CURRENT TREND

Inflammatory bowel disease and hepatitis B and C

Maladies inflammatoires chroniques intestinales et hépatites B et C

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Summary The risk of viral B and C hepatitis has long been considered to be increased in patients with inflammatory bowel disease (IBD). Blood transfusion and surgery have been identified as the two main risk factors, suggesting nosocomial transmission could be involved. However, recent epidemiologic surveys have found that prevalence in IBD patients is similar to or even lower than that in the general population. Part of the explanation of these recent data may lie in the application of protective measures against viral infection (hepatitis B virus [HBV] vaccination and hepatitis C virus [HCV]-free blood transfusions). Sometimes fatal viral reactivations have been reported in patients on immunosuppressive therapy. Two periods can be distinguished: a) during therapy, a rise in viremia associated with a decrease of immune-mediated hepatic lesions; b) after cessation of therapy, an immune rebound with a destruction of virus-infected hepatocytes. For HBV, preemptive strategy consisting of an antiviral analog is efficient in chronic HBs antigen carriers. For HCV, the impact of immunosuppressive drugs on the natural history is unclear. Most studies report improved comfort although no biopsies were performed before and after immunosuppressive treatment. Physicians managing IBD patients should be aware of the need for screening and institute preventive measures against B and C hepatitis.

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Résumé Les patients atteints de maladies inflammatoires chroniques intestinales (MICI) ont longtemps été considérés comme à risque d’hépatites B et C. Les deux principaux facteurs de risque comprenaient la transfusion sanguine et la chirurgie, suggérant l’existence d’une transmission nosocomiale. Cependant, des études épidémiologiques récentes retrouvent...
Inflammatory bowel disease and hepatitis B and C

Introduction

Hepatitis caused by HBV or HCV infection constitutes a major public health challenge worldwide because the high prevalence and chronic disease can be countered by effective but costly treatments. In France, a cross-sectional survey conducted in 2004 by the Health Surveillance Agency (de veille sanitaire) enabled an estimate of the national prevalence. Compared with the 1994 figures, the prevalence of HCV infection remained stable while the prevalence of HBs antigen increased. 367,055 persons (0.84%) were positive for anti-HCV antibodies and among this population, 221,386 persons (65%) were positive for HCV RNA and thus potentially carriers of chronic HCV infection. The prevalence of HBs antigen was 0.65% (280,821 persons). Risk factors clearly identified were at-risk sexual behavior, drug use and blood transfusion before 1991. The well-known nosocomial risk is however more difficult to assess. Certain studies have for instance evaluated the risk related to endoscopic procedures with biopsies. Patients with IBD are subject to repeated hospitalizations and exposed to invasive procedures (endoscopy, surgery). These patients could thus constitute a population at risk of HBV or HCV infection.

Immunosuppressors, corticosteroids, purine analogs (azathioprine, 6-mercaptopurine), cyclosporin and methotrexate play all a central role in the treatment of IBD. In 1995, a new therapeutic class, anti-TNF compounds such as infliximab (Remicade®) revolutionized the treatment of refractory IBD. Indications for using this drug have increased steadily due to the importance of the clinical improvement observed. Several case reports of viral reactivations have been described in patients receiving immunosuppressive therapy for IBD, sometimes leading to severe or fatal hepatitis. All available evidence has been collected from case reports or small series.

Our objective was to ascertain the risk of B and C viral hepatitis in patients with IBD. In addition, we examined the reported cases of viral reactivation in patients on immunosuppressive treatment to learn more about the practical consequences and guidelines proposed by learned societies.

Prevalence of viral B and C hepatitis in IBD

Few studies have been devoted to the prevalence of hepatitis in IBD (Table 1). The advent of anti-TNF therapy in the late 1990s focused attention on the importance of knowing the patient’s virological status in order to prevent potentially fatal reactivation. In this context, Longo et al. [6] and Biancone et al. [7] reported epidemiology data on the prevalence of IBD in France and Italy, respectively. These studies, conducted from January to September 1998 in France and June 1997 to March 1999 in Italy included 117 and 332 patients, respectively, with similar clinical characteristics: mean age 41 years and mean disease duration 8.2 years. The French study [6] determined the prevalence of anti-HCV antibodies with a third generation ELISA. The rate observed, 5.98% (7/117), was higher in the study population than in a control population composed of volunteers (1.15%) [8]. The only significant factor identified by multivariate analysis as independently related with increased prevalence of anti-HCV antibodies was blood transfusion. History of surgery, the number of colonoscopic procedures and the immunosuppressor class were not risk factors for viral C transmission [6].

The multicentric survey reported by Biancone et al. [7] examined viral B and C markers in an IBD population of 332 patients with Crohn’s disease and 162 patients with ulcerative colitis. Serology tests were positive for viral B or C hepatitis in 24.7% of patients with Crohn’s disease. The proportion of patients with anti-HCV antibodies was not significantly different between the control group (5.1%) and the IBD patients (7.4%). Conversely, the subgroup of patients aged less than 50 years had a higher anti-HCV antibody prevalence in the IBD group (6.8%) than in the control group (1.9%; p = 0.01). This difference was explained by a greater proportion of patients who had undergone surgery.
of preventive measures in Spanish hospitals [11]. Furthermore, effective anti-HBV vaccination covering only 12% of the IBD population, the authors emphasized the importance of strengthening the vaccination program in these patients.

Unlike the first studies conducted in 2000 which observed positive HBV and HCV serologies in up to 24% of their IBD populations, the larger more recent study conducted by the Spanish group found prevalences equivalent in the IBD and general populations. Safe blood donation, generalized vaccination, progress in screening and measures against nosocomial infection have contributed to these results. At the present time, the IBD population does not appear to be a population at risk of hepatitis.

### Reactivation of viral B and C hepatitis and IBD medication

Immunosuppressors play a central role in the therapeutic armamentarium for IBD, but caution is required in case of an associated viral hepatitis. It should be noted however that while numerous case reports of viral reactivation have had an unfavorable impact on the use of immunosuppressors in these patients, the conclusions actually drawn by the authors have been contradictory [10,12–14]. Many specialists are involved, particularly rheumatologists and dermatologists as well as oncologists-hematologists (aplasia-inducing chemotherapy) and transplantation teams. Experimental and clinical studies have shown that T-cell mediated immunity is implicated in the pathophysiological mechanisms underlying viral B and C infections [15]. By modulating the T-cell mediated immune reaction, immunosuppressors could reduce lysis of liver cells and immune-mediated viral clearance.

Two phases of immunosuppressor-related viral reactivation can be distinguished [16]:

1. **a)** an initial phase of increased viremia after starting treatment due to reduced cell lysis and immune-mediated hepatic lesions;
2. **b)** followed, at treatment withdrawal, by immune rebound with destruction of the infected liver cells and a fall in the viral load (Fig. 1).

#### Table 1 Prevalence of hepatitis B and C markers in IBD patients.

<table>
<thead>
<tr>
<th>Studies</th>
<th>IBD</th>
<th>Number of patients</th>
<th>Mean age (years)</th>
<th>HBs antigen (%)</th>
<th>Anti-HBs (%)</th>
<th>Anti-HBc (%)</th>
<th>Anti-HCV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longo et al., 2000 [6]</td>
<td>CD</td>
<td>117</td>
<td>41 ± 16</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5.98/1.15</td>
</tr>
<tr>
<td></td>
<td>UC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biancone et al., 2001 [7]</td>
<td>CD</td>
<td>332</td>
<td>41 ± 15</td>
<td>2.1/2.1</td>
<td>14.4/7.7</td>
<td>10.9/5.1</td>
<td>7.4/5.1</td>
</tr>
<tr>
<td></td>
<td>UC</td>
<td>162</td>
<td></td>
<td>0.64/2.1</td>
<td>15.8/7.7</td>
<td>11.5/5.1</td>
<td>0.6/5.1</td>
</tr>
<tr>
<td>Esteve et al., 2004 [10]</td>
<td>CD</td>
<td>80</td>
<td>38.2</td>
<td>3.7/—</td>
<td>—</td>
<td>—</td>
<td>1.2/—</td>
</tr>
<tr>
<td>Bargiggia et al., 2005 [9]</td>
<td>CD</td>
<td>302</td>
<td>38</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>6.2/—</td>
</tr>
<tr>
<td></td>
<td>UC</td>
<td>211</td>
<td>39</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>10.9/—</td>
</tr>
<tr>
<td>Loras et al., 2009 [11]</td>
<td>CD</td>
<td>1128</td>
<td>44.1</td>
<td>0.6/1.7</td>
<td>17</td>
<td>7.1/10.6</td>
<td>2.3/2.6</td>
</tr>
<tr>
<td></td>
<td>UC</td>
<td>928</td>
<td></td>
<td>0.8/1.7</td>
<td>14.9</td>
<td>8/10.6</td>
<td>1.3/2.6</td>
</tr>
</tbody>
</table>

**IBD:** inflammatory bowel disease; **UC:** ulcerative colitis; **CD:** Crohn’s disease.
Thus several cases of viral cure have been described at withdrawal of the immunosuppressor treatment [17].

In addition, with stronger immunosuppression, the immune rebound is greater, with more deleterious clinical and biological consequences. The time to reactivation appears to be somewhere between 1 and 3 months, corresponding to restoration of immune function. These reactivations are generally well tolerated. Conversely, serious deterioration of liver function has been described in patients with hepatic fibrosis [18]. For hepatitis B, clinical studies have demonstrated the usefulness of preventive treatment with lamivudine to reduce the risk of reactivation, the severity of the immunological rebound and mortality [19—21].

**Corticosteroid therapy**

**HBV**

Since the early 1980s, the use of corticosteroids has been incriminated in the over-expression of HBV-DNA and HBc antigen in the liver [22]. This phenomenon can be explained in vivo by decreased T-cell activity and by the consequent decrease in hepatocyte lysis and thus viral clearance. In vitro, Tur-Kaspa et al. described a glucocorticosteroid responsive element located in the HBV genome which enables viral over-expression [23]. Interrupting or tapering off corticosteroids leads to immune rebound with lysis of the infected cells [24].

The effects of corticosteroids in IBD patients have not been described in a prospective study. Sometimes fatal viral reactivation has mainly been described in the context of malignant hematological disease among patients given chemotherapy protocols with corticosteroids [25—27]. Factors predictive of reactivation are the use of corticosteroids, presence of HBs antigen, high pretherapeutic viral load, male sex and young age [21,28]. The risk is hard to assess, ranging from 20 to 48% and associated with 7 to 41% mortality depending on the study [29,30]. Other cases have been reported in the framework of benign chronic inflammatory diseases such as rheumatoid arthritis [31], pemphigus vulgaris and dermatomyositis [32]. The severity of the reactivation depends largely on the presence of an underlying liver disease [33]. In case of doubt, a liver biopsy may be necessary.

**HCV**

There have been no prospective studies on the effect of corticosteroids on the natural history of HCV infection in patients with IBD. A few studies have shown that the administration of corticosteroids increases viral load and decreases serum transaminase levels. At withdrawal, the immune rebound with increased transaminase levels has no clinical expression [34]. The available data on recurrence in the graft after liver transplantation suggest that corticosteroids should be tapered off slowly to limit the risk of early recurrent viral C hepatitis and the risk of cholestatic fibrosing hepatitis [35,36]. Severe acute viral C hepatitis has been described in patients under major immunosuppression during polychemotherapy protocols for malignant hematological disease [37]. However, the stage of severe liver failure is rarely reached. Biancone et al. reported a series of eight patients with Crohn’s disease with viral B and C hepatitis whose continuation of immunosuppressive treatment had no impact on the natural history of the C hepatitis [12]. For one patient however, interrupting the corticosteroids led to viral C reactivation with a 10-fold increase in transaminases.

**Purine analogues (azathioprine, 6-mercaptopurine)**

**HBV**

In addition to its immunosuppressive effect, azathioprine appears to favor viral B replication in vivo [38]. The natural history of HBV has not been studied prospectively in a population of IBD patients taking azathioprine [38]. In one prospective monocentric study, David-Neto et al. confirmed the deleterious effects of azathioprine in a population of kidney graft recipients with viral hepatitis. At discontinuation of the immunosuppressor, serum transaminase levels declined and the chronic liver disease progressed with increased mortality secondary to cirrhosis and infections [39,40]. Azathioprine also has a direct toxic effect on the liver, although an underlying viral hepatitis must always be considered [41].

**HCV**

In vitro, azathioprine inhibits viral replication of flaviviridae, which include HCV [42]. A retrospective study in liver transplant recipients on azathioprine with viral C hepatitis demonstrated the beneficial effect of azathioprine in terms of decreased histological activity and progression of HCV in the graft [43]. Studies in kidney transplant recipients led to the same conclusions [44].

**Methotrexate**

Several cases of methotrexate-induced cirrhosis were described in the 1970—1980s leading learned societies to propose liver biopsy for cumulative doses greater than 1500 mg. At the present time, methotrexate appears to be involved in the progression of fibrosis as a cofactor associated with excessive alcohol intake or a dysmetabolic syndrome [45]. The ECCO guidelines thus recommend monitoring transaminase levels but not systematic liver biopsy [46].

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*Figure 1* Changes in alanine aminotransferase (ALT) and serum hepatitis B virus DNA (HBV-DNA) in a patient during and after withdrawal of prednisolone [16].
HBV
At low dose, methotrexate would decrease immune response but without a direct effect on viral replication. There have been no prospective studies in IBD patients. Several cases of reactivation have been reported during and after withdrawal of methotrexate in rheumatology [47] and hematology [48] patients. Some have been fatal.

HCV
Here again, extrapolating from data obtained in series of rheumatoid arthritis patients with hepatitis C, methotrexate does not appear to play any role in the natural history of HCV infection [31]. A first retrospective series reporting seven patients taking methotrexate noted that reactivation had not occurred in six out of seven and that in the one case of reactivation, there was no clinical expression and favorable outcome with ribavirin [49]. Three other patients with rheumatoid arthritis taking methotrexate for 6 months had a liver biopsy which did not demonstrate fibrosis or any evidence in favor of cirrhosis [50].

Cyclosporin

HBV
Used since the late 1980s for IBD, cyclosporin is a powerful immunosuppressor prescribed in combination regimens for severe corticoid-resistant acute colitis [51]. In vitro, cyclosporin appears to inhibit viral B replication [52]. Conversely, in vivo, the available evidence obtained in kidney transplant recipients positive for HBs antigen, fibrosis progressed more rapidly, reaching the stage of cirrhosis in 15% of the patients taking cyclosporin [53]. Cases of fatal fulminating hepatitis have also been described [54].

HCV
In vitro, cyclosporin would diminish genome replication as well as expression of viral C proteins in addition to its immunosuppressive effect [55]. This inhibition would use the cyclophilin pathway, a new therapeutic target for these patients [56,57]. Prospective evidence of the natural history of HCV infection is not available for IBD patients. In 2006, a multicentric prospective study of 66 patients who had liver transplantation for recurrent HCV compared the effect of immunosuppressive treatment on viral load and the histological fibrosis score. These two parameters were not significantly affected by cyclosporin [58]. In rheumatology, certain authors advocate cyclosporin for patients with autoimmune disease and viral C hepatitis since this regimen appears to be effective without risk of reactivation [59].

Anti-TNFα

Anti-TNFα compounds have been accused of increasing the risk of severe infection, particularly intracellular germs such as Mycobacterium tuberculosis [60].

HBV
In vitro and in animal models TNFα would favor clearance and control of viral B replication [61]. This phenomenon would depend both on the quantity of TNFα and the balance with interferonα [62]. Thus, theoretically TNFα blockade could stimulate viral replication and consequently aggravate the liver disease. The effect of anti-TNFα compounds on the natural history of HBV infection has not been studied prospectively in IBD populations. About 15 cases of reactivation, some fatal, have been described in HBs antigen-positive IBD, rheumatology and dermatology patients (Table 2). Available drugs in rheumatology include infliximab, adalimumab and etanercept. At the present time, there have been no reports of viral reactivation with adalimumab given alone. Reactivation would occur on average 2 to 3 months after discontinuing infliximab [10] and generally after the third infusion [62]. These reactivations occur at a low dose, from 3 mg/kg. In the literature, etanercept appears to induce less viral reactivation compared with infliximab. This difference would be explained by their different pharmacological and biochemical properties; etanercept does not link to the soluble TNFα receptor [62]. This should be confirmed.

Cases of reactivation have been described in occult carriers of HBV who are negative for HBs antigen and positive for anti-HBc antibody [63]. These patients should have a liver biopsy to search for viral DNA; biopsy would be more sensitive for assessing risk but less reliable as a routine test. Ultrason sensitive PCR should thus be proposed to search for viral DNA in the serum despite the lack of sensitivity and specificity [64]. Based on the experience in oncology-hematology, several cases of viral reactivation in patients taking anti-TNFα drugs have been treated with success with lamivudine (a nucleoside inhibitor) [10,65].

HCV
TNFα plays a key role in the HCV-linked inflammatory process. Its level would be significantly correlated with biological and histological disease severity, but not with viral replication [66]. It is involved in resistance to interferon α treatment [67]. Theoretically, anti-TNFα compounds would have a beneficial impact on the natural history of HCV infection. One double-blind randomized controlled phase II study examined the usefulness of etanercept as adjuvant treatment in naive patients with chronic C hepatitis given bitherapy using interferon-α and ribavirin [68]. At 24 months, HCV RNA was undetectable in 63% of patients in the etanercept group compared with 32% in the control group (p = 0.04). In addition, adverse effects were less frequent in the etanercept group, emphasizing its safety for the treatment of chronic C hepatitis.

Several other cases and series of patients treated with etanercept or other anti-TNFα compounds have confirmed the absence of severe acute hepatitis in patients with an associated chronic C hepatitis (Table 3). One of the main limitations of these studies is the lack of pre- and post-therapy biopsies. The fact that the transaminase level or the viral C load are not elevated cannot rule out the presence of severe histological lesions [69]. In this context, the clinician could rely on non-invasive markers for the initial work-up and follow-up.

Like the majority of immunosuppressive compounds, anti-TNFα drugs have no known direct toxic effect on the liver. The product description does however list the possibility of transaminase elevation which, above five
<table>
<thead>
<tr>
<th>Studies</th>
<th>Patients</th>
<th>Age/sex</th>
<th>Immunosuppressors</th>
<th>Duration of Anti-TNF therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ostuni et al., 2003 [82]</td>
<td>1 RA</td>
<td>49/M</td>
<td>IFX, MTX</td>
<td>16 months</td>
<td>Acute hepatitis secondary to HBV reactivation, favorable outcome with lamivudine</td>
</tr>
<tr>
<td>Michel et al., 2003 [83]</td>
<td>1 Still’s disease</td>
<td>28/F</td>
<td>IFX</td>
<td>2 infusions</td>
<td>2 weeks after the second infusion, fulminating hepatitis requiring liver transplantation</td>
</tr>
<tr>
<td>Esteve et al., 2004 [10]</td>
<td>3 CD</td>
<td>34/M, 38/M 26/M</td>
<td>IFX, IFX/AZA, IFX/AZA</td>
<td>3–5 infusions</td>
<td>2 cases of HBV reactivation at withdrawal of IFX (2–3 months after the last infusion) with 1 death by varice rupture</td>
</tr>
<tr>
<td>Oniánkitan et al., 2004 [84]</td>
<td>1 ASP</td>
<td>32/M</td>
<td>IFX</td>
<td>1 year</td>
<td>Patient on lamivudine, no reactivation</td>
</tr>
<tr>
<td>Valle García-Sanchez et al., 2004 [85]</td>
<td>1 CD</td>
<td>40/F</td>
<td>IFX</td>
<td>6 infusions</td>
<td>Transaminase reduction but continued viral replication despite introduction of lamivudine</td>
</tr>
<tr>
<td>Wendling et al., 2005 [86]</td>
<td>1 ASP</td>
<td>35/F</td>
<td>IFX/MTX</td>
<td>3 infusions</td>
<td>Normal liver tests after lamivudine</td>
</tr>
<tr>
<td>Ueno et al., 2005 [87]</td>
<td>1 CD</td>
<td>28/F</td>
<td>IFX</td>
<td>1 infusion</td>
<td>Transaminase 2xN with spontaneous return to normal. Persistence of viral DNA in blood</td>
</tr>
<tr>
<td>Anelli et al., 2005 [88]</td>
<td>1 RA</td>
<td>36/F</td>
<td>IFX</td>
<td>&gt; 2 infusions</td>
<td>HBV DNA clearance in blood, paradoxical increase in transaminase level</td>
</tr>
<tr>
<td>Millonig et al., 2006 [89]</td>
<td>1 CD</td>
<td>50/M</td>
<td>IFX/AZA</td>
<td>3 infusions</td>
<td>1 months after the 3rd infusion, HBV reactivation with sub-fulminant hepatitis. Favorable outcome with lamivudine</td>
</tr>
<tr>
<td>Roux et al., 2006 [65]</td>
<td>1 ASP</td>
<td>49/M</td>
<td>IFX</td>
<td>7 months</td>
<td>Lamivudine prophylaxis, no viral reactivation</td>
</tr>
<tr>
<td>Colbert et al., 2007 [13]</td>
<td>1 CD</td>
<td>54/M</td>
<td>ETA/MTX then ADA/MTX</td>
<td>11 months then 10 months</td>
<td>Lamivudine prophylaxis at anti-TNF introduction, normal liver tests</td>
</tr>
<tr>
<td>Madonia et al., 2007 [63]</td>
<td>1 CD</td>
<td>41/F</td>
<td>IFX/Prednisone</td>
<td>6 infusions</td>
<td>Lamivudine introduced 20 months after beginning ETA, reduction of viral B load</td>
</tr>
<tr>
<td>Montiel et al., 2008 [90]</td>
<td>1 ASP</td>
<td>73/M</td>
<td>ETA/Prednisone</td>
<td>14 months</td>
<td>Acute hepatitis, withdrawal of AZA, IFX and introduction of lamivudine. At 1 months, death by fulminant hepatitis</td>
</tr>
<tr>
<td>Ojiro et al., 2008 [91]</td>
<td>1 CD</td>
<td>43/F</td>
<td>IFX/6-MP</td>
<td>4 infusions</td>
<td>1 month after last infusion, hepatitis, transaminase elevation, HBV DNA+. Introduction of lamivudine. 10 months later, anti-HBs serocoversion</td>
</tr>
<tr>
<td>Caroll and Bond, 2008 [62]</td>
<td>1 RA</td>
<td>73/M</td>
<td>ETA</td>
<td>5 months</td>
<td>Reactivation 14 months after ETA, favorable course with lamivudine. No new reactivation after new ETA challenge with lamivudine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Viral B replication and transaminase elevation. Favorable course at withdrawal of IFX and introduction of lamivudine. IFX challenge with lamivudine, no recurrence</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Studies</th>
<th>Patients</th>
<th>Age (years)/sex</th>
<th>Immunosuppressors</th>
<th>Duration of IFX treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campbell et al., 2001 [92]</td>
<td>1 CD</td>
<td>39/M</td>
<td>IFX</td>
<td>1 infusion</td>
<td>Stable liver tests, no viral reactivation</td>
</tr>
<tr>
<td>Peterson et al., 2003 [93]</td>
<td>24 PR</td>
<td>Not reported</td>
<td>IFX or ETA</td>
<td>≥ 1 month</td>
<td>Stable liver tests. Viral load unchanged, in one case, RNA undetectable 1 month after onset of ETA</td>
</tr>
<tr>
<td>Holtmann et al., 2003 [94]</td>
<td>2 CD</td>
<td>26/F, 32/M</td>
<td>IFX/AZA</td>
<td>1 infusion</td>
<td>Stable liver tests and viral load unchanged, in one case, RNA undetectable 1 month after onset of ETA</td>
</tr>
<tr>
<td>Parke and Reveille, 2004 [95]</td>
<td>5 PR</td>
<td>Mean age: 47.2 ± 3.77 yr</td>
<td>IFX/ETA</td>
<td>8 ± 4.4 months (IFX)</td>
<td>Stable liver tests during treatment Decreased viral replication in 1 patient at treatment withdrawal</td>
</tr>
<tr>
<td>Oniankitan et al., 2004 [84]</td>
<td>1 PR</td>
<td>66/F</td>
<td>IFX/MTX</td>
<td>≥ 4 infusions</td>
<td>Viral load unchanged</td>
</tr>
<tr>
<td>Magliocco and Gottlieb, 2004 [96]</td>
<td>3 Pso + RPso</td>
<td>51/M, 54/M, 52/M</td>
<td>ETA</td>
<td>≥ 3 months</td>
<td>Stable liver tests</td>
</tr>
<tr>
<td>Roux et al., 2006 [65]</td>
<td>3 PR</td>
<td>49/F, 50/F, 63/F</td>
<td>ETA/ADA/MTX, ETA/MTX, ETA</td>
<td>≥ 6 months</td>
<td>Stable liver tests and viral load unchanged</td>
</tr>
<tr>
<td>De Simone et al., 2006 [97]</td>
<td>2 Pso</td>
<td>43/M, 62/M</td>
<td>ETA</td>
<td>≥ 1 yr</td>
<td>No effect on liver tests or viral load</td>
</tr>
<tr>
<td>Rokhsar et al., 2006 [98]</td>
<td>1 Pso</td>
<td>53/M</td>
<td>ETA/MTX</td>
<td>≥ 1 yr</td>
<td>Viral load unchanged</td>
</tr>
<tr>
<td>Cecchi et al., 2006 [103]</td>
<td>1 Psoa</td>
<td>45/M</td>
<td>ETA/MTX, ETA</td>
<td>1 yr</td>
<td>Stable liver tests and viral load unchanged</td>
</tr>
<tr>
<td>Aslanidis et al., 2007 [99]</td>
<td>1 ASP, 1 Psoa</td>
<td>41/M, 47/F</td>
<td>IFX, IFX then ADA</td>
<td>≥ 1 yr</td>
<td>Stable liver tests and viral load unchanged</td>
</tr>
<tr>
<td>Marotte et al., 2007 [100]</td>
<td>9 patients with rheumatoid manifestations</td>
<td>Mean age: 57 yr/1M and 8F</td>
<td>ETA</td>
<td>3 months</td>
<td>Stable liver tests and viral load unchanged</td>
</tr>
<tr>
<td>Cansu et al., 2008 [101]</td>
<td>3 PR</td>
<td>55/F, 62/F, 58/F</td>
<td>ETA, ETA, ETA/MTX</td>
<td>≥ 21 months</td>
<td>Transaminases unchanged, increased viral replication in 2 patients at a non-significant level Persistent elevation of ALAT levels leading to withdrawal. Significant increase (≥ 2Log) in 4 cases. Stable liver tests for the others</td>
</tr>
<tr>
<td>Ferri et al., 2008 [102]</td>
<td>31 PR</td>
<td>59 ± 13 yr/23F and 8M</td>
<td>11 IFX/17 ETA/3 ADA</td>
<td>≥ 3 months</td>
<td>Persistent elevation of ALAT levels leading to withdrawal. Stable liver tests for the others</td>
</tr>
</tbody>
</table>

PR: polyarthrite rheumatoid; ASP: ankylosing spondylarthritis; MTX: methotrexate; IFX: infliximab; ETA: etanercept; CD: Crohn’s disease; AZA: azathioprine; Pso: psoriasis; PsoA: psoriatic arthritis; M: male; F: female.
times the normal, indicates the drug should be discontinued.

In light of these data, the risk and gravity of immunosuppressor-related viral reactivation is significant for HBV, with a risk of fatal outcome. For HCV, very few cases of transaminase elevation have been reported, always without clinical expression, in patients taking immunosuppressors.

**Recommendations for clinical practice**

**Is screening necessary?**

**HBV**

Patients programmed for immunosuppressor treatment should be screened for HBs antigen and anti-HBs and anti-HBc antibodies systematically in order to ascertain the viral status at treatment onset and to vaccinate if needed [70]. Based on expert opinions gathered from gastroenterologists [71], rheumatologists [72] and dermatologists [73], screening is indispensable before initiating anti-TNFα therapy. Chronic viral B hepatitis is mentioned in the precautions of the marketing approval for infliximab and adalimumab. We recommend first intention search for HBs antigen and anti-HBc and anti-HBs antibodies.

**HCV**

There is less agreement concerning systematic screening for hepatitis C. The precautions for use of infliximab and adalimumab do not cite any case of fatal reactivation in patients with chronic C hepatitis taking immunosuppressors. Nevertheless, in agreement with expert opinions cited above, we recommend systematic screening for anti-HCV antibodies because there is a curative treatment and progression to cirrhosis in IBD patients would have a negative impact on future management. HIV serology tests should also be ordered if the HBV or HCV serology is positive.

**Clinical situations**

**HBV (Fig. 2)**

**Sero-negative patients.** Although this population may not be at risk [11], vaccination should be mandatory. Contamination by HBV and its potential consequences, particularly the risk of reactivation due to immunosuppression, should be prevented. The anti-HBV vaccine is an inactivated vaccine so immunosuppression is not contraindicated. Conversely the efficacy of this vaccination in patients taking immunosuppressors is uncertain. The serological response should thus be monitored to administer a booster if needed [74].

**HBs antigen-positive patients.** According to the EASL [70] and the AASLD [75] recommendations, patients taking immunosuppressors should be given preventive antiviral treatment (nucleotide or nucleoside analog) for 6 to 12 months after interruption of immunosuppressive treatment. Patients whose baseline viral load is less than 2000 IU/mL should be given an analog for 6 months. If the baseline viral load is greater than 2000 IU/mL, the analog should be continued until the same objectives as for an immunocompetent patient are reached, i.e. 6 to 12 months after HBs seroconversion in an HBs antigen-positive patient and until HBs antigen clearance in an HBs-negative patient. For most situations, lamivudine is used and appears to be sufficient in patients with low viral load and low risk of resistance [70]. If the viral load and the risk of resistance are high and if the estimated treatment duration is greater than 12 months, entecavir or tenofovir should be preferred [70]. IFNα should not be used because it could exacerbate Crohn’s disease [76] and favor myelosuppression.

**HBs antigen-negative patients.** Cases of reactivation have been described in HBs antigen-negative but HBC antibody-positive patients, associated or not with anti-HBs antibodies [63]. Due to the lack of information on occult reactivation, the EASL recommends regular surveillance of transaminase levels and HBV DNA in order to initiate analog treatment early before the development of cell damage.
Acute infection. If acute viral B hepatitis develops, the rate of chronic disease ranges from 90% in newborns to 5% in adults [77]. The rate of chronic disease is higher in immunodepressed populations [78]. By analogy, the risk of chronic disease would be higher in patients on immunosuppressors, particularly certain drugs which have a directly favorable impact on viral replication. It would be advisable to discontinue immunosuppressive treatment.

HCV
Seronegative patients. As no vaccination exists, general preventive measures should be taken to reduce the risk of contamination.

Chronic infection. Immunosuppressors should be prescribed in the IBD population. There have been exceptional cases of elevated transaminase levels without clinical expression in patients with powerful immunosuppressive treatment for hematological cancer. Regular surveillance of liver function could thus be proposed for patients treated with an immunosuppressive combination. The role of non-invasive markers of fibrosis or the need for a liver biopsy should be discussed [79]. Classically, TH1 immune response is described in Crohn’s disease. In vitro, IFN-α potentiates TH1 response and by consequence aggravates the natural history of Crohn’s disease [79,80]. Nevertheless, for certain authors, the use of IFN-α has no impact on the clinical activity of the disease [7,9]. In ulcerative colitis, interferon does not appear to have any deleterious effect [81].

Acute infection. There have not been any reports of acute HCV infection in patients on immunosuppressors. We thus recommend standard treatment without systematic interruption of immunosuppression.

Conclusion
In the late 1990s, patients with IBD were considered to be at risk of HCV and HBV infection. Blood transfusion and surgery were incriminated, raising the hypothesis of nosocomial transmission. A recent multicentric study conducted in Spain and including more than 2000 patients with IBD found a similar prevalence in the IBD and general populations [11]. These findings would probably be explained by the impact of safety measures for blood transfusions, improved surgical asepsia and universal anti-HBV vaccination. Because of sometimes fatal reactivation in patients on immunosuppressive treatments exposed to HBV infection, clinicians should carefully screen IBD patients for viral hepatitis. Special attention should be given to patients taking new more powerful immunosuppressors which increase the magnitude of the immune rebound. By analogy with management practices in hematological cancer patients, preventive treatment with lamivudine can be expected to be effective and should thus be given to prevent viral B reactivation. The impact of immunosuppressors on the natural history of HCV infection is more controversial. Since there is no preventive treatment, regular surveillance of liver function and non-invasive markers of fibrosis is recommended. Clinicians managing patients with IBD should be aware of the importance of preventive measures such as anti-HBV vaccination and screening for hepatitis before initiating immunosuppressive treatment.

References


Inflammatory bowel disease and hepatitis B and C


