Infliximab in Ankylosing Spondylitis Associated With Chronic Hepatitis B Infection. Role of Lamivudine Therapy

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Anti-tumor necrosis factor-a (TNF) therapy has been associated with reactivation of hepatitis B virus infection. Case reports have suggested the concomitant need of lamivudine treatment in patients with HBV infection treated with antiTNFα agents. We describe a case of ankylosing spondylitis with positive HBV surface antigen (HBsAg) treated with infliximab and lamivudine. Clinical response was excellent but when lamivudine therapy was stopped, reactivation of replication viral occurred. After the reintroduction of lamivudine, viral replication was controlled and liver function tests were normalized. Preventive long-term lamivudine therapy is mandatory when anti-TNFα therapy is maintained in patients with chronic HBV infection.

Key words: Ankylosing spondylitis. Hepatitis B. Infliximab.
Since 1996 he had received treatment with sulfasalazine and different non-steroidal anti-inflammatory (NSAID) drugs, in spite of which SA was persistently active, with a BASDAI of 6 (0-10), BASFI of 50 (0-100), nocturnal pain of 7 (0-10), and C-reactive protein (CRP) of 16.3 mg/dL.

In April 2004 the determination of the HBV viral DNA load was 237 copies/mL. Before receiving infliximab he began treatment with lamivudin, 100 mg day. In November 2004, the viral load was below 200 copies/mL (Table). The patient signed an informed consent and began treatment with infliximab, in April 2005 at a dose of 5 mg/kg on weeks 0, 2, 6, and afterward every 8 weeks. On week 12 he had improvement on the BASDAI of 70% and the CRP normalized. During follow-up, beginning in June 2005, after receiving 4 infusions of infliximab, there was an increase in viral replication, with a concomitant increase of transaminases. The patient accepted abandoning lamivudin treatment 4 weeks before. Treatment with lamivudin was reinstated, with a temporal suspension of infliximab and periodic controls of viral replication and transaminase concentrations. The patient continued treatment with infliximab and lamivudin, with a good control of SA symptoms (BASDAI <2), normal transaminases, and control of viral replication (Table).

### Discussion

Published data indicated that the administration of infliximab in patients with chronic HBV infection leads to an increased risk of viral reactivation, but that this risk is potentially controllable with lamivudin concomitant treatment.

Lamivudin is a retroviral inhibitor of reverse transcriptase which has shown its effectiveness for the control of viral reactivation in patients with chronic HBV infection who receive chemotherapy for oncological neoplasia and organ transplant.12-14 Although the pathogenic mechanisms are not entirely clear, experimental in vitro studies and animal models have shown that TNF inhibits HBV replication and stimulates T cell specific responses, which would imply the elimination of viruses from infected hepatocytes.15-17 These findings lead us to think that the administration of TNFα antagonists would increase the expression of viral antigens and the reactivation of viral replication.

Several cases of chronic infection with HPV and infliximab treatment for Crohn's disease, spodyloarthritis, and rheumatoid arthritis have been reported. Because the use of infliximab in Crohn's disease is limited, in many cases, to 3 doses, we will discuss mainly rheumatic diseases which require the continued administration of infliximab.

Oniankitan et al9 communicated a case of SA with chronic HBV infection treated with infliximab and methotrexate for 1 year without deterioration of liver function. In this case, 1 year before receiving infliximab, the patient had been treated with lamivudin and viral replication remained stable. Wendling et al8 published another case of SA with chronic HBV infection who received methotrexate and infliximab and showed a good therapeutic response. During follow-up, transaminases increased, as did the viral replication. Lamivudin was begun 4 months later and transaminases returned to normal levels and the viral load was undetectable. Ostuni et al10 communicated a case of rheumatoid arthritis and HBV infection which developed acute hepatitis and who, upon suspending treatment and starting lamivudin showed normalization of transaminase levels and control of viral replication. Our case confirms these findings. In addition, our case exemplifies that while treatment with lamivudin is maintained; replication is controlled, increasing rapidly upon suspension and reinstatement leads back to the initial effect. An additional problem is the possible appearance of resistance that occurs with prolonged use of lamivudin, something that has been seen in transplant patients.18,19 All of these questions require controlled studies and larger cohorts in order to be answered.

Until more data is available, it seems reasonable to recommend that: a) a serological HBV panel must be documented in all patients who are candidates to receive immunosuppressants in general and anti-TNFα in particular, and in those patients who have not been immunized, insuring that this is done; b) if the patient is HBsAg positive, treatment with lamivudin must be started and control of viral replication achieved before using anti-TNFα therapy; c) if the patient is HBsAg negative and anti-HBc positive, monthly follow-up of HBsAg must

<table>
<thead>
<tr>
<th>Date</th>
<th>ALT/AST, U/mL</th>
<th>Viral DNA, Copies/mL</th>
<th>Concomitant Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 2004</td>
<td>28/19</td>
<td>237</td>
<td>Lamivudin</td>
</tr>
<tr>
<td>November 2004</td>
<td>31/18</td>
<td>&lt;200</td>
<td>Lamivudin</td>
</tr>
<tr>
<td>April 2005</td>
<td>20/18</td>
<td>397</td>
<td>Lamivudin</td>
</tr>
<tr>
<td>June 2005</td>
<td>21/17</td>
<td>10 400</td>
<td>Infliximab</td>
</tr>
<tr>
<td>August 2005</td>
<td>27/21</td>
<td>284 000</td>
<td>Lamivudin</td>
</tr>
<tr>
<td>October 2005</td>
<td>162/65</td>
<td>38 900</td>
<td>Lamivudin</td>
</tr>
<tr>
<td>December 2005</td>
<td>61/33</td>
<td>18 300</td>
<td>Lamivudin + infliximab</td>
</tr>
<tr>
<td>March 2006</td>
<td>37/23</td>
<td>21 100</td>
<td>Lamivudin + infliximab</td>
</tr>
<tr>
<td>June 2006</td>
<td>41/21</td>
<td>5460</td>
<td>Lamivudin + infliximab</td>
</tr>
<tr>
<td>October 2006</td>
<td>24/15</td>
<td>13 100</td>
<td>Lamivudin + infliximab</td>
</tr>
</tbody>
</table>
be carried out and if it becomes positive, install lamivudin
treatment. 

\( b \) once treatment has been installed, a strict
control of ALT and HBV DNA must be followed (every
4-8 weeks) at least for 3 months after the last dose of

\( c \) if a viral reactivation occurs, resistance
and the possibility of sing another agent, such as adenofir,
must be contemplated.

References

1. Peterson JR, Hsu FC, Simkin PA, Wener MH. Effect of tumour necrosis
factor alfa antagonists on derum transaminases and viraemia in patients with
2003;62:1078-82.

2. Calabrese LH, Zein N, Vassilopoulos D. Safety of antitumour necrosis factor
therapy in patients with chronic viral infections: hepatitis B, hepatitis C and

3. Ovuni P, Botios C, Punzi L, Sfriso P, Todesco S. Hepatitis B reactivation
in a chronic hepatitis B surface antigen carrier with rheumatoid arthritis

influenzam in a patient with hepatitis B virus-treated for an adult onset Still’s

hepatitis B reactivation following inflixam in Crohn’s disease patients:

therapy in a patient with Crohn’s disease and chronic hepatitis B virus

Influenzam therapy for Crohn’s disease in a patient with chronic hepatitis B.

S, et al. Reactivation of a latent precore mutant hepatitis B virus related
chronic hepatitis during influenza B treatment for severe spondyloarthropathy.

JM, et al. Influenzam therapy for rheumatic diseases in patients with chronic

hepatitis B after influenza B in Crohn’s disease: Need for HBV-screening?

2003;362:2089-94.

of hepatitis B virus reactivation in cancer patients undergoing cytotoxic
chemotherapy: a prospective study of 626 patients with identification of risk

13. Rossi G. Phosphorylation of lamivudine of hepatitis B reactivation in chronic
HBsAg carriers with hamoto-oncological neoplasias with chemotherapy.

therapy for hepatitis B reactivation in NAHB carriers after organ transplantation:

15. Guidotti LG, Rochford R, Chung J, Shapiro M, Purcell R, Chisari FV. Viral
clearance without destruction of infected cells during acute HBV infection.

of tumour necrosis factor alpha induces impaired proliferation of hepatitis

17. Wong GH, Goodfellow DV. Tumour necrosis factors alpha and beta inhibit

lamivudine therapy based on HBV DNA level in HBsAg-positive kidney

19. Fabrizi F, Dulai G, Dierx V, Bunnasradit S, Martin P. Lamivudine for the
treatment of hepatitis B virus-related liver disease after renal transplantation:

20. Nathan DM, Angus PW, Gibson PR. Hepatitis B and C virus infections
and anti-tumor necrosis factor alpha therapy: Guidelines for clinical approach.