Long-term safety of anti-TNF agents on the liver of patients with spondyloarthritis and potential occult hepatitis B viral infection: an observational multicentre study

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Abstract

Objective

The aim of the study was to retrospectively evaluate the long-term safety profile of anti-tumour necrosis factor (TNF)-α agents on the liver of patients with spondyloarthritis (SpA) and a previously resolved hepatitis B virus (HBV) infection.

Methods

Medical records from 992 consecutive outpatients receiving anti-TNF-α therapy between 2007 and 2015 were retrospectively reviewed. HBV infection was assessed evaluating HBV surface antigen (HBsAg), antibodies to HBsAg (anti-HBs), antibodies to hepatitis B core (anti-HBc), and HBV-DNA levels. In patients with a previously resolved HBV infection, serum levels of aminotransferase (AST/ALT) were also assessed every three months, while HBsAg and HBV-DNA every six months.

Results

We identified 131 consecutive patients (70 males, 61 females) with SpA and resolved HBV infection. At baseline none of the patients were positive for HBV-DNA, and AST/ALT levels were within the normal range with no subsequent increase during the observational treatment period. None received antiviral therapy prior to or during anti-TNF drug administration. At the end of the follow-up period (75.50±33.37 months) no viral reactivation was observed in anti-HBc positive patients, regardless of anti-HBs positivity. During the whole follow-up, HBV-DNA was undetectable in all patients, HBsAg remained negative, and it was not necessary to discontinue biologic therapy because of liver damage.

Conclusion

Our results confirm that pre-emptive antiviral prophylaxis may not be necessary routine, but strict monitoring for AST/ALT levels, as well as for changes in HBV serology and HBV-DNA remain necessary and seem a realistic and cost-effective approach to identify early viral reactivation.

Key words

spondyloarthritis, hepatitis B virus, tumour necrosis factor inhibitors, drug safety

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Introduction

Drugs inhibiting tumour necrosis factor (TNF)-α biological activity represent an evolving class of medications that have revolutionised the treatment of chronic inflammatory diseases with rheumatologic, dermatologic and gastrointestinal involvement since their introduction over 15 years ago, allowing a disease control that was once unattainable, and strikingly improving the course of many of these diseases and patients' outcome (1-3).

On the other hand, it is known that therapy with TNF-α blockers can be associated with an increased risk of *de novo* infections and chronic or latent viral reactivation. Indeed, TNF-α is a proinflammatory cytokine that plays a key-role in the host immune responses to several types of infections (4). Elevated levels of TNF-α are seen in both serum and hepatocytes of patients with chronic hepatitis B virus (HBV) infection and are secreted by HBV-specific cytotoxic T lymphocytes. In particular, TNF-α is involved in controlling or clearing HBV from infected hepatocytes by stimulating HBV-specific T cell response, which might destroy virus-infected hepatocytes (5).

Therefore, inhibition of TNF-α enables the virus to evade host antiviral defense mechanisms, and TNF-α blockers are likely to promote HBV replication, reactivation, and potentially fatal liver failure in patients with concurrent HBV infection.

A growing number of papers have raised concerns about the use of TNF-α blockers in chronic HBV carrier rheumatologic patients, though only a few have addressed whether their use is safe in potential HBV occult infection. Moreover, most of these studies have been focused on patients affected by rheumatoid arthritis (RA), and very few data are available for patients affected by spondyloarthritis (SpA).

The American College of Rheumatology has recently recommended that for a patient with natural immunity from prior exposure to hepatitis B, RA treatment should be the same as that of unexposed patients, as long as the patient's viral load is monitored regularly, every 6–12 months (6).

The aim of our study was to assess long-term safety of anti-TNF-α agents in SpA patients with a past HBV infection by assessing the frequency of viral reactivation or serological reversion.

Patients and methods

This is an observational multicentre study carried out in centres specialised in the diagnosis and treatment of chronic inflammatory autoimmune diseases. Medical records from 992 consecutive outpatients receiving anti-TNF-α therapy because of active SpA between 2007 and 2015 were retrospectively reviewed for the presence of HBV infection by a serological evaluation, including hepatitis B surface antigen (HBsAg), antibodies to HBsAg (anti-HBs), antibodies to hepatitis B core (anti-HBc), and HBV-DNA levels. Anti-TNF agents employed were: infliximab, a chimeric anti-TNF-α monoclonal antibody; etanercept, a fusion protein of the TNF receptor and the Fc region of human IgG_1; adalimumab, a fully humanised monoclonal antibody against human TNF-α; golimumab, a fully human anti-TNF-α monoclonal antibody. Inclusion criteria for this analysis were as follows: subjects ≥18 years of age, diagnosis of SpA, current treatment with an anti-TNF-α agent, and seropositivity for past HBV infection (HBsAg negativity and HBcAb ± anti-HBs positive results).

Information was collected on demographic data, disease duration, use of anti-TNF agents, disease-modifying anti-rheumatic drugs (DMARDs), corticosteroids, HBV infection status and eventual comorbidities.

We aimed to evaluate the safety profile of anti-TNF-α agents by evaluating HBV reactivation or reversion in patients with SpA and resolved or occult hepatitis B.

The study endpoints were: i) the number of patients with increased aminotransferase levels throughout the study period; ii) variations in serum HBsAg levels; iii) the number of patients with increased serum HBV-DNA levels during anti-TNF-α therapy; iv) the number of patients needing antiviral therapy while on anti-TNF-α treatment; v) the frequency of therapy dis-

continuation because of viral infection during TNF-α inhibition.

The patients were recorded every three months for clinical indices of disease activity, use of drugs, and aminotransferase levels. Furthermore, assessment for HBV reactivation (defined as the serum appearance of either HBsAg or HBV-DNA) was carried out every six months.

Serum alanine (ALT) and aspartate aminotransferase (AST) were determined with standard laboratory methods. HBV markers were identified by the following techniques: HBsAg, anti-HBs, anti-HBc by CLIA [Chemiluminescence Immuno Assay] and the HBV-DNA by real time-PCR assay. The study was approved by the local ethics committee (Azienda Ospedaliera Universitaria Senese; Code: SPASI_2015 Study).

Results

We identified 131 consecutive Italian patients with SpA and resolved hepatitis B (70 males, 61 females) out of 992 subjects treated with anti-TNF-α agents and evaluated for HBV markers; further 84 patients with positive findings of HBsAg or HBV DNA or only anti-HBs at baseline and 25 patients with missing data on HBV status were excluded. Among selected patients, 131 were positive for anti-HBc and 109 were positive for both anti-HBc and anti-HBs (83%). No patient was positive for HBV-DNA at baseline. Thirty of 131 patients (22.8%) had been previously treated with other anti TNF agents.

The mean age of the patients was 60.63±9.59 years, and their mean disease duration was 98.64±42.60 months (range 24–300). Among the 131 patients, 55 (42%) suffered from ankylosing spondylitis, 2 (1.5%) were diagnosed with radiographic axial SpA, and 74 (56.5%) with peripheral SpA. Psoriasis was detected in 26 (19.8%) patients, inflammatory bowel diseases in 9 (6.8%), and uveitis in a further 9 (6.8%) subjects. Table I provides data about previously administered treatments and current anti-TNF-α regimen in all enrolled patients. Table II summarises comorbidities found in our SpA patients.

The results of aminotransferases were within the normal range at baseline and during the whole follow-up; similarly, HBV-DNA was undetectable throughout the study period, HBsAg remained negative, and no patient received antiviral therapy prior to or during anti-TNF treatment.

At the end of the follow-up (mean period: 75.50±33.37 months, range 6–144 months) no case of viral reactivation was observed in anti-HBc positive patients, regardless of anti-HBs positivity, and it was not necessary to stop biologic therapy because of viral infection.

Table I. Previously administered treatments, current anti-TNF regimen, and concomitant anti-rheumatic therapies in the 131 patients included in the study.

Previous DMARDs (*)	n. (%)
Methotrexate (MTX)	74 (56)
Cyclosporine (CsA)	8 (6)
Sulfasalazine (SSZ)	11 (8.4)
Leflunomide (LEF)	6 (4.5)
Hydroxychloroquine	2 (1.5)
Gold salts	1 (0.75)
Never DMARDs	40 (30)
Type of current anti-TNF agent (*) and concomitant DMARDs	
Etanercept	64 patients (49%) (29 in monotherapy, 31 with MTX, 3 with SSZ, 1 with CsA)
Infliximab	32 patients (24%) (18 as monotherapy, 10 with MTX, 3 with SSZ, 1 with CsA)
Adalimumab	31 patients (24%) (16 in monotherapy, 12 with MTX, 2 with LEF, 1 with CsA)
Golimumab	4 patients (3%) (3 with MTX, 1 as monotherapy)
n. of anti-TNF agents used for each patient (%)	
1 agent	131 pts (100)
2 agents	23 pts (17.5)
3 agents	7 pts (5.3)
Other concomitant anti-rheumatic treatments (%)	
Glucocorticoids (prednisone 5-12.5/day mg or equivalent)	51 (39%)

DMARDs: disease-modifying anti-rheumatic drugs; n.: number; TNF: tumour necrosis factor. Other acronyms are specified in the table when used for the first time.

Discussion

The present study evaluated the clinical course of patients with a past HBV infection and SpA treated with anti-TNF-α agents for a mean observation period of 75.50±33.37 months (range 6–144), showing that no patient experienced reactivation of viral replication.

Patients who experienced HBV infection are also called occult carriers: they have HBcAb ± anti-HBs, undetectable serum HBV-DNA, and HBsAg negativity as well as normal ALT levels. However, a subgroup of patients may present persistent viral genomes in the liver tissue at very low levels (7, 8). The concomitant presence of anti-HBc and anti-HBs indicates the persistence of a strong immune response with a considerably lower risk of reactivation. Nevertheless, the effective containment of the infection may be adversely affected by immunosuppressive treatment (9-12).

To date, data about the risk of HBV reactivation in rheumatologic patients treated with anti-TNF agents are still limited and contradictory. In particular, during the past years the rate of reactivation has been found to range between 1.7 and 10% of patients presenting a past HBV infection and treated with anti-TNF agents because of a peculiar rheumatologic disease (13-20). Notably, the rate of reactivation was found lower in anti-HBc positive patients than in HBsAg positive carriers (14), and higher among patients with a low titer of anti-HBs at baseline (21). However, viral reactivation often resolved

Table II. Comorbidities identified in the cohort of patients evaluated in our study.

Type of involvement	Comorbidities	n. (%)
Cardiovascular	Hypertension	39 (29.7)
	Dyslipidaemia	13 (10)
	Ischaemic heart disease	8 (6)
	Hypertensive heart disease	5 (3.8)
	Hypercholesterolaemia	3 (2.3)
Endocrine-metabolic	Diabetes mellitus	10 (7.6)
	Fatty liver disease	5 (3.8)
	Multinodular thyroid goiter	1 (0.75)
	Autoimmune thyroid disease	1 (0.75)
Gastrointestinal	Gastroesophageal reflux disease	3 (2.3)
	Gastritis related to Helicobacter pylori	1 (0.75)
	Oesophagitis	1 (0.75)
	Gastroduodenitis	1 (0.75)
Respiratory	Chronic obstructive pulmonary disease	1 (0.75)
	Asthma	1 (0.75)
Other	Osteoporosis	6 (4.6)
	Thalassemic trait	2 (1.5)
	Anaemia	1 (0.75)
	Obesity	1 (0.75)
	Kidney failure	1 (0.75)

spontaneously in such patients, without any antiviral prophylaxis (15, 18, 20).

In our retrospective analysis, no cases of HBV reactivation or serological reversion were recorded during a mean period of 75 months, thus supporting the evidence of an excellent long-term liver safety profile for anti-TNF-α agents in patients with a past HBV infection. Nevertheless, as for other studies (22-26), in our cohort of patients most of the potential occult carriers were also anti-HBs positive, perhaps influencing the lack of HBV reactivation (27, 28). Moreover, as previously suggested (25, 29), the absence of viral reactivation could be related to the low doses of corticosteroids administered in anti-HBc positive patients.

As regards the level of aminotransferases, a significant higher risk of persistent abnormal liver function has been highlighted in rheumatologic patients with a previous HBV infection who received anti-TNF-α agents in comparison with anti-HBc negative subjects (30). On this issue, we recently assessed the safety of long-term anti-TNF-α therapy in 146 rheumatologic patients with resolved HBV infection: we did not observe any HBV reactivation, though the prevalence of elevated aminotransferases was significantly higher in patients with previous HBV infection compared to controls, but not for levels greater than two times the upper reference limit. This finding was probably due to the significant older age of anti-HBc positive patients, possibly associated with an increased number of comorbidities and liver susceptibility rather than immunosuppression (31).

In contrast to data reported so far, other studies did not observe any sign of HBV reactivation during anti-TNF-α therapy administered for a mean period lasting between 12 months and six years (22-29, 32-38). In accordance with these findings we also confirmed the substantial safety of TNF-α blockers in a previous study on 12 Italian patients with past HBV infection who did not receive any prophylaxis during a mean anti-TNF-α treatment of 41 months (39).

A further important issue is represented by the significant decrease of anti-HBs titer during anti-TNF-α therapy in resolved HBV infection or vaccinated patients (21-24, 32). This may be explained with a decreased frequency of circulating CD27 memory B cells in patients undergoing TNF-α inhibition (40) and with the important role played by TNF-α in the acquisition of anti-HBs antibodies after HBV vaccination (41). On this last point, Tamori et al found that anti-HBs level remained high when anti-HBs titers were elevated at baseline; conversely, anti-HBs level decreased significantly in patients with middle and low anti-HBs titers at baseline (24). Anyhow, the decrease of anti-HBs after anti-TNF-α therapy represents a potential risk for HBV infection, and a significant lowering might become relevant during a long-term treatment (24). Unfortunately, we did not monitor anti-HBs levels during follow-up, and evaluation of anti-HBs antibodies as a monitoring marker for HBV reactivation is an intriguing aim for future studies.

Our study has some limitations: firstly, this is a retrospective study: therefore, some unrecognised bias might have been introduced. Secondly, it would have been interesting to monitor anti-HBs levels during the follow-up, but sadly these data were not available.

Conclusions

Optimal management and outcome of patients with past HBV infection is still unclear and remains controversial especially because of the paucity of studies with an adequately long-term follow-up. In this context, our experience suggests that routinely pre-emptive antiviral prophylaxis may not be necessary in HBsAg-negative/anti-HBc-positive patients undergoing TNF-α blockers, especially when anti-HBs antibodies are also present. Conversely, regular AST/ALT dosage and HBV-DNA monitoring seem a correct, realistic and cost-effective approach aimed at identifying early viral reactivation, whose occurrence is low, but not negligible.

References

1. CARROLL MB, FORGIONE MA: Use of tumor necrosis factor alpha inhibitors in hepatitis B surface antigen-positive patients: a literature review and potential mechanisms of action. *Clin Rheumatol* 2010; 29: 1021-29.
2. FABBRONI M, CANTARINI L, CASO F *et al*.: Drug retention rates and treatment discontinuation among anti-TNF-α agents in psoriatic arthritis and ankylosing spondylitis in clinical practice. *Mediators Inflamm* 2014; 2014: 862969.
3. GIOVANNINI L, ORLANDI M, LODATO C *et al*.: One year in review 2015: spondyloarthritis. *Clin Exp Rheumatol* 2015; 33: 769-78.
4. BRADLEY JR: TNF-mediated inflammatory disease. *J Pathol* 2008; 214: 149-60.
5. GANEM D, PRINCE AM: Hepatitis B virus infection-natural history and clinical consequences. *N Engl J Med* 2004; 350: 1118-29.
6. SINGH JA, SAAG KG, BRIDGES SL JR, *et al*.: 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid

Arthritis. *Arthritis Rheumatol* 2016; 68: 1-26.
7. RAIMONDO G, POLLICINO T, CACCIOLA I, SQUADRITO G: Occult hepatitis B virus infection. *J Hepatol* 2007; 46:160-70.
8. ZOULIM F: New insight on hepatitis B virus persistence from the study of intrahepatic viral cccDNA. *J Hepatol* 2005; 42: 302-08.
9. LUNEL-FABIANI F, MASSON C, DUCANCELLE A: Systemic diseases and biotherapies: understanding, evaluating, and preventing the risk of hepatitis B reactivation. *Joint Bone Spine* 2014; 81: 478-84.
10. ITO S, NAKAZONO K, MURASAWA A *et al*.: Development of fulminant hepatitis B (precore variant mutant type) after the discontinuation of low-dose methotrexate therapy in a rheumatoid arthritis patient. *Arthritis Rheum* 2001; 44:339-42.
11. GWAK GY, KOH KC, KIM HY: Fatal hepatic failure associated with hepatitis B virus reactivation in a hepatitis B surface antigen-negative patient with rheumatoid arthritis receiving low dose methotrexate. *Clin Exp Rheumatol* 2007; 25: 888-89.
12. WATANABE K, TAKASE K, OHNO S, IDEGUCHI H, NOZAKI A, ISHIGATSUBO Y: Reactivation of hepatitis B virus in a hepatitis B surface antigen-negative patient with rheumatoid arthritis treated with methotrexate. *Mod Rheumatol* 2012; 22: 470-73.
13. URATA Y, UESATO R, TANAKA D *et al*.: Prevalence of reactivation of hepatitis B virus replication in rheumatoid arthritis patients. *Mod Rheumatol* 2011; 21: 16-23.
14. PÉREZ-ALVAREZ R, DÍAZ-LAGARES C, GARCÍA-HERNÁNDEZ F *et al*.: Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. *Medicine* (Baltimore) 2011; 90: 359-71.
15. MORI S: Past hepatitis B virus infection in rheumatoid arthritis patients receiving biological and/or nonbiological disease-modifying antirheumatic drugs. *Mod Rheumatol* 2011; 21: 621-27.
16. LEE YH, BAE SC, SONG GG: Hepatitis B virus (HBV) reactivation in rheumatic patients with hepatitis core antigen (HBV occult carriers) undergoing anti-tumor necrosis factor therapy. *Clin Exp Rheumatol* 2013; 31: 118-21.
17. CANTINI F, BOCCIA S, GOLETTI D *et al*.: HBV reactivation in patients treated with antitumor necrosis factor-alpha (TNF-α) agents for rheumatic and dermatologic conditions: a systematic review and meta-analysis. *Int J Rheumatol* 2014; 2014: 926836.
18. NAKAMURA J, NAGASHIMA T, NAGATANI K, YOSHIO T, IWAMOTO M, MINOTA S: Reactivation of hepatitis B virus in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs. *Int J Rheum Dis* 2016; 19: 470-5.
19. XUAN D, YU Y, SHAO L, WANG J, ZHANG W, ZOU H: Hepatitis reactivation in patients with rheumatic diseases after immunosuppressive therapy - a report of long-term follow-up of serial cases and literature review. *Clin Rheumatol* 2014; 33: 577-86.
20. MORI S, FUJIYAMA S: Hepatitis B virus reactivation associated with antirheumatic therapy: Risk and prophylaxis recommendations. *World J Gastroenterol* 2015; 21: 10274-89.
21. KATO M, ATSUMI T, KURITA T *et al*.: Hepatitis B virus reactivation by immunosuppressive therapy in patients with autoimmune diseases: risk analysis in Hepatitis B surface antigen-negative cases. *J Rheumatol* 2011; 38: 2209-14.
22. VASSILOPOULOS D, APOSTOLOPOULOU A, HADZIYANNIS E *et al*.: Long-term safety of anti-TNF treatment in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. *Ann Rheum Dis* 2010; 69: 1352-5.
23. LAN JL, CHEN YM, HSIEH TY *et al*.: Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy. *Ann Rheum Dis* 2011; 70: 1719-25.
24. TAMORI A, KOIKE T, GOTO H *et al*.: Prospective study of reactivation of hepatitis B virus in patients with rheumatoid arthritis who received immunosuppressive therapy: evaluation of both HBsAg-positive and HBsAg-negative cohorts. *J Gastroenterol* 2011; 46: 556-64.
25. BIONDO MI, GERMANO V, PIETROSANTI M *et al*.: Lack of hepatitis B virus reactivation after anti-tumour necrosis factor treatment in potential occult carriers with chronic inflammatory arthropathies. *Eur J Intern Med* 2014; 25: 482-4.
26. BALLANTI E, CONIGLIARO P, CHIMENTI MS *et al*.: Use of anti-tumor necrosis factor alpha therapy in patients with concurrent rheumatoid arthritis and hepatitis B or hepatitis C: a retrospective analysis of 32 patients. *Drug Dev Res* 2014; 75: S42-5.
27. ROQUE-AFONSO AM, FERAY C, SAMUEL D *et al*.: Antibodies to hepatitis B surface antigen prevent viral reactivation in recipients of liver grafts from anti-HBC positive donors. *Gut* 2002; 50: 95-9.
28. TAN J, ZHOU J, ZHAO P, WEI J: Prospective study of HBV reactivation risk in rheumatoid arthritis patients who received conventional disease-modifying antirheumatic drugs. *Clin Rheumatol* 2012; 31: 1169-75.
29. CAPORALI R, BOBBIO-PALLAVICINI F, ATZENI F *et al*.: Safety of tumor necrosis factor alpha blockers in hepatitis B virus occult carriers (hepatitis B surface antigen negative/anti-hepatitis B core antigen positive) with rheumatic diseases. *Arthritis Care Res* 2010; 62: 749-54.
30. KIM YJ, BAE SC, SUNG YK *et al*.: Possible reactivation of potential hepatitis B virus occult infection by tumor necrosis factor-alpha blocker in the treatment of rheumatic diseases. *J Rheumatol* 2010; 37: 346-50.
31. BARONE M, NOTARNICOLA A, LOPALCO G *et al*.: Safety of long-term biologic therapy in rheumatologic patients with a previously resolved hepatitis B viral infection. *Hepatology* 2015; 62: 40-6.
32. CHARPIN C, GUIS S, COLSON P *et al*.: Safety of TNF-blocking agents in rheumatic patients with serology suggesting past hepatitis B state: results from a cohort of 21 patients. *Arthritis Res Ther* 2009; 11: R179.
33. CASSANO N, MASTRANDREA V, PRINCIPI M *et al*.: Anti-tumor necrosis factor treatment in occult hepatitis B virus infection: a retrospective analysis of 62 patients with psoriatic disease. *J Biol Regul Homeost Agents* 2011; 25: 285-9.
34. PAPA A, FELICE C, MARZO M *et al*.: Prevalence and natural history of hepatitis B and C infections in a large population of IBD patients treated with anti-tumor necrosis factor-α agents. *J Crohns Colitis* 2013; 7: 113-9.
35. GIARDINA AR, FERRARO D, CICCIA F *et al*.: No detection of occult HBV-DNA in patients with various rheumatic diseases treated with anti-TNF agents: a two-year prospective study. *Clin Exp Rheumatol* 2013; 31: 25-30.
36. LAURENTI R, GIOVANNANGELI F, GUBINELLI E *et al*.: Long-term safety of anti-TNF adalimumab in HBc antibody-positive psoriatic arthritis patients: a retrospective case series of 8 patients. *Clin Dev Immunol* 2013; 2013: 410521.
37. YE H, ZHANG XW, MU R *et al*.: Anti-TNF therapy in patients with HBV infection - analysis of 87 patients with inflammatory arthritis. *Clin Rheumatol* 2014; 33: 119-23.
38. NAVARRO R, CONCHA-GARZÓN MJ, CASTAÑO C, CASAL C, GUIU A, DAUDÉN E: Outcome of patients with serology suggestive of past hepatitis B virus infection during antitumor necrosis factor therapy for psoriasis. *Int J Dermatol* 2014; 53: 909-11.
39. GIANNITTI C, SEBASTIANI GD, MANGANELLI S, GALEAZZI M: Safety of anti-tumor necrosis factor agents in rheumatic potential carriers of occult hepatitis B virus. *J Rheumatol* 2011; 38: 780-1.
40. ANOLIK JH, RAVIKUMAR R, BARNARD J *et al*.: Cutting edge: anti-tumor necrosis factor therapy in rheumatoid arthritis inhibits memory B lymphocytes via effects on lymphoid germinal centers and follicular dendritic cell networks. *J Immunol* 2008; 180: 688-92.
41. VELU V, SARAVANAN S, NANDAKUMAR S *et al*.: Relationship between T-lymphocyte cytokine levels and sero-response to hepatitis B vaccines. *World J Gastroenterol* 2008; 14: 3534-40.