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Original Article

The clinical roles of rheumatoid factor in the treatment of chronic hepatitis C infection

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Abstract: Objective: The hepatitis C virus infection is associated with arthritis. However, the clinical roles of the rheumatoid factor in patients who received anti-viral treatment are not as clear. Methods: To identify the association between the rheumatoid factor and the treatment response in hepatitis C virus infected patients, we enrolled patients who received anti-viral treatment with peg-interferon plus weight-based ribavirin according to response guided therapy. Patients who had a mix type hepatitis C infection, any autoimmune diseases, hepatitis B co-infection or intolerance to the side effects of therapy were excluded. Patients were divided into a rheumatoid factor (RF) positive (>20 IU/ml) group and a rheumatoid negative group. The patient's characteristics, treatment response, dynamic changing of the rheumatoid factor and factors influenced the sustained virus response (SVR) of therapy, which were analyzed. Results: A total of 271 patients completed the anti-viral treatment and analysis. The positive rate of the rheumatoid factor is 47.23% (128/271). In the RF positive group, the SVR rate was 82.8%, 71.0%, 96.6% for overall, genotype 1 infected, and non-genotype 1 infected patients, respectively. In the RF negative group, the SVR rate was 77.6%, 66.7%, 91.9% for overall, genotype 1 infected, and non-genotype 1 infected patients, respectively. There is a trend toward a higher SVR rate in RF positive patients, but no statistical difference was noted. In RF positive patients who achieved SVR, the RF values reduced significantly (56.4±78.0 vs. 39.4±39.6, P<0.001) after treatment but not in the non-SVR group (43.8±25.9 vs. 31.7±13.5, P=0.074). In the RF negative group, 37.8% and 34.4% of the patients' RF became positive after treatment in the SVR group and in the non-SVR group. A lower virus load (<800,000 copies/ml), non-genotype 1 infection, alanine aminotransferase (ALT) rapid normalization, rapid viral response (RVR) and complete early viral response (cEVR) are significant predictive factors associated with SVR. The present or dynamic change of the rheumatoid factor cannot predict the effect of the treatment response. Conclusions: The rheumatoid factor was positive in 47% of the chronic hepatitis C virus infected patients. In the RF positive group, the treatment response was better but not statistically significant. After treatment, the RF value was significantly reduced in cured patients.

Keywords: Antiviral treatment, hepatitis C, rheumatoid factor

Introduction

HCV infection is associated with high prevalence of extrahepatic manifestations and autoimmune biomarkers [1]. Many studies have discussed about the extrahepatic involvement of HCV, such as Sjogren's Syndrome [2], arthritis [3], fibromyalgia [4], and cryoglobulinemia [5]. There were also many studies which described the autoantibody production of HCV, such as cryglobulins, rheumatoid factor (RF) [6], antinuclear antibodies [7], antiphospholipid antibodies [8], anti-smooth muscle antibodies [9], and anti-extractable nuclear antigens antibodies [10]. The rheumatoid factor is one of the highest prevalent autoantibodies in patients with HCV and present in 50-80% of cases [11]. However, limited data is available which describes the relationship of the RF values and disease activity of HCV.

Rheumatoid factors were first identified by Waaler in 1940 [12]. The autoantibodies are directed against the Fc portion of immunoglobulin G and commonly detected in HCV-infected patients. The mechanism of the circulating RF is unclear. Over-activation and proliferation of B lymphocytes is a possible mechanism for RF production, via the interaction with surface protein of HCV [13]. Testing for RF is primarily used for the diagnosis of rheumatoid arthritis, but RF is also present in other rheumatic diseases and chronic infections. The level of RF is associated with the disease activity and radiologic damage in patients with rheumatoid arthritis [14]. Thus, in patients with HCV infection without autoimmune diseases and positive in RF, we hypothesized that the level of RF should be related to the disease activity of HCV. We collected the RF values in patients with HCV who underwent pegylated interferon alpha (Peg-IFN α) plus ribavirin therapy, and analyzed the changes of RF values in treatment of HCV. We also analyzed the relationship of the RF and treatment response of HCV.

Materials and methods

Study population

Patients with HCV infection and abnormal alanine aminotransferase (ALT) level (>36 U/L) who underwent Peg-IFN α (2a or 2b) plus ribavirin at Chiayi Chang Gung Memorial Hospital were included. Exclusion criteria included the following: rheumatoid arthritis, any autoimmune diseases, unknown arthritis, hepatitis B virus co-infection, mixed genotype of HCV, human immunodeficiency virus co-infection, and withdrawal of treatment.

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB: 100-1025B).

Treatment

All patients underwent Peg-IFN α (2a or 2b) weekly plus body weight based ribavirin daily. The virological response after 4 weeks treatment decided the duration of therapy. Patients who had a rapid virological response (RVR, undetectable viral load after 4 weeks treatment) received 24 weeks of therapy, and patients who were without an RVR had an early virological response (EVR, undetectable viral load or drop by 99% after 12 weeks of treatment) received 48 weeks of therapy. Someone who didn't get an EVR at week 12 was defined as a null responder. An undetectable viral load at 24 weeks after treatment ended was defined as sustained virological response (SVR). If the ALT level became normal (<36 U/L) before week 12, it was defined as an ALT rapid normalization. After treatment, we follow up for 3 years to see if any autoimmune disease or rheumatoid arthritis happened in these patients.

Laboratory methods

Rheumatoid factor was measured by laser nephelometry for the IgM isotype (IMMAGE Immunochemistry Systems RHF) and defined as positive if the value was >20 IU/ml. The hepatitis C virus RNA was detected by the Abbot HCV Amplification Reagent Kit. The other laboratory examination included white blood count, hemoglobin, and platelets, which were checked before and during the treatment to see if there are any associations between RF and SVR. Ultrasound (US) scanning was performed by hepatologists, using a Toshiba system (Aplio-300; Toshiba, Tokyo, Japan) with a 3.75-MHz convex probe to diagnose liver cirrhosis and fatty liver. The diagnosis of liver cirrhosis was according to a score system, which considered four factors, including liver surface, liver parenchyma, hepatic vessels and spleen size [15]. Nonalcoholic fatty liver disease was classified into none, mild, moderate and severe according to the presentation of the hepatorenal echo contrast and liver brightness, deep attenuation, and vessel blurring [16].

Statistical analyses

The means were calculated for continuous variables. The chi-square test was used to compare the distribution of categorical variables between the groups. To compare continuous variables among the groups, a student's t-test or ANOVA test was used. Univariate analysis was used to identify possible factors for sustained response. Data management and statistical analyses were performed with SPSS software version 17.0 (SPSS Inc., Chicago, IL). A *P*-value of <0.05 was considered to be statistically significant.

Results

From March 2009 to June 2013, there were 271 patients, 147 male and 124 female, with a

Table 1. Comparison of baseline characteristics between patients with and without rheumatoid factor (RF)

	RF positive N=128	RF negative N=143	P
Age (yrs)	57.6±10.7	57.2±11.2	0.740
Sex (M/F)	61/67	86/57	0.039
BMI	25.6±3.2	25.2±3.4	0.303
Genotype (1/non-1)	69/59	81/62	0.651
Log HCV-RNA (copies/ml)	5.8±0.9	5.6±1.0	0.063
HCV RNA (>400,000/<400,000)	84/44	83/60	0.200
HCV RNA (>800,000/<800,000)	66/62	66/77	0.374
Cirrhosis (+/-)	19/109	17/126	0.474
Fatty liver (+/-)	26/102	24/119	0.455
ALT (U/L)	115.3±85.9	112.1±77.2	0.752
WBC (10^3/mm^3)	6.0±1.7	6.3±5.3	0.447
Platelet (10^4/mm^3)	174.2±65.4	180.2±51.3	0.406
Hemoglobin (g/dL)	14.2±1.5	14.4±1.5	0.238

Table 2. Treatment response in genotype 1 and non-genotype 1 patients

	Genotype 1	Genotype 2 or 3	P
Null responder	5/150 (3.3%)	1/121 (0.8%)	0.163
RVR	64/150 (42.7%)	94/121 (77.7%)	<0.001
cEVR	129/150 (86.0%)	118/121 (97.5%)	0.001
ETR	136/150 (90.7%)	118/121 (97.5%)	0.021
SVR	103/150 (68.7%)	114/121 (94.2%)	<0.001

history of complete antiviral treatment for HCV enrolled in this study. Of these, 150 patients had HCV genotype 1 infection, 119 patients had HCV genotype 2 infection and 2 patients had genotype 3 infection.

The positive rate of RF is 47.23% in chronic hepatitis C infected patients. 128 patients were RF positive and 143 patients were RF negative. A comparison of baseline characteristics between patients with and without RF was shown in **Table 1**. The RVR and SVR rates in patients with a HCV genotype 1 were 42.7% (64/150) and 68.7% (103/150) respectively. In patients with a HCV non-genotype 1 infection, the RVR and SVR rates were 77.7% (94/121) and 94.2% (114/121), respectively (**Table 2**). The treatment response in patients with HCV genotype 1 was significantly better than patients with HCV non-genotype 1 (**Figure 1**). At the same time, the SVR rate was 82.8% in patients with a positive RF, and 77.6% in patients with a negative RF. In the patients with HCV genotype 1, the SVR rate was 71% in patients with a positive RF, and 66.7% in patients with a negative RF. In the patients with HCV non-genotype 1, the SVR rate was 96.6% in patients with a positive RF, and 91.9% in a negative RF (**Figure 2**). There is a trend for higher SVR rates in patients with a positive RF, but no statistical differences were noted.

The RF values before and after antiviral treatment were analyzed in the whole population. In patients with initially positive RF who achieved SVR after antiviral therapy, the pre-treatment RF values reduced significantly after therapy (56.4±78.0 vs. 39.4±39.6, P<0.001). There was a similar effect in patients with an initially positive RF who did not achieve SVR after antiviral therapy (43.8± 25.9 vs. 31.7±13.5, P=0.074), but there wasn't a statistical significance. However, in patients with an initial negative RF, some patients' RF became positive after the Peg-IFN plus ribavirin treatment whether they achieved SVR or not (37.8% in SVR group and 34.4% in non-SVR group, P=0.721) (**Table 3**). There was no any autoimmune disease or rheumatoid arthritis happened in these 271 patients after 3 years follow up.

We also examined the influence of potentially important prognostic factors on SVR, such as age, sex, body mass index, RF positivity, RF value, HCV genotype, and HCV viral load. Other factors, which were measured, were RVR, complete early viral response (cEVR), end of treatment response (ETR), cirrhosis, fatty liver, Peg-IFN α 2a or 2b, initial alanine aminotransferase (ALT) level, ALT rapid normalization, white cell count, platelet count, and hemoglobin. Overall, 217 (80.0%) of the 271 treated patients showed SVR to treatment. This is in comparison to patients with SVR and non-SVR, as those with HCV genotype 1 infection had significantly lower SVR rates compared to patients with HCV non-genotype 1 infection. Patients who achieved SVR had a lower HCV viral load (<800,000 copies/ml), higher rates of RVR,

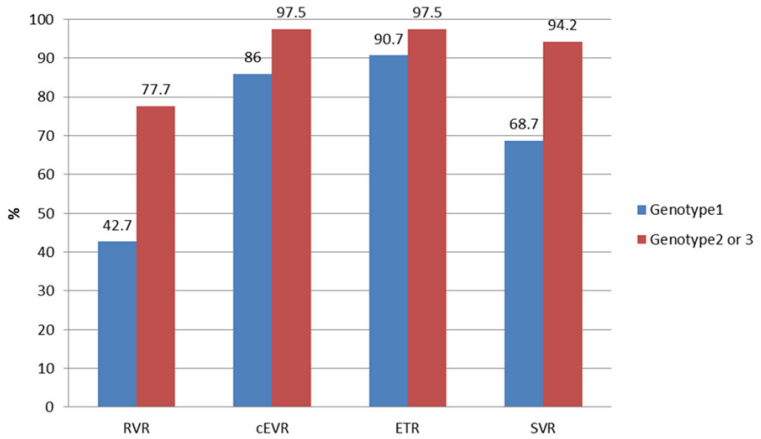

Figure 1. Treatment response in genotype 1 and non-genotype 1 patients. The treatment response in patients with HCV genotype 1 was significantly better than for patients with HCV non-genotype 1.

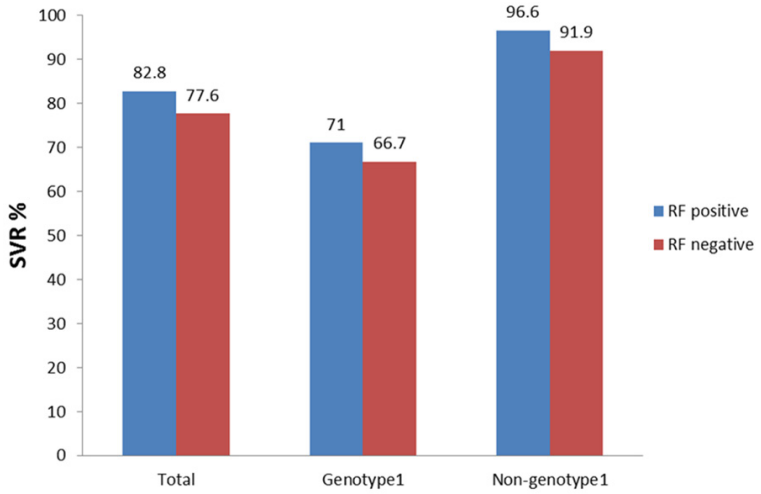

Figure 2. Association of serum rheumatoid factor with the SVR. In the RF positive group, the SVR rate was 82.8%, 71.0%, 96.6% in overall, genotype 1 infected, and non-genotype 1 infected patients, respectively. In the RF negative group, the SVR rate was 77.6%, 66.7%, 91.9% in overall, genotype 1 infected, and non-genotype 1 infected patients, respectively. There is a trend about a higher SVR rate in RF positive patients, but no statistical difference is noted.

higher rates of complete early viral response (cEVR), higher rates of end treatment response (ETR), and higher rates of alanine aminotransferase (ALT) rapid normalization, when compared to patients with non-SVR (**Table 4**). There was no difference in RF seropositivity, RF value before treatment, and RF value after treatment.

Discussion

Currently, we presented the largest retrospective study to evaluate the dynamic change of RF values in the Peg-IFN plus ribavirin combination therapy and the impact of RF values on the therapeutic effect in Taiwanese patients with HCV. Patients with serum RF positive had higher SVR rates than those with serum RF negative in our study, but there was no statistical difference. A dynamic change of RF value is not significantly related to treatment response.

In our study, the possible RF related autoimmune diseases were excluded, and those were also undetected in our follow up. In the patients who had initially positive RF and achieved SVR, the RF value reduced significantly after complete treatment, but was not totally eliminated. This demonstrated that HCV is one of the etiologies of RF production, and the HCV related RF values are associated with disease activity of HCV. The complexity of RF production could be found in the control group of patients with initially negative RF as well. The RF values elevated and changed to positive in some patients of the control group, even in some patients who achieved SVR. The latter results let us to think about whether the interferon therapy can induce RF production or not. Although the precise mechanisms of Peg-IFN α are not yet clear, previous studies showed the immunomodulating effects of interferon may be related to enhancement of macrophage, cytotoxic T cell, and natural killer cell activity [17]. More HCV-specific CD4+ and CD8+ T cell responses were noted in patients with EVR and SVR, compared with either treatment-naïve patients or null responders [18]. Peg-IFN plus ribavirin therapy may alter the cytokine profile by suppressing interleukin-10 (IL-10) production but maintaining interleukin-12 (IL-12) and tumor necrosis factor alpha (TNF-α) production [19]. IL-10 is well characterized as an anti-inflammatory cytokine, which diminishes

Table 3. Rheumatoid factor values in patients with HCV-related chronic hepatitis

	RF before treatment	RF after treatment	P
RF positive (n=128)			
Non-SVR (n=22)	43.8±25.9	31.7±13.5	0.074#
	Positive n=22 (100%)	Positive n=15 (68.2%)	0.846*
SVR (n=106)	56.4±78.0	39.4±39.6	<0.001#
	Positive n=106 (100%)	Positive n=70 (66.0%)	0.846*
RF negative (n=143)			
Non-SVR (n=32)	<20 IU/mL	25.7±4.8	
	Positive n=0 (0%)	Positive n=11 (34.4%)	0.721*
SVR (n=111)	<20 IU/mL	32.1±21.4	
	Positive n=0 (0%)	Positive n=42 (37.8%)	0.721*

*Comparison between the non-SVR and the SVR group. #Comparison between RF before and after treatment.

Table 4. Comparisons between patients with SVR and Non-SVR

	SVR (n=217)	Non-SVR (n=54)	P
Age (yrs)	56.7±11.3	60.1±8.8	0.044
Sex (M/F)	123/94	24/30	0.106
BMI	25.4±3.3	25.4±3.5	0.867
RF (+/-)	106/111	22/32	0.286
RF value (IU/mL)	56.4±78.0	43.8±25.9	0.456
RF elevation after treatment (+/-)	61/156	21/33	0.123
RF value after treatment	36.5±33.7	29.1±10.9	0.274
Genotype (1/non-1)	103/114	47/7	<0.001
Log HCV-RNA (copies/ml)	5.59±0.99	6.06±0.76	0.001
HCV RNA (>400,000/<400,000)	123/94	44/10	0.001
HCV RNA (>800,000/<800,000)	95/122	37/17	0.001
RVR (+/-)	145/72	13/41	<0.001
cEVR (+/-)	211/6	36/18	<0.001
ETR (+/-)	214/3	40/14	<0.001
Cirrhosis (+/-)	28/189	8/46	0.711
Fatty liver (+/-)	39/178	11/43	0.684
PEG-IFN α (2a/2b)	50/167	15/39	0.466
ALT (U/L)	115.0±82.2	108.4±77.9	0.608
ALT rapid normalization (+/-)	164/52	28/25	0.001
WBC (10^3/mm^3)	6.0±1.8	6.9±8.3	0.145
Platelet (10^4/mm^3)	180.3±58.4	165.6±57.7	0.105
Hemoglobin (g/dL)	14.3±1.5	14.4±1.5	0.648

the capacity of innate immune cells to kill pathogens, as well as reduces their capacity to generate and maintain responsive antigen-specific T cells [20]. IL-12 causes a generalized up regulation in production of all antibodies and therefore acts as a strong adjuvant for humoral as well as cellular immunity [21]. There is a physiological role for TNF-α in regulating the development and organization of splenic follicular architecture and in the maturation of the humoral immune response [22]. Overall, the effect of pegylated interferon therapy is both in cell-mediated immunity and humoral immunity. Since the RF production is associated with over activation and proliferation of B lymphocytes which belong to humoral immunity, our study may demonstrate that Peg-IFN plus ribavirin therapy can induce RF production. Furthermore, in the general population, the frequency of RF positive individuals ranges from 1.3-4% in Caucasians to 30% in some tribes of North American Indians [23-26]. In the present study, the proportion of elevation of RF values after antiviral therapy in patients with initially negative RF was higher than in the general population, in both the SVR and the non-SVR groups. These also proved the effect of Peg-IFN therapy on the generation of RF.

Previous studies have identified several independent factors associated with Peg-IFN plus the ribavirin treatment response: HCV genotypes 2 or 3, viral load less than 2 million copies/mL, age of 40 years or less, minimal liver fibrosis stage, female sex, and lighter baseline body weight [27, 28]. Moreover, during the antiviral therapy period, a rapid virological response (RVR) is considered to be the strongest independent factor associated with an SVR [29]. Our study shows that HCV non-genotype 1 and

RVR suggest better treatment efficacy, and these results are comparable with the previous study. We tried to define the relationship about RF positivity, values, dynamic change, and SVR, but there was no statistical meaning. This result may be related to the nonspecificity of RFs. Although the possible autoimmune diseases were excluded in our study, there were still a lot of factors which could affect the RFs. Except for HCV, it has been recognized for a long time that the RF is associated with many infectious diseases, such as: Chlamydia pneumoniae, Klebsiella pneumoniae, syphilis, Coxsackie B, cytomegalovirus, dengue, the Epstein-Barr virus, hepatitis A, hepatitis B, Herpes simplex, human immunodeficiency virus, measles, parvovirus, rubella, chagas, malaria, onchocerciasis, and toxoplasmosis [30]. Therefore, there is no obvious effect on RF values during the Peg-IFN plus ribavirin therapy for HCV. However, the ALT rapid normalization found a good prognostic factor, and the serum ALT level was an easy examination for clinical practice.

In conclusions, a positive RF was often found in chronic hepatitis C patients. A positive RF had a better treatment response after Peg-IFN plus ribavirin therapy but was not statistically significant. The RF value was significantly reduced after treatment in the SVR group. Only the lower virus load (<800,000 copies/ml), non-genotype 1 infection, alanine aminotransferase (ALT) rapid normalization, rapid viral response (RVR) and complete early viral response (cEVR) significantly predicted the treatment response but not the rheumatoid factor.

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Disclosure of conflict of interest

None.

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References

[1] Cacoub P, Poynard T, Ghillani P, Charlotte F, Olivi M, Piette JC and Opolon P. Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment Virus C. Arthritis Rheum 1999; 42: 2204-2212.

[2] Haddad J, Deny P, Munz-Gotheil C, Ambrosini JC, Trinchet JC, Pateron D, Mal F, Callard P and Beaugrand M. Lymphocytic sialadenitis of Sjogren's syndrome associated with chronic hepatitis C virus liver disease. Lancet 1992; 339: 321-323.

[3] Rosner I, Rozenbaum M, Toubi E, Kessel A, Naschitz JE and Zuckerman E. The case for hepatitis C arthritis. Semin Arthritis Rheum 2004; 33: 375-387.

[4] Narvaez J, Nolla JM and Valverde-Garcia J. Lack of association of fibromyalgia with hepatitis C virus infection. J Rheumatol 2005; 32: 1118-1121.

[5] Saadoun D, Landau DA, Calabrese LH and Cacoub PP. Hepatitis C-associated mixed cryoglobulinaemia: a crossroad between autoimmunity and lymphoproliferation. Rheumatology (Oxford) 2007; 46: 1234-1242.

[6] Koga T, Migita K, Miyashita T, Maeda Y, Nakamura M, Abiru S, Myoji M, Komori A, Yano K, Yatsuhashi H, Eguchi K and Ishibashi H. Determination of anti-cyclic citrullinated peptide antibodies in the sera of patients with liver diseases. Clin Exp Rheumatol 2008; 26: 121-124.

[7] Hsieh MY, Dai CY, Lee LP, Huang JF, Tsai WC, Hou NJ, Lin ZY, Chen SC, Wang LY, Chang WY, Chuang WL and Yu ML. Antinuclear antibody is associated with a more advanced fibrosis and lower RNA levels of hepatitis C virus in patients with chronic hepatitis C. J Clin Pathol 2008; 61: 333-337.

[8] Harada M, Fujisawa Y, Sakisaka S, Kawaguchi T, Taniguchi E, Sakamoto M, Sumie S, Sasatomi K, Koga H, Torimura T, Ueno T, Gondo K, Yoshida H, Tanikawa K and Sata M. High prevalence of anticardiolipin antibodies in hepatitis C virus infection: lack of effects on thrombocytopenia and thrombotic complications. J Gastroenterol 2000; 35: 272-277.

[9] Clifford BD, Donahue D, Smith L, Cable E, Luttig B, Manns M and Bonkovsky HL. High prevalence of serological markers of autoimmunity in patients with chronic hepatitis C. Hepatology 1995; 21: 613-619.

[10] Omagari K, Ohba K, Kadokawa Y, Hayashida K, Isomoto H, Takeshima F, Mizuta Y, Murata I and Kohno S. Anti-extractable nuclear antigens (ENA) antibodies in patients with chronic hepatitis C before and after treatment with interferon. Autoimmunity 2003; 36: 269-273.

[11] Lormeau C, Falgarone G, Roulot D and Boissier MC. Rheumatologic manifestations of chronic hepatitis C infection. Joint Bone Spine 2006; 73: 633-638.

[12] Waaler E. On the occurrence of a factor in human serum activating the specific agglutintion

of sheep blood corpuscles. 1939. APMIS 2007; 115: 422-438; discussion 439.
[13] Yang DH, Ho LJ and Lai JH. Useful biomarkers for assessment of hepatitis C virus infection-associated autoimmune disorders. World J Gastroenterol 2014; 20: 2962-2970.
[14] Knijff-Dutmer E, Drossaers-Bakker W, Verhoeven A, van der Sluijs Veer G, Boers M, van der Linden S and van de Laar M. Rheumatoid factor measured by fluoroimmunoassay: a responsive measure of rheumatoid arthritis disease activity that is associated with joint damage. Ann Rheum Dis 2002; 61: 603-607.
[15] Hung CH, Lu SN, Wang JH, Lee CM, Chen TM, Tung HD, Chen CH, Huang WS and Changchien CS. Correlation between ultrasonographic and pathologic diagnoses of hepatitis B and C virus-related cirrhosis. J Gastroenterol 2003; 38: 153-157.
[16] Hamaguchi M, Kojima T, Itoh Y, Harano Y, Fujii K, Nakajima T, Kato T, Takeda N, Okuda J, Ida K, Kawahito Y, Yoshikawa T and Okanoue T. The severity of ultrasonographic findings in nonalcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. Am J Gastroenterol 2007; 102: 2708-2715.
[17] Dianzani F. Biological basis for the clinical use of interferon. Gut 1993; 34: S74-76.
[18] Pillai V, Lee WM, Thiele DL and Karandikar NJ. Clinical responders to antiviral therapy of chronic HCV infection show elevated antiviral CD4+ and CD8+ T-cell responses. J Viral Hepat 2007; 14: 318-329.
[19] Barnes E, Salio M, Cerundolo V, Medlin J, Murphy S, Dusheiko G and Klenerman P. Impact of alpha interferon and ribavirin on the function of maturing dendritic cells. Antimicrob Agents Chemother 2004; 48: 3382-3389.
[20] Cyktor JC and Turner J. Interleukin-10 and immunity against prokaryotic and eukaryotic intracellular pathogens. Infect Immun 2011; 79: 2964-2973.
[21] Pasparakis M, Alexopoulou L, Episkopou V and Kollias G. Immune and inflammatory responses in TNF alpha-deficient mice: a critical requirement for TNF alpha in the formation of primary B cell follicles, follicular dendritic cell networks and germinal centers, and in the maturation of the humoral immune response. J Exp Med 1996; 184: 1397-1411.
[22] Husby G, Gran JT and Johannessen A. Epidemiological and genetic aspects of IgM rheumatoid factors. Scand J Rheumatol Suppl 1988; 75: 213-218.
[23] Metzger DW, Buchanan JM, Collins JT, Lester TL, Murray KS, Van Cleave VH, Vogel LA and Dunnick WA. Enhancement of humoral immunity by interleukin-12. Ann N Y Acad Sci 1996; 795: 100-115.
[24] van Schaardenburg D, Lagaay AM, Otten HG and Breedveld FC. The relation between class-specific serum rheumatoid factors and age in the general population. Br J Rheumatol 1993; 32: 546-549.
[25] Jacobsson LT, Knowler WC, Pillemer S, Hanson RL, Pettitt DJ, Nelson RG, del Puente A, McCance DR, Charles MA and Bennett PH. Rheumatoid arthritis and mortality. A longitudinal study in Pima Indians. Arthritis Rheum 1993; 36: 1045-1053.
[26] Newkirk MM, LePage K, Niwa T and Rubin L. Advanced glycation endproducts (AGE) on IgG, a target for circulating antibodies in North American Indians with rheumatoid arthritis (RA). Cell Mol Biol (Noisy-le-grand) 1998; 44: 1129-1138.
[27] Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, Bain V, Heathcote J, Zeuzem S, Trepo C and Albrecht J. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). Lancet 1998; 352: 1426-1432.
[28] Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M and Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001; 358: 958-965.
[29] Yu ML, Dai CY, Huang JF, Chiu CF, Yang YH, Hou NJ, Lee LP, Hsieh MY, Lin ZY, Chen SC, Wang LY, Chang WY and Chuang WL. Rapid virological response and treatment duration for chronic hepatitis C genotype 1 patients: a randomized trial. Hepatology 2008; 47: 1884-1893.
[30] Newkirk MM. Rheumatoid factors: host resistance or autoimmunity? Clin Immunol 2002; 104: 1-13.