaminases, liver disease is significantly less severe than in chronic HCV patients with elevated transaminases [7—10]. Liver damage in most HCV patients with normal transaminases is usually stable over time, with minimal or mild necro-inflammation and minimal or absent fibrosis (cirrhosis is rare), making this group of patients with a favorable prognosis [11,12]. Nevertheless, 20—30% of these patients may eventually progress to significant necro-inflammation and fibrosis over time despite normal ALT. This is the reason why in the last few years, this group of patients was considered more candidates for treatment with antiviral therapy [13]. But the final decision whether treats or not, this group of patients needs to be individualized and take into account different clinical, prognostic factors including: age, HCV genotype, liver histology, patient motivation, adherence, extrahepatic manifestation of HCV and comorbidity [14,15]. In the largest multinational study on chronic HCV infected patients with normal transaminases, it was concluded that efficacy and safety of antiviral combination therapy in that group of patients was similar to that with elevated transaminases even with a lower dose of ribavirin in genotype 1 in addition to improvement in the quality of life and less fatigue in those with SVR [6].

Egypt has the highest prevalence of HCV in the world, ranging from 6 to 28% with an average of approximately 13.8% in the general population [16—19], and genotype 4 represents over 90% of Egyptian cases [20]. We therefore investigated the correlation between normal transaminases (AST and/or ALT) and liver fibrosis and response to combined antiviral therapy.

Patients and methods

This retrospective cross-sectional observational study consists of 4277 Egyptian chronic HCV patients, who had been treated with Peg-IFN/RBV between the years 2007 and 2010 at Cairo-Fatemic Hospital (Ministry of Health and population), Cairo, Egypt. The study population included IFN-naive chronic HCV patients who were diagnosed by anti-HCV antibodies, HCV-RNA by reverse transcription-polymerase chain reaction (RT-PCR) in addition to the histological evidence of chronic hepatitis. Adult, age ranged from 18 to 60 years, patients of both sexes, who received combined antiviral therapy and were able to continue the follow-up period were included. The study was approved by the ethical committee of the Ministry of Health and Population and all patients were consented for the blood sampling and possible data application in future research. The consent was designed to explain the treatment process that might extend up to 48 weeks, importance adherence to treatment, possible side effects and adverse effects.

Interferon-naive Egyptian patients, chronically infected with HCV, were enrolled in if they fulfilled all the standards of care inclusion and exclusion criteria for interferon therapy which applied on a national wide program controlled by the National committee for the treatment of viral hepatitis. We treat according to international guidelines with some modifications, F4 was not treated under governmental coverage, otherwise we treat fibrosis stage $\geq$ F1 by Metavir score. A standardized enrolment questionnaire was completed by the patients' physicians. Each patient was subjected to a detailed medical history and clinical assessment with special emphasis on body mass index (BMI). Recorded parameters include:

- laboratory parameters: complete blood picture, baseline liver biochemical profile (we defined patients with normal transaminases when the patients' values did not exceed the upper limit of normal of the laboratory reference and it is repeated for the patients before we decide to evaluate for treatment), serum creatinine, ANA, serum alpha feto-protein (AFP), free TSH, anti-schistosomal antibody and fasting blood glucose level;
- virological parameters: baseline, weeks 12, 24, and 48 of antiviral therapy, we tried to have SVR, but at the time of preparation of this manuscript, no enough data were available about SVR, logistic difficulties, economic factors as well as drop out were cofactors;
- histological parameters: grade of necro-inflammation, stage of fibrosis according to the Metavir scoring system [21].

Follow-up: clinical and laboratory follow-up to report the possible adverse side effects and treatment response.

Statistical analysis

The descriptive statistics were provided with mean $\pm$ standard deviation (SD) or median for non-parametric data. The χ^2 test and *t*-student test were employed for analysis of qualitative or quantitative variables, respectively. Pearson correlation was done to correlate continuous variables, while Spearman correlation for correlating fibrosis stages with other variables. In all the tests, *P*-values were significant if less than 0.05.

Results

The study included 4277 chronic hepatitis C patients. The demographics, laboratory and histopathological parameters of all the studied patients are showed in Table 1. The mean age of studied patients was 41.57 + 9.8, male/female were

Table 1 Demographic features, laboratory parameters and histopathological features of patients with chronic hepatitis C virus (HCV) $n = 4277$.

Age (mean ± SD)	41.57 ± 9.8
Sex (M/F)	3488/789 (81.5/18.5%)
BMI (mean ± SD)	28.13 ± 4.3
Glucose (mg/dL)	99.67 ± 29.8
Creatinine (mg/dL)	0.896 ± 0.19
Albumin (g/L)	4.2 ± 47
ALP (IU/L)	184.2 ± 188.12
AST (U/L)	56.34 ± 36.3
ALT (U/L)	63.62 ± 41.96
Bil. T (mg/dL)	0.79 ± 0.27
AFP	6.29 ± 11.7
TLC/cmm	6.5 ± 1.8
ANC/cmm	3.42 ± 1.2
Hb (g/dL)	14.19 ± 1.5
Platelets (th/cmm)	215.08 ± 62.57
PC (%)	86.69 ± 10.5
TSH	1.56 ± 0.98
HCV-RNA	12.07 ± 117.007

Activity grade	*n*	%	Fibrosis stage	*n*	%
≤ A1	2569	60.1	≤ F1	2501	58.5
≥ A2	1708	39.9	≥ F2	1776	41.5

Laboratory data were presented as mean ± SD.

3488/789 (81.5/18.5%), mean values of transaminases were for ALT = 63.62 ± 41.96 and for AST = 56.34 ± 36.3, mean HCV viral load in studied patients was 12.07 ± 117.007; 2569/4277 (60.1%) and 1708/4277 (39.9%) out of the studied patients showed HAI ≤ A1 and ≥ A2, respectively while fibrosis stage was ≤ F1 in 2501/4277 (58.5%) and ≥ F2 in 1776/4277 (41.5%) out of the studied patients.

Out of 4277 chronic hepatitis C patients, 943 patients (22%) had normal transaminases (ALT and AST) and 3334 patients (78%) had elevated transaminases (ALT and/or AST). Demographic features, laboratory parameters, viral response, histopathological data of both groups (normal and elevated transaminases) are shown in Table 2. Both groups were age and gender matched, BMI and AFP were significantly elevated in elevated transaminases group compared with normal group while platelets count was significantly reduced in elevated transaminases group. The number of patients with mild HAI (≤ A1) was significantly higher in normal transaminases group compared with elevated group (599/943, 63.5% vs 1970/3334, 59.1%, respectively, *P*-value = 0.01), while the number of patients with mild degree of fibrosis (stage ≤ F1) was significantly higher in normal transaminases group (600/943, 63.6% vs 1901/3334, 57%, *P*-value < 0.01) while more patients with higher degree of fibrosis (≥ F2) were significantly found in elevated transaminases group (1433/3334, 43% vs 343/943, 36.4%, respectively. *P*-value was < 0.01). HCV viral load was not significantly higher in elevated transaminases group compared with normal group. The early and end of treatment response were not significantly different between studied groups. As regarding patients with normal and elevated AST only or ALT only, demographic, laboratory and histopathological features are shown in Table 3. In multivariate logistic regression in which response to treatment is the dependent variable, female gender, less activity grades and fibrosis stages are significant independent factors ($P < 0.01$ for each). However, age and level of transaminases were insignificant independent factor associated with response to treatment.

Discussion

Elevation of serum ALT and AST levels usually serve as an important markers of liver injury, although there is little correlation between ALT level elevation and the degree of liver injury assessed though liver biopsy [6]. Serum ALT levels remain for long periods within normal range in 25—30% of chronic HCV carriers, while an additional 40% have ALT less than twice the upper limit of normal [21,22]. Most authors have defined persistent normal ALT (PNALT) when ALT measurements persists less than 40 U/L on two or three different occasions separated by at least 1 month, over a period of 6 months [23].

In our study when we compared patients with normal both aminotransferases (ALT and AST) with the other group of elevated both aminotransferases, we found that there is no statistically significant difference regarding age, sex, and BMI but when separating the aminotransferases, the significant statistical difference appears regarding sex in each AST and ALT separately that is proved by the available literature which suggests that PNALT are characterized by a higher prevalence of female sex only [10,24,25]. No major difference statistically between both groups in serum HCV-RNA titer (genotype 4) that exists in any other HCV genotypes worldwide, although European [21] and Japanese [26] studies show a trend towards a higher relative frequency of

Table 2 Demographic features, laboratory parameters, viral response, HAI score and Fibrosis stages among patients with normal and elevated transaminases.

	Normal transaminases	Elevated transaminases	*P*-value
Age (mean ± SD)	41.65 ± 9.64	41.54 ± 9.84	0.773
Sex (M/F)	750/193	2738/596	0.7
BMI (mean ± SD)	27.81 ± 4.55	28.22 ± 4.26	0.014
Platelets (mean ± SD)	223 ± 59	212 ± 63	<0.01 (S)
AFP, median (IQR)	2.5 (3.2)	3.5 (5.2)	<0.01 (S)
HCV viral load × 10^5, median (IQR)	4.9 (1.9)	4.98 (1.75)	0.36
EVR	854 (90.6%)	3027(90.8%)	0.84
W24	644 (68.3%)	2227 (66.8%)	0.43
ETR (W48)	520 (55.1%)	1757 (52.7%)	0.29
HAI			
A1	599 (63.5%)	1364 (40.9%)	0.01 (S)
≥A2	344 (36.5%)	1970 (59.1%)	
Fibrosis stage			
≤ F1	600 (63.6%)	1901 (57.0%)	<0.01 (S)
≥ F2	343 (36.4%)	1433 (43.0%)	

P-value < 0.05 = Significant.

genotype (2a, 2b) in patients with normal transferases. This can be explained by the behaviour of chronic infection with HCV genotype 2, which often runs a course of mild necro-inflammation with persistently normal ALT for long periods of time intermingled with ALT flares and a rapid progression of fibrosis [27]. To some extent, this can also explain the results of our patients in which there is a statistical significant predominance of normal aminotransferases (AST and/or ALT) in patients with mild histological activity index and mild stages of fibrosis compared to other groups of patients with elevated aminotransferases (AST and/or ALT) (A1 in 63.5% vs A1 in 59.1% and ≤ F1 in 63.6% vs ≤ F1 in 57%; $P < 0.001$), respectively inspite of the behaviour of HCV genotype 4 which is more severe than other types. That is matched with a review of three large randomized trials which has shown that patients with PNALT have significantly lower inflammation and fibrosis scores on liver biopsy than patients with elevated ALT [10].

The decision whether to initiate antiviral therapy in HCV-infected patients with persistently normal ALT values is controversial [28—30]. Some experts believe that liver disease progression is uncommon in most of these persons, thus the adverse events associated with current treatment would outweigh the probability of benefit of therapy. The recommendations of AASLD practice guidelines [31] suggest that regardless of the serum aminotransferase levels, the decision to initiate therapy with interferon and ribavirin should be individualized based on the severity of liver disease by liver biopsy, the potential of serious side effects, the likelihood of response, and the presence of co-morbid

Table 3 Demographic, laboratory features and histopathological features in patients with normal and elevated AST and ALT.

	Normal AST *n* = 1662		Elevated AST *n* = 2615		*P*-value	Normal ALT *n* = 1308		Elevated ALT *n* = 2969		*P*-value
Age (Mean ± SD)	39.96 ± 10.01		42.59 ± 9.59		0.00	42.26 ± 9.83		41.26 ± 9.83		0.003
Sex (M/F)	1389/273		2099/516		0.01 (S)	1031/277		2457/512		0.002(S)
BMI(Mean ± SD)	27.62 ± 4.39		28.46 ± 4.25		0.00	28.07 ± 4.47		28.16 ± 4.26		0.561
AFP	4 ± 5.10		7.77 ± 14.25		0.00	4.80 ± 7.81		6.96 ± 13.02		0.00
Platelets, cmm	226.09 ± 60.77		208.06 ± 62.70		0.00	220.50 ± 60.44		212.69 ± 63.35		0.00
HCV-RNA/105	10.55 ± 65.75		13.04 ± 140.08		.522	9.29 ± 49.50		13.28 ± 136.17		.333
Activity grade	*n*	%	*n*	%		*n*	%	*n*	%	
≤ A1	1156	69.6	1413	54	< 0.01 (S)	822	62.8	1747	58.8	< 0.01 (S)
≥ A2	506	30.4	1202	46		486	37.2	1222	41.2	
Fibrosis stage	*n*	%	*n*	%		*n*	%	*n*	%	
< F2	1160	69.8	1341	51.3	< 0.01 (S)	818	62.5	1683	56.7	< 0.01 (S)
≥ F2	502	30.2	1274	48.7		490	37.5	1286	43.3	

ALT: serum alanine aminotransferase; AST: aspartate aminotransferase. Laboratory data were presented as mean ± SD.

conditions (Grade III). All these data and new findings definitively establish that the decision whether to treat or not to treat patients with hepatitis C should not be based on ALT levels alone but rather on a range of parameters that should include the patient's age and motivation, disease duration and stage, the virological profile and a careful evaluation of the benefit/risk ratio in the individual case. A modified Markov model to predict morbidity and mortality in patients with normal ALT has been provided [32]. This modelling suggests that treatment of N-ALT patients would decrease HCV morbidity and mortality and that these patients should be considered candidates for treatment just as others are.

There are only a few clinical studies with antiviral treatment in chronic HCV infection with normal transaminases because they have been excluded from the large randomized treatment studies so the efficacy and safety of combined therapy was not very clear. In patients with normal transaminases (randomized 491 patients) with genotypes 1, 2 and 3 [33], it was concluded that there is no difference in the efficacy and safety between patients with normal ALT and patients with elevated ALT. Compared to our study that contains larger pool of patients with normal transaminases AST and ALT (943 patients) mostly genotype 4, there was higher percentage of end treatment response in the group of patients with normal transaminases than others with elevated transaminases but without statistical significance (68.3% vs 66.8%, $P < 0.43$ at W24 and 55.1% vs 52.7%, $P < 0.29$ at W48, respectively). In another recent study on 88 patients with normal ALT (genotypes 1, 2, 3), they found that younger and leaner patients and those with chronic HCV genotype non-1 and lower baseline HCV-RNA were more likely to achieve SVR so they conclude that patients with normal ALT have comparable or even higher SVR rates than HCV patients with abnormal ALT levels and they suggest that immediate therapy in those selected cases might be preferred [34]. In conclusion: normal transaminases are frequently encountered in chronic HCV Egyptian patients (22%). They show low AFP level in addition to mild degree of activity and stage of fibrosis with no correlation with response to therapy.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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References

[1] National Institute of Health, USA. NIH consensus statement on management of hepatitis C. NIH Consensus State Sci Statements 2002;19:1—46.

[2] Ghany MG, Strader MG, Thomas DL, Seef LB. Diagnosis management and treatment of hepatitis C: an update AASLD practice guidelines. Hepatology 2009;49:1335—74.

[3] Alberti A, Noventa F, Benvgnu L, Boccato S, Gatta A. Prevalence of liver disease in a population of asymptomatic individuals with hepatitis C virus infection. Ann Intern Med 2002;137:961—4.

[4] Prati D, Shiffman ML, Diago M, Gane E, Rajender Reedy K, Pockros P, et al. Viral and metabolic factors influencing alanine aminotransferase activity in patients with chronic hepatitis C. J Hepatol 2006;44:679—85.

[5] Prati D, Tailoi E, Zanella A, Della Tore E, Butelli S, del Vecchio E, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med 2002;137:1—10.

[6] Zapata R. Clinical approach to the patients with chronic hepatitis C infection and normal aminotransferases. Ann Hepatol 2010;9(1):S72—9.

[7] Puoti C, Castellacci R, Montagnese F. Hepatitis C virus carriers with persistently normal aminotransferase levels: healthy people or true patients? Dig Liver Dis 2000;32:634—43.

[8] Persico M, Persico E, Suozzo R, Conte S, De Seta M, Coppola M, et al. Natural history of hepatitis C virus carriers with persistently normal aminotransferase levels. Gastroenterology 2000;118:760—4.

[9] Zeuzem S, Alberti A, Rosenberg W, Marcellin P, Daigo M, Negro F, et al. Review Article: Management of patients with chronic hepatitis C virus infection and normal alanine aminotransferase activity. Aliment Pharmacol Ther 2006;24:1133—49.

[10] Shiffman ML, Diago M, Tran A, Pockros P, Reindollar R, Prati D, et al. Chronic hepatitis C in patients with persistently normal alanine aminotransferase levels. Clin Gasreoenterol Hepatol 2006;4:645—52.

[11] Martinot-Peignoux M, Boyer N, Cazals-Hatem D, Pham BN, Gervais A, Le Breton V, et al. Prospective study on anti hepatitis C virus- positive patients with persistently normal serum alanine aminotransferase with or without detectable serum hepatitis C virus RNA. Hepatology 2001;34:1000—5.

[12] Persioco M, Perrotta S, Persico E, Terracciano L, Folgori A, Ruggeri L, et al. Hepatitis C virus carriers with persistently normal ALT levels: Biological peculiarities and update of the natural history of liver disease at 10 years. J Viral Hepat 2006;13:290—6.

[13] Okanoue T, Minami M, Makiyama A, Sumida Y, Yasui K, Itoh Y. Natural course of asymptomatic hepatitis C virus- infected patients and hepatocellular carcinoma after Interferon therapy. Clin Gastroenterol Hepatol 2005;3(10 Suppl 2):S89—91.

[14] Puoti C. Hepatitis C virus with normal transaminase levels. Dig Dis 2007;25:277—8.

[15] Fried MW. Hepatitis C infection with normal liver chemistry tests. Clin Gastroentrol Hepatol 2008;6:503—5.

[16] Abdel-Aziz F, Habib M, Mohamed MK, Abdel-Hamid M, Gamil F, Madkour S, et al. Hepatitis C virus (HCV) infection in a community in the Nile Delta: population description and HCV prevalence. Hepatology 2000;32:111—5.

[17] Frank C, Mohamed MK, Strickland GT, Lavanchy D, Arthur RR, Magder LS, et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet 2000;355:887—91.

[18] Nafeh MA, Medhat A, Shehata M, Mikhail NN, Swifee Y, Abdel-Hamid M, et al. Hepatitis C in a community in Upper Egypt: I Cross-sectional survey. Am J Trop Med Hyg 2000;63:236—41.

[19] El-Sadawy M, Ragab H, el-Toukhy H, el-Mor Ael L, Mangoud AM, Eissa MH, et al. Hepatitis C virus infection at Sharkia Governorate Egypt: seroprevalence and associated risk factors. J Egypt Soc Parasitol 2004;34:367—84.

[20] Zainab D, Mezban MD, Adil Ed Wakil MD. Hepatitis C in Egypt. Am J Gastroenterol 2006.

[21] Marcellin P, Levy S, Erlinger S. Therapy of hepatitis C: patients with normal aminotransferase levels. Hepatology 1997;26:S133—6.
[22] Puoti C, Castellacci R, Montagnese F, Zaltron S, Stornaiuolo G, Bergami N, et al. Histological and virological features and follow-up of hepatitis C virus carriers with normal aminotransferase levels: the Italian prospective study of the asymptomatic C carriers (ISACC). J Hepatol 2002;37:117—23.
[23] Puoti C, Guido M, Mangia A, Persico M, Prati D. Clinical management of HCV carriers with normal aminotransferases levels. Dig Liver Dis 2003;35:362—9.
[24] Persico M, Persico E, Suozzo R, Conte S, De Seta M, Coppola L, et al. Natural history of hepatitis C virus carriers with persistently normal aminotransferase levels. Gastroenterology 2000;118:760—4.
[25] Calvaruso V, Craxi A. Implication of normal liver enzymes in liver disease. J Viral Hepat 2009;16(8):529—36.
[26] Shindo M, Arai K, Sokawa Y, Okuno T. The virological and histological states of anti-hepatitis C virus-positive subjects with normal liver biochemical values. Hepatology 1995;22: 418—25.
[27] Rumi MG, De Filippi F, La Vecchia C, Donato MF, Gallus S, Del Ninno E, et al. Hepatitis C reactivation in patients with chronic infection with genotypes 1b and 2c: a retrospective cohort study of 206 untreated patients. Gut 2005;54(3): 402—6.
[28] Prieto M, Olaso V, Verdu C, Cordoba J, Gisbert C, Rayon M, et al. Does the healthy hepatitis C virus carrier state really exist? An analysis using polymerase chain reaction. Hepatology 1995;22:413—7.
[29] Bacon BR. Treatment of patients with hepatitis C and normal serum aminotransferase levels. Hepatology 2002;36:S179—84.
[30] Pradat P, Alberti A, Poynard T, Esteban JI, Weiland O, Marcellin P, et al. Predictive value of ALT levels for histologic findings in chronic hepatitis C: a European collaborative study. Hepatology 2002;36(1):973—7.
[31] Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. Hepatology 2004;9:1147.
[32] Deuffic-Burban S, Babany G, Lonjon-Domanec I, Deltenre P, Canva-Delcambre V, Dharancy S, et al. Impact of pegylated interferon and ribavirin on morbidity and mortality in patients with chronic hepatitis C and normal aminotransferases in France. Hepatology 2009;50(5):1351—9.
[33] Zeuzem S, Diago M, Gane E, Reddy KR, Pockros P, Prati D, et al. Peg interferon alpha 2-a(40 kilodalton) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. Gastroenterology 2004;127:1724—32.
[34] Puoti C, Pellicelli AM, Romano M, Mecenate F, Guarisco R, Barbarini G, et al. Treatment of hepatitis C virus carriers with persistently normal alanine aminotransferase levels with peg interferon alpha 2-a and ribavirin: a multicentric study. Liver Int 2009;29:1479—84.