Anti-tumor necrosis factor-α (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 anti-TNFα 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.

Infliximab in en la espondilitis anquilosante asociada a infección crónica por el virus de la hepatitis B. Papel del tratamiento con lamivudina

El tratamiento con agentes contra el factor de necrosis tumoral (TNF) alfa se ha asociado a la reactivación de la infección crónica por el virus de la hepatitis B. Algunos casos publicados indican la necesidad de tratamiento crónico con lamivudina cuando se utilizan los agentes anti-TNFα. Describimos el caso de un paciente con espondilitis anquilosante y antígeno de superficie positivo tratado con infliximab y lamivudina. La respuesta clínica fue excelente, pero cuando el paciente interrumpió el tratamiento con lamivudina, se observó reactivación de la replicación viral. Una vez reinstaurado dicho tratamiento, se controló nuevamente la replicación viral y se normalizaron las concentraciones de transaminasas. Esta observación indica que en pacientes con infección crónica por VHB que necesitan tratamiento anti-TNFα, se requiere un tratamiento preventivo a largo plazo con lamivudina.

Palabras clave: Espondilitis anquilosante. Hepatitis B. Infliximab.

Introduction

Infliximab, a chimeric monoclonal antibody directed against tumor necrosis factor (TNF) alpha, is a widely employed treatment in spondyloarthritidies, rheumatoid arthritis, and Crohn’s disease. Since its approval for use, questions have surfaced on its safety. Although the debate continues regarding the safety of TNFα antagonist treatment in patients with chronic hepatitis C virus infection, published data indicate that its use is relatively safe.1,2 On the other hand, chronic infection due to hepatitis B virus (HBV) seems to show an ever growing body of evidence, manifested through published cases, of a reactivation of the virus when treatment with anti-TNFα is started.5-10 HBV infection is one of the most common chronic viral infections worldwide and affects approximately 400 million persons.11 We describe the case of a patient with ankylosing spondylitis (SA) and chronic HBV infection treated with lamivudin and infliximab.

Clinical Case

A 32-year-old white male was diagnosed with SA in 1996, being classified as such using the New York criteria. The serological profile for HBV showed he was HBsAg positive, had positive anti-HBe as well as HBe antibodies, and negative HBe antigen, and anti-HBs antibodies. ALT and AST determinations had always been normal.
Since 1996 he had received treatment with sulphasalazine 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, suggesting the use of infliximab.

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, 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).

### Concentrations of Transaminases and Viral DNA During Treatment With Infliximab and Lamivudin

<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>Infliximab</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>

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 oncohematological neoplasia and organ transplant. 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. These findings lead us to think that the administration of TNF inhibitors 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, spondyloarthritis, 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 al. 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 al. 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 al, 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. 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, insure 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

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be carried out and if it becomes positive, install lamivudin treatment.\(^\text{20}\) d) 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 treatment; and e) if a viral reactivation occurs, resistance and the possibility of using another agent, such as adenofir, must be contemplated.

References


