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Asymptomatic reactivation of hepatitis B virus after prolonged treatment with etanercept

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Abstract

Etanercept is an anti-tumor necrosis factor α (anti-TNFα) drug used for treating immunomediated inflammatory diseases. It is least associated with hepatitis B virus (HBV) reactivation. We present a 71-year-old man with psoriasis refractory to phototherapy and acitretin, which led to etanercept monotherapy. Before anti-TNFα treatment, past contact with HBV was elicited; antibodies to HBc and HBs were positive whereas HBsAg was negative. Seven years after treatment initiation, while the patient was completely asymptomatic, a transaminase elevation was found and a reactivation of HBV was documented, with a high viral load of the virus. He started entecavir therapy and, after a 14-month follow-up, the viral load is still detectable at a low level, as well as HBsAg. We emphasize the late and asymptomatic reactivation of HBV associated with soluble anti-TNFα monotherapy. This case reinforces the importance of current recommendations for periodic monitoring of viral load and HBV markers in all patients that have had prior contact with HBV (positive anti-HBc), with or without indication for treatment of HBV (HBsAg and HBV-DNA negative).

Keywords: hepatitis B virus, hepatitis B virus reactivation, etanercept, anti-TNFα, psoriasis

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Introduction

Hepatitis B virus (HBV) reactivation associated with anti-tumor necrosis factor α (anti-TNFα) drugs for the treatment of immunomediated inflammatory diseases is rarely reported in the absence of surface hepatitis B antigen (HBsAg) (1). Etanercept, a soluble anti-TNFα, is the least associated with HBV reactivation (2). Clinical hepatitis reactivation has a wide spectrum, ranging from asymptomatic cases to potentially fatal fulminant hepatic failure (3, 4). In 2015, the European Centre for Disease Prevention and Control (ECDC) estimated the prevalence of HBV infection as 0.9%; in Portugal, it is estimated that 0.4 to 1.0% of the population is positive for HBsAg (5). The highest published reported incidence of HBV reactivation in patients with past HBV infection is 5%, including one fatal case due to liver failure (6). Therefore it is considered safe, and the European Association for the Study of the Liver (EASL) (7) recommends that patients with past HBV infection (anti-HBc positive and anti-HBs positive) in the absence of HBsAg (and negative for HBV-DNA) should start anti-TNFα therapy with clinical and analytical monitoring and serial HBV-DNA testing (3, 8).

Case report

We present the case of a 71-year-old man followed at the Dermatology Outpatient Clinic since 2002 due to plaque psoriasis. He started on phototherapy and acitretin with insufficient response (Psoriasis Area and Severity Index [PASI] 11.4), and so etanercept 50 mg per week was prescribed in 2010, with PASI 0 at 20 weeks' follow-up. Before anti-TNFα treatment, past contact with HBV was elicited: antibodies to HBc and HBs (quantified titer: 29.30 IU/l) were positive with HBsAg being negative; anti-HIV and anti-HCV were both negative (Table 1). He has been on etanercept continuously since 2010, treatment was interrupted for 2 months in 2015, with recurrence of psoriatic lesions, and he resumed treatment again with efficacy. In October 2015, HBV screening elicited the same serological markers.

In September 2017, asymptomatic transaminase elevation was found (alanine aminotransferase [ALT] 99 IU/l, aspartate aminotransferase [AST] 66 IU/l), and etanercept was immediately stopped (PASI 0 at this date) on suspicion of toxicity. On reevaluation in November 2017, transaminases were still on the rise (ALT 431 IU/l, AST 220 IU/l), HBsAg became positive, and a high viral load of HBV was found (16,000,000 IU/ml). He was sent to the Infectious Diseases Clinic in December 2017 and on the same day started entecavir. The patient remained completely asymptomatic, without hyperbilirubinemia or coagulopathy. The HBV was genotype A, without detected resistances.

After 1 month of entecavir therapy, the viral load was 11,871 IU/ml (a decrease of three logarithms) and transaminases were

Table 1 | Evolution of hepatitis B virus (HBV) serological status.

	Mar 2010	Oct 2015	Nov 2017	Jan 2018	Mar 2018	Jun 2018	Oct 2018	Nov 2018	Mar 2019
HBsAg (NR ‹ 0.9 – R › 1.1)	0.37	0.20	**217.40**	–	–	–	–	–	–
Anti-HBc (NR ‹ 0.9 – R › 1.1)	**7.27**	**9.40**	**8.70**	–	–	–	–	–	–
Anti-HBs (IU/l)	**29.30**	**2.29**	**79.99**	–	–	–	**4.44**	–	–
Anti-HBe (NR ‹ 0.9 – R › 1.1)	–	–	0.00	–	–	–	–	–	–
HBeAg (NR ‹ 0.9 – R › 1.1)	–	–	**982.5**	–	–	–	–	–	–
HBV-DNA	–	–	**16,000,000 UI/ml 7.20 log^{10}**	**11,871 UI/ml 4.07 log^{10}**	**626 UI/ml 2.80 log^{10}**	**262 UI/ml 2.42 log^{10}**	**315 UI/ml 2.50 log^{10}**	**157 UI/ml 2.20 log^{10}**	**258 UI/ml 2.41 log^{10}**

NR = non-reactive, R = reactive, IU = international units.

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within normal values. At 3 months of therapy, he had HBV-DNA of 626 IU/ml and abdominal ultrasonography was irrelevant except for steatosis. At 14 months of therapy, viral load is still detectable at a low level as well as HBsAg. Consequently, the patient will maintain entecavir even without immunosuppression. He remained asymptomatic during the entire follow-up period. At 17 months' follow-up since etanercept was stopped, he is only being treated with topical medications for psoriasis and has a PASI score of 2.

Discussion

We emphasize the late and asymptomatic reactivation of HBV associated with soluble anti-TNFα monotherapy in a 71-year-old patient suffering from psoriasis. In our specific case, unfortunately, the HBV viral load prior to the start of etanercept was not measured.

The majority of publications in this field are in the scope of rheumatological diseases. Tamori et al., for example, designed a prospective study to clarify the prevalence of HBV reactivation in rheumatoid arthritis patients receiving long-term immunosuppressive therapy. Among 42 HBsAg-negative and anti-HBc-positive patients that received anti-TNFα therapy, no HBV reactivation occurred (9). More recently, Lee et al. published an extensive review of 269 cases of HBsAg-negative and anti-HBc-positive patients with rheumatic diseases treated with etanercept, which resulted in seven HBV reactivations (2.6%), but the majority of patients were also treated with a disease-modifying anti-rheumatic drug besides etanercept (10). To our knowledge, this is the first report of HBV reactivation in a patient receiving etanercept monotherapy for treatment of plaque psoriasis with a negative HBsAg prior to treatment (1, 6, 11, 12).

This case reinforces the importance of current recommendations for periodic monitoring of viral load and HBV markers in all patients that had prior contact with HBV (positive anti-HBc), with or without indication for treatment of HBV (HBsAg and HBV-DNA negative). A patient with a positive viral load followed by a rise in transaminases may avoid clinical hepatitis if appropriately treated. This monitoring is essential for the early recognition of viral reactivation, which may be absolutely asymptomatic or severe enough to cause death (3, 4, 7, 13). After reactivation of HBV, the therapy for psoriasis may be compromised.

References

1. Pauly MP, Tucker LY, Szpakowski JL, Ready JB, Baer D, Hwang J, et al. Incidence of Hepatitis B virus reactivation and hepatotoxicity in patients receiving long-term treatment with tumor necrosis factor antagonists. Clin Gastroenterol Hepatol. 2018;16:1964–73.
2. Baddley JW, Cantini F, Goletti D, Gómez-Reino JJ, Mylonakis E, San-Juan R, et al. ESCMID Study group for infections in compromised hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (soluble immune effector molecules [I]: anti-tumor necrosis factor-α agents). Clin Microbiol Infect. 2018;24:S10–20.
3. Abramson A, Menter A, Perrillo R. Psoriasis, hepatitis B, and the tumor necrosis factor-alpha inhibitory agents: a review and recommendations for management. J Am Acad Dermatol. 2012;67:1349–61.
4. Murdaca G, Spanò F, Contatore M, Guastalla A, Penza E, Magnani O, et al. Infection risk associated with anti-TNF-α agents: a review. Expert Opin Drug Saf. 2015;14:571–82.
5. Direcao Geral da Saude. Programa Nacional para as Hepatites Virais 2017. [Internet]. Portugal. Available from www.dgs.pt/portal-da-estatistica-da-saude/diretorio-deinformacao/diretorio-de-informacao/por-serie-869733-pdf.aspx?v=11736b14-73e6-4b34-a8e8-d22502108547.
6. Pérez-Alvarez R, Díaz-Lagares C, García-Hernández F, Lopez-Roses L, Brito-Zerón P, Pérez-de-Liz M, 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.
7. Lampertico P, Agarwal K, Berg T, Buti M, Janssen HLA, Papatheodoridis G, et al. EASL 2017 Clinical practice guidelines on the management of Hepatitis B virus infection. J Hepatol. 2017;67:370–98.
8. Viganò M, Degasperi E, Aghemo A, Lampertico P, Colombo M. Anti-TNF drugs in patients with Hepatitis B or C virus infection: safety and clinical management. Expert Opin Biol Ther. 2012;12:193–207.
9. Tamori A, Koike T, Goto H, Wakitani S, Tada M, Morikawa 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.
10. 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.
11. Sanz-Bueno J, Vanaclocha F, García-Doval I, Torrado R, Carretero G, Daudén E, et al. Risk of reactivation of Hepatitis B virus infection in psoriasis patients treated with biologics: a retrospective analysis of 20 cases from the BIOBADADERM database. Actas Dermosifiliogr. 2015;106:477–82.
12. Clarke WT, Amin SS, Papamichael K, Feuerstein JD, Cheifetz AS. Patients with core antibody positive and surface antigen negative Hepatitis B (anti-HBc+, HBsAg-) on anti-TNF therapy have a low rate of reactivation. Clin Immunol. 2018;191:59–62.
13. Nast A, Gisondi P, Ormerod AD, Saiaq P, Smith C, Spuls PI, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris—Update 2015—Short version—EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol. 2015;29:2277–94.