The implications of anti-tumour necrosis factor therapy for viral infection in patients with inflammatory bowel disease

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Introduction: Anti-tumour necrosis factor (TNF) therapy is increasingly used in the management of inflammatory bowel disease; however, concerns have been raised regarding risk of infection with such drugs. Little is known about their effect upon viral infection.

Sources of data: A search of PubMed using the terms ‘infliximab’, ‘etanercept’, ‘adalimumab’ or ‘anti-TNF therapy’ combined with the names of specific viruses was performed. A search of cited papers was used to identify further relevant reports.

Areas of agreement: Numerous reports of the use of anti-TNF in patients with chronic or latent viral infection appear in the literature. Specific problems related to hepatitis B virus and varicella zoster virus may exist. The safety profile of anti-TNF in chronic viral infection is generally reassuring.

Areas of controversy: Numerous consensus statements relating to pre-treatment serology or vaccination have recently appeared; however, significant variation exists in their recommendations.

Growing points: Increasing awareness of the implications of anti-TNF therapy on viral infection may allow safer use of such drugs.

Areas timely for developing research: The clinical and cost-effectiveness of screening for viral infections prior to anti-TNF requires further study.

Keywords: anti-TNF/viral infection/hepatitis B virus/varicella zoster virus
Introduction

The inflammatory bowel diseases (IBD), Crohn’s disease and ulcerative colitis are chronic intestinal conditions associated with significant morbidity and reduced quality of life for patients. In the absence of curative therapy, traditional treatment strategies have included the use of corticosteroids to induce remission, and 5-aminosalicylate-containing drugs as maintenance therapy; however, such agents are often of limited efficacy, and corticosteroid dependence, associated with significant adverse effects, is common.

The failure of medical therapy often leads to a need for surgery, with up to 38% of patients with Crohn’s disease and 29% of those with ulcerative colitis ultimately requiring surgery for their disease. As a result, treatment paradigms have evolved in the last 10–15 years towards the earlier initiation of more potent therapies, including thiopurine antimetabolites (6-mercaptopurine/azathioprine), methotrexate, calcineurin antagonists and agents targeting the pro-inflammatory cytokine tumour necrosis factor (TNF) alpha.

Whilst such drugs are effective in controlling IBD, concerns have been raised regarding their safety profile, especially with regard to infectious complications, including opportunistic viral, bacterial, fungal and parasitic infection. In this regard, the safety of anti-TNF drugs has received particular attention, largely driven by the theoretical risks associated with blocking a critical central mediator of the immune response. Initial experience with anti-TNF drugs, including infliximab (a chimeric murine-human IgG), adalimumab (fully human IgG) and etanercept (fusion protein targeting the soluble TNF receptor) has revealed specific risks of mycobacterial and granulomatous infections, invasive mycoses and *Pneumocystis jerovici*. However, the consequences of anti-TNF therapy with regard to viral infection are less well documented.

This review highlights and summarizes pertinent aspects of the literature regarding viral infection and anti-TNF drugs, specifically addressing the questions: (i) What is the risk of viral infection or reactivation associated with anti-TNF therapy? (ii) What has been the experience of using anti-TNF treatment in patients with chronic or latent viral infection? (iii) What measures can reduce the risk of viral infection in patients treated with anti-TNF?

What is the risk of viral infection or reactivation associated with anti-TNF therapy?

Viral infections are a common problem in patients receiving intense immunosuppression in the setting of organ transplantation and in
those with HIV infection. Specific problems reflect four particular scenarios: (i) alteration in the immunological control of chronic viral infection such as hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV) may alter the natural history of the disease and be associated with more rapid progression or the development of complications, (ii) reactivation of latent viral infection leading to symptomatic recurrent infection (e.g. cytomegalovirus (CMV), varicella zoster virus (VZV), herpes simplex (HSV), JC polyomavirus), (iii) the development of virus associated dysplasia or malignancy due to impaired viral control (e.g. human papilloma virus (HPV) and cervical dysplasia, Epstein–Barr virus (EBV) and lymphoproliferative disease) and (iv) increased susceptibility to acute infection (e.g. influenza).

The consequences of the more modest degrees of immunosuppression employed in patients with IBD are less well documented. Although problems related to all the above viral infections have been recorded in patients receiving immunosuppressive therapy for IBD, studies of the particular risks associated with individual agents have proven difficult due to the common practice of using a combination of drugs, including corticosteroids in many patients. Viruses have been reported to cause up to 31% of all infections and 11% of serious infections occurring in anti-TNF-treated patients with rheumatic diseases. In large cohorts of IBD patients receiving infliximab, herpes virus infection including primary or reactivated HSV, CMV, EBV or VZV has been noted to account for the majority of viral complications.

Registry studies of anti-TNF-treated IBD patients have shown that concomitant corticosteroid use is the most significant risk factor for any type of infectious complication. Similarly, a case–control study of the risk of opportunistic infections (including viral) in patients with IBD demonstrated a modest increased risk associated with the use of corticosteroids, thiopurines or anti-TNF agents (odds ratio [OR] = 2.9), but a somewhat greater risk when such drugs were combined (OR = 14.5). However, such studies have been underpowered to analyse the risks of specific infective agents with each individual drug, and other groups have reported conflicting results. In IBD patients, thiopurine use has been shown to be a risk factor for reactivation of VZV, CMV and HSV, whereas studies in the rheumatology literature implicate corticosteroid use as a more significant risk factor for VZV reactivation. More recently, a large registry study demonstrated anti-TNF monoclonal antibodies to be a risk factor for VZV reactivation, even after adjustment for immunosuppressant or corticosteroid use.

Experience with anti-TNF drugs in patients with known chronic viral infection remains limited, with hepatitis B, C or HIV infection until
recently considered absolute contraindications. However, whilst the overall risk of viral infection in patients treated with anti-TNF remains inadequately quantified, a growing literature of case reports and series now allow a number of cautious observations to be made regarding specific viral infections and anti-TNF therapy.

What has been the experience of using anti-TNF treatment in patients with chronic or latent viral infection?

Human herpes viruses

Evidence of exposure to members of the human herpes virus family is ubiquitous in most adult populations. Following initial infection, latent infection is established in neural (herpes simplex virus and varicella zoster virus) or haematopoietic cells (Epstein–Barr virus and cytomegalovirus). TNF is critically involved in the regulation of herpes virus replication and dissemination, and clinical experience with anti-TNF agents has demonstrated herpes virus reactivation to be a relatively common infectious complication, in a small number of cases resulting in serious adverse events.

Herpes simplex virus

In immunocompromized patients, reactivation of labial or genital HSV infection may be more frequent or extensive, and has a greater potential to cause disseminated disease. However, few reports of HSV reactivation associated with anti-TNF therapy have been recorded in the UK or US pharmacovigilance data sets, and only two detailed reports appear in the literature. A patient treated with methotrexate was reported to have developed disseminated cutaneous HSV-2, TB and pulmonary aspergillosis following infliximab treatment, whilst a child developed disseminated HSV-1 infection following three induction doses of infliximab for juvenile arthritis. Both patients recovered with anti-viral therapy.

Varicella zoster virus

Varicella zoster reactivation is well documented in patients receiving anti-TNF therapy, although in many patients concomitant corticosteroid therapy, a known risk for VZV reactivation, may have been a confounding factor. A recently published analysis of data from a German Biologicals Registry of patients with rheumatoid arthritis reported a doubling of risk associated with infliximab or adalimumab even after adjustment for steroid use, to a rate of 11/1000 per year. This analysis also demonstrated VZV reactivation may be more severe
in anti-TNF-treated patients, with 18% of cases affecting multiple dermatomes and 13% of patients needing hospitalization. Whilst up to 5% of patients may develop repeated recurrences, simple cessation of anti-TNF therapy until vesicles have resolved combined with conventional anti-viral therapy (aciclovir or valaciclovir) may allow the subsequent safe re-initiation of anti-TNF therapy in the majority.

Although VZV reactivation may be more common, a number of cases of severe acute primary varicella infection in patients receiving anti-TNF therapy have been reported, including a fatality. Primary varicella infection in adults is often more severe than in children, but a notable feature of the reported cases is the presence of an atypical rash, highlighting the requirement to have a high index of suspicion for the diagnosis in any patient becoming unwell and developing a rash whilst on anti-TNF treatment.

**Cytomegalovirus**

CMV infection and reactivation present a common problem in patients immunosuppressed in the setting of organ or stem cell transplantation or HIV. Similarly, in IBD patients on a variety of immunosuppressant medications, evidence of reactivation of CMV (detected by CMV PCR) may be a frequent finding, although clinically relevant disease appears to be uncommon. In prospective studies of the effect of infliximab treatment on viral reactivation in patients with Crohn’s disease or rheumatoid arthritis, no evidence of systemic CMV reactivation (as assessed by CMV PCR) occurred. Similarly reactivation of CMV in colonic tissue does not appear to result from infliximab treatment.

A small number of cases of severe CMV reactivation have been recorded in patients treated with anti-TNF therapy including hepatitis, retinitis and disseminated infection including the haemophagocytic syndrome, all successfully treated with ganciclovir.

**Epstein–Barr virus**

Epstein–Barr virus is associated with lymphoproliferative disease in immunosuppressed patients, with up to 80% of post-transplant non-Hodgkins lymphoma EBV positive. In such patients the risk of lymphoproliferative disease approximately correlates with viral loads, allowing monitoring and prediction of risk. In adults, infliximab treatment has been demonstrated to result in transient elevations in EBV viral load in a minority of patients, although viral loads do not approach levels considered high risk for lymphoproliferative disease. In a paediatric population, EBV reactivation was observed in 28% of patients, and of interest viral loads increased to a greater degree than in adult subjects; however, the long-term
significance of minor transient elevations in EBV load remain to be determined.  

The absolute risk of lymphoma in IBD patients remains uncertain, with the best available data suggesting a 2- to 4-fold increase in risk, largely related to the effect of thiopurine therapy. An additional small increase in lymphoma risk associated with anti-TNF therapy has been described, although the EBV status was unknown in many cases. It is interesting to note that a number of cases of lymphoproliferative disease have been reported in patients treated with anti-TNF therapy, which regressed upon cessation of therapy.

**Hepatitis B virus**

Hepatitis B infection affects up to 370 million people worldwide, with a prevalence of up to 1% in Western Europe and the USA. Higher rates are reported in Southern Europe and specific ethnic groups. Although studies in cohorts of IBD patients in Southern Europe have previously reported a higher prevalence of HBV infection amongst IBD patients, a recent Spanish multicentre study found similar rates of serological evidence of infection as in the background population.

Reactivation of chronic HBV infection is a recognized complication of immunosuppression used in organ transplantation or cancer chemotherapy. Without antiviral therapy, up to 50% of HBsAg patients may develop evidence of reactivation, a risk particularly associated with corticosteroid-containing treatment regimens. Reactivation associated with immunosuppression may be present in one of the two ways; most commonly at the cessation of therapy as immune reconstitution occurs, triggering an immune response against the HBV-expressing hepatocytes, or in those on long-term immunosuppression, as an accelerated course of HBV infection. TNF-α is known to be a central mediator of anti-HBV responses. It is therefore of little surprise that in the limited number of patients with HBV infection who have received anti-TNF drugs, evidence of viral reactivation (increased viral loads with or without increased transaminases) was observed in the majority where prophylactic anti-viral therapy was not used, with clinical outcomes ranging from apparent viral clearance to fatal hepatitis (Table 1). The majority of cases of reactivation have occurred in HBsAg patients; however, some patients have been HBsAg, anti-HBc antibody positive, implying they are occult carriers as may occur in patients with co-existing HCV infection, or are infected with viral strains carrying mutations in the S-gene (escape mutants). This scenario may have implications for pre-treatment screening strategies (see below).
<table>
<thead>
<tr>
<th>Indication</th>
<th>Age/sex</th>
<th>Pre-treatment ALT</th>
<th>Pre-treatment serology</th>
<th>Anti-TNF drug</th>
<th>Duration of therapy</th>
<th>Lamivudine prophylaxis</th>
<th>Outcome/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV reactivation</td>
<td>RA</td>
<td>49/M Normal</td>
<td>HBsAg⁺, anti-HBe⁺, anti-HBc⁻</td>
<td>IFX</td>
<td>8 infusions</td>
<td>No</td>
<td>Acute hepatitis (peak ALT 573). Treated with lamivudine. Alive</td>
</tr>
<tr>
<td></td>
<td>CD</td>
<td>34/M Not reported</td>
<td>(Retrospectively tested)</td>
<td>IFX</td>
<td>4 infusions</td>
<td>No</td>
<td>Acute hepatitis (peak ALT 2089). Resolved without antiviral therapy. Alive</td>
</tr>
<tr>
<td></td>
<td>CD</td>
<td>38/M Not reported</td>
<td>HBsAg⁺, HBeAg⁻, anti-HBc⁺ (Retrospectively tested)</td>
<td>IFX</td>
<td>3 infusions</td>
<td>No</td>
<td>Sub-acute liver failure. Died</td>
</tr>
<tr>
<td></td>
<td>CD</td>
<td>50/M Normal</td>
<td>HBsAg⁺, HBeAg⁻, anti-HBc⁺ (Retrospectively tested)</td>
<td>IFX</td>
<td>3 infusions</td>
<td>No</td>
<td>Sub-fulminant hepatitis (ALT 983). Treated with lamivudine. Alive. Retrospective analysis showed HBsAg⁺, DNA 20 IU/mL detector.</td>
</tr>
<tr>
<td></td>
<td>CD</td>
<td>28/F Normal</td>
<td>HBsAg⁺, anti-HBe⁺, anti-HBc⁻</td>
<td>IFX</td>
<td>1 infusion</td>
<td>No</td>
<td>Increased HBV DNA and hepatitis (peak ALT 43). Not treated with the antiviral therapy. Alive</td>
</tr>
<tr>
<td></td>
<td>SA</td>
<td>35/F Normal</td>
<td>HBsAg⁺, HBeAg⁻, anti-HBe⁺</td>
<td>IFX</td>
<td>3 infusions</td>
<td>No</td>
<td>Increased HBV DNA and hepatitis (peak ALT × 10 ULN). Treated with lamivudine and IFX successfully continued</td>
</tr>
<tr>
<td></td>
<td>AS</td>
<td>43/M Normal</td>
<td>HBsAg⁺, HBeAg⁻, anti-HBe⁺, anti-HBc⁻</td>
<td>IFX</td>
<td>14 weeks</td>
<td>No</td>
<td>ALT increased to 49. HBV DNA became positive. Successfully treated with lamivudine</td>
</tr>
<tr>
<td></td>
<td>CD</td>
<td>41/F Normal</td>
<td>HBsAg⁻</td>
<td>IFX</td>
<td>&gt;1 year</td>
<td>No</td>
<td>Initial five doses of IFX without problems. After further single infusion HBV DNA increase and hepatitis (peak ALT × 12 ULN). Became HBsAg⁺. Treated with lamivudine</td>
</tr>
<tr>
<td></td>
<td>CD</td>
<td>54/M Not reported</td>
<td>HBsAg⁺, HBeAg⁺</td>
<td>IFX</td>
<td>2 years</td>
<td>No</td>
<td>Fatal hepatitis. Died despite lamivudine therapy Initially anti-HBs⁻. Peak ALT 65. Became HBsAg⁺. Successfully treated with lamivudine, allowing restarting of therapy</td>
</tr>
<tr>
<td></td>
<td>AS</td>
<td>73/M Normal</td>
<td>HBsAg⁺, anti-HBs⁺, anti-HBc⁺, anti-HBe⁺</td>
<td>ETA</td>
<td>14 months</td>
<td>No</td>
<td>Increased HBV DNA. Peak ALT 239. Treated with lamivudine without effect, therefore IFX stopped. Successfully restarted 6 months later on lamivudine prophylaxis Hepatitis (peak ALT 234). Later successfully restarted ETA with lamivudine prophylaxis Slight increase in transaminases. HBV DNA became detectable</td>
</tr>
<tr>
<td></td>
<td>CD</td>
<td>43/F Normal</td>
<td>HBsAg⁺, anti-HBe⁺, anti-HBc⁻</td>
<td>IFX</td>
<td>4 infusions</td>
<td>No</td>
<td>Increased HBV DNA. Peak ALT 239. Treated with lamivudine without effect, therefore IFX stopped. Successfully restarted 6 months later on lamivudine prophylaxis Hepatitis (peak ALT 234). Later successfully restarted ETA with lamivudine prophylaxis Slight increase in transaminases. HBV DNA became detectable</td>
</tr>
<tr>
<td></td>
<td>RA</td>
<td>62/F Normal</td>
<td>HBsAg⁺, HBeAg⁺ anti-HBc⁻</td>
<td>ETA</td>
<td>2 years</td>
<td>No</td>
<td>Transaminases remained normal. HBV DNA became detectable</td>
</tr>
<tr>
<td></td>
<td>RA</td>
<td>48/F Normal</td>
<td>HBsAg⁺</td>
<td>ETA</td>
<td>13 months</td>
<td>No</td>
<td>Transaminases remained normal. HBV DNA became detectable</td>
</tr>
<tr>
<td></td>
<td>AS</td>
<td>38/F Normal</td>
<td>HBsAg⁺, anti-HBe⁺</td>
<td>ETA</td>
<td>12 months</td>
<td>No</td>
<td>Transaminases remained normal. HBV DNA became detectable</td>
</tr>
<tr>
<td>No HBV reactivation</td>
<td>RA</td>
<td>64/F Normal</td>
<td>HBsAg⁺</td>
<td>ETA</td>
<td>30 months</td>
<td>No</td>
<td>No change in HBV DNA or transaminases</td>
</tr>
<tr>
<td></td>
<td>RA</td>
<td>63/M Normal</td>
<td>HBsAg⁺</td>
<td>ETA/ADA</td>
<td>18 months</td>
<td>No</td>
<td>No change in transaminases. HBV DNA not measured</td>
</tr>
</tbody>
</table>

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Table 1 Continued

<table>
<thead>
<tr>
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<th>Lamivudine prophylaxis</th>
<th>Outcome/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA 63/F</td>
<td>Normal</td>
<td></td>
<td>HBsAg⁺, HBeAg⁻, anti-HBc⁺, anti-HBe⁻</td>
<td>ADA/ETA</td>
<td>26 months</td>
<td>No</td>
<td>No change in HBV DNA</td>
</tr>
<tr>
<td>Stills 28/F</td>
<td>100</td>
<td></td>
<td>HBsAg⁺, anti-HBe⁺</td>
<td>IFX</td>
<td>2 infusions</td>
<td>No</td>
<td>Fulminant hepatitis requiring liver transplant. However, HBV DNA negative throughout</td>
</tr>
<tr>
<td>RA 32/F</td>
<td>Normal</td>
<td></td>
<td>HBsAg⁺</td>
<td>ADA</td>
<td>24 months</td>
<td>No</td>
<td>Mild transient transaminase rise (peak ALT 54). No change in HBV DNA</td>
</tr>
<tr>
<td>AS 41/M</td>
<td>Normal</td>
<td></td>
<td>HBsAg⁺, HBeAg⁻, anti-HBe⁺, anti-HBc⁻</td>
<td>IFX</td>
<td>24 months</td>
<td>No</td>
<td>Peak ALT 85. No antiviral prophylaxis, no evidence of reactivation—DNA remained negative</td>
</tr>
<tr>
<td>RA 36/F</td>
<td>Normal</td>
<td></td>
<td>HBsAg⁺, HBeAg⁻, anti-HBc⁺, anti-HBe⁺</td>
<td>IFX</td>
<td>1 year</td>
<td>No</td>
<td>HBV DNA became undetectable</td>
</tr>
<tr>
<td>CD 40/M</td>
<td>127</td>
<td></td>
<td>HBsAg⁺, anti-HBc⁺, anti-HBe⁺</td>
<td>IFX</td>
<td>6 infusions</td>
<td>No</td>
<td>Received lamivudine therapy. Alive</td>
</tr>
<tr>
<td>RA 58/F</td>
<td>Normal</td>
<td></td>
<td>HBsAg⁺, HBeAg⁺</td>
<td>IFX/ETA</td>
<td>15 months</td>
<td>Yes</td>
<td>No reactivation observed.</td>
</tr>
<tr>
<td>CD 26/M</td>
<td>67</td>
<td></td>
<td>HBsAg⁺, HBeAg⁺ anti-HBc⁺</td>
<td>IFX</td>
<td>5 infusions</td>
<td>Yes</td>
<td>No reactivation observed.</td>
</tr>
<tr>
<td>AS 32/M</td>
<td>Normal</td>
<td></td>
<td>HBsAg⁺</td>
<td>IFX</td>
<td>9 infusions</td>
<td>Yes</td>
<td>Alive</td>
</tr>
<tr>
<td>RA 54/M</td>
<td>Normal</td>
<td></td>
<td>HBsAg⁺, HBeAg⁺, anti-HBe⁺, anti-HBc⁻</td>
<td>ETA/ADA</td>
<td>21 months</td>
<td>Yes</td>
<td>No change in HBV DNA</td>
</tr>
<tr>
<td>RA 53/M</td>
<td>Normal</td>
<td></td>
<td>HBsAg⁺, HBeAg⁺, anti-HBe⁺, anti-HBc⁻</td>
<td>ETA</td>
<td>&gt;2 years</td>
<td>Yes</td>
<td>No change in HBV DNA</td>
</tr>
<tr>
<td>SA 49/M</td>
<td>Normal</td>
<td></td>
<td>HBsAg⁺</td>
<td>IFX</td>
<td>7 months</td>
<td>Yes</td>
<td>No change in HBV DNA</td>
</tr>
</tbody>
</table>

Case information derived from refs 28–35. CD, Crohn's disease; RA, rheumatoid arthritis; AS, ankylosing spondylitis; SA, spondyloarthropathy; IFX, infliximab; ETA, etanercept; ADA, adalimumab.
In patients found to be infected with HBV, the optimal management is undefined. Some authors have advocated simple monitoring of HBV DNA and transaminases, based upon the observation that HBV does not reactivate in all anti-TNF-treated patients. However, since reactivation is unpredictable and has in a number of cases resulted in the need for liver transplantation or even death, this is a potentially risky strategy. Furthermore, anti-viral drugs are of limited efficacy if acute reactivation occurs. In contrast, in patients treated with prophylactic lamivudine, the safe and effective use of anti-TNF agents appears possible, although with prolonged use of this drug viral resistance can be detected in up to 30% after 1 year and 70% by 5 years. The emergence of resistance has been associated with HBV reactivation in IBD patients on long-term anti-TNF therapy.35 The role of alternative anti-viral drugs including tenofovir, adefovir or entecavir in such patients awaits investigation. When employed, anti-viral therapy should be initiated prior to anti-TNF treatment and continued for 3–6 months beyond its cessation.

**Hepatitis C virus**

Almost 170 million people worldwide are infected with hepatitis C virus. As with HBV, its prevalence shows marked geographical variation, affecting 0.6–2% of the population in Northern Europe and North America, rising to 3–5% in Southern Europe, and up to 10% in some ethnic groups.27 The role of TNF-α in HCV infection appears to somewhat contrast that in the HBV infection. It is known that elevated serum TNF levels predict the failure of interferon therapy, and that liver inflammation may actually be perpetuated by this cytokine.

The safety of anti-TNF therapy in patients with HCV infection was directly addressed in early trials using etanercept alongside conventional interferon/ribavirin treatment, which demonstrated a doubling of the rate of viral clearance without apparent adverse effect.36 This has led to large numbers of reports of the use of anti-TNF in HCV-infected patients for a variety of indications including IBD, rheumatoid arthritis and psoriasis. Such reports confirm the favourable short-term safety profile of all three widely available anti-TNF drugs (infliximab, adalimumab and etanercept).37–39 However, the authors of one case series have cautioned that anti-TNF therapy may promote the development of HCV-associated mixed cryoglobulinaemia.40

The longer term safety of anti-TNF agents in patients with HCV infection also remains to be proven. Studies of viral loads and transaminases, whilst reassuring, may not accurately reflect the risk of progression or underlying degree of liver fibrosis. Studies with longitudinal
assessment of liver histology or non-invasive markers of fibrosis are currently lacking, or inadequate in detail to permit reliable conclusions. Similarly, it is important to note that reported experience has largely concerned patients with minimal histological abnormalities on liver biopsy, and the safety of anti-TNF drugs in those with more advanced liver disease is unknown.

Finally, both HBV and HCV infection are associated with the development of hepatocellular carcinoma, in the presence or absence of cirrhosis, and any potential effect upon this specific risk awaits definition.

Overall it appears that the use of anti-TNF therapy in HCV infected patients may not present such problems as in HBV patients. Treatment of the underlying HCV is only indicated where conventional criteria are met, and it is of note that interferon therapy may be relatively contraindicated in patients with IBD, in whom it has been associated with exacerbation of intestinal inflammation.

**Human immunodeficiency virus**

The *in vivo* role of TNF-α in the HIV infection is unsettled but as in HCV infection, it appears to contribute to disease pathogenesis, and *in vitro* evidence suggests TNF may promote viral replication. However, the use of anti-TNF drugs, themselves associated with opportunistic infection, in patients with HIV is controversial. The earliest report of the use of etanercept in a HIV-infected patient with psoriasis appeared to confirm this, with treatment stopped due to recurrent polymicrobial infection. However, this patient had a severely suppressed CD4⁺ count, and more recent reports of the use of anti-TNF therapy in HIV patients with CD4⁺ counts >200/mL have demonstrated an acceptable safety profile in this patient group.

As with HCV, anti-TNF drugs have even been studied as potential adjuvant therapies in HIV. In 11 patients receiving highly active antiretroviral therapy (HAART), a single dose of etanercept had no significant effect on viral loads nor CD4⁺ count. Similarly, in six patients with CD4⁺ counts <200/mL, two doses of infliximab had no adverse effect. In a third study, using etanercept in addition to standard therapy in HIV-associated pulmonary tuberculosis, a trend towards better clinical outcomes was noted, without clear effect upon HIV viral load or opportunistic infection risk.

A number of groups have now reported experience using adalimumab, infliximab or etanercept in HIV-positive patients for a range of rheumatological conditions or IBD, for durations up to 4 years, without apparent adverse clinical effects, or detrimental effect upon viral loads or CD4⁺ cell counts. Such patients have largely been
HAART treated with effectively normal CD4⁺ counts and highly suppressed viral loads; the safety of anti-TNF therapy in patients with low CD4⁺ counts, high viral loads, or who are receiving concomitant immunosuppressive therapy cannot be inferred from currently available data.

**Human papilloma virus**

Human papilloma virus infection is associated with manifestations ranging from cutaneous warts to cervical dysplasia and cervical or anogenital neoplasia. Prolonged immunosuppression may be associated with greater rates of progression to dysplastic or neoplastic lesions. In studies of IBD patients receiving immunosuppression, including anti-TNF therapy, pap smear abnormalities have been reported to be more common, although this finding has not been universally replicated. However, any specific risk attributable to anti-TNF treatment is uncertain, as the majority of patients were also treated with concomitant or previous immunosuppressive therapies. Florid cases of acute anogenital condylomata have been reported to occur in patients receiving etanercept or infliximab, suggesting anti-TNF drugs may increase the severity of infection.

**JC virus**

Reactivation of latent JC virus is associated with progressive multifocal leukoencephalopathy (PML), a rare, usually fatal neurological disease. Although known to occur in patients with profound immunosuppression related to advanced HIV infection or organ transplantation, the condition has now been noted in association with the use of therapeutic antibodies targeting α₄-integrin (natalizumab) and CD20 (rituximab). However, anti-TNF therapy does not appear to result in the JC reactivation or represent a significant risk factor for PML.

**Acute influenza infection**

The consequences of anti-TNF agents on susceptibility to acute influenza infection are unknown. Consensus statements generally consider all IBD patients on immunosuppressive medications to be at increased risk, and recommend annual influenza vaccination, as do British Association of Rheumatology anti-TNF guidelines. Anti-TNF treatment may diminish the degree of protective immunity resulting from vaccination, but levels achieved appear adequate to justify this
approach. Although cohort studies of IBD patients have shown very low levels of influenza vaccination uptake, adverse clinical consequences due to this remain unproven.

What measures can reduce the risk of viral infection in patients treated with anti-TNF?

Informed by increasing clinical experience, a number of guidelines and consensus statements have been produced by learned societies regarding screening, vaccination and prophylaxis of viral infection in patients receiving therapeutic immunosuppression, including anti-TNF drugs. As highlighted above, few methodologically sound studies are available to aid guideline formulation; consequently significant variation exists between recommendations made in the gastroenterology, dermatology and rheumatology literature. A summary of relevant consensus statements is shown in Table 2.

Specific questions, which remain to be answered, include the most clinical and cost-effective serological strategies of screening for conditions such as HBV, HCV and HIV in groups with varying background prevalence and risk of infection. For example, whilst HBV testing is consistently supported, in the formulation of the recent European Crohn’s and Colitis Organization (ECCO) statement no consensus could be reached regarding testing for HCV infection, although universal HIV testing was advocated. Although other consensus groups advocate HBV testing, none specifies the appropriate serological strategy. HBsAg testing is used in case finding and screening in some settings, particularly where prevalence is low, but is inadequate in the assessment of patients prior to anti-TNF therapy, particularly as HBV reactivation in HBsAg cases has been reported. Additional testing for anti-HBs and anti-HBc may reveal previous viral exposure, and may allow more accurate assessment of risk, such as measurement of HBV DNA.

The most appropriate point at which to perform such testing is unsettled. The current paradigm in IBD therapy is largely ‘step-up’ treatment, where anti-TNF drugs are mostly employed in patients with inadequate responses to other immunomodulator drugs, particularly thiopurines or corticosteroids. Since concerns have been raised regarding the accuracy of serology and the safety and efficacy of vaccination in patients receiving such immunosuppressive therapies, and it is estimated that 80% of IBD patients will receive steroids, 40% will be treated with thiopurines and 20% will require anti-TNF therapy, some have advocated universal assessment (and vaccination as indicated) at the time of diagnosis of IBD.
<table>
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<tr>
<th>Guideline</th>
<th>Recommended assessment and serology</th>
<th>Vaccination recommendations</th>
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<tr>
<td>European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in IBD (2009)\textsuperscript{50}</td>
<td>HBV infection: test all IBD patients (HBsAg, anti-HBs, anti-HBC) HCV: no consensus on testing HIV: consider testing in all patients with IBD VZV: ascertain medical history of chickenpox, shingles or vaccination HSV: screening unnecessary. Previous infection not a contraindication CMV: screening unnecessary EBV: screening not recommended HPV: regular cervical cytology recommended</td>
<td>Confirm routine vaccinations complete and if needed vaccinate at diagnosis of IBD for VZV, HPV, influenza, pneumococcal, HBV Influenza: annual trivalent vaccination in all IBD patients on immunomodulators Avoid live vaccines Consider oral antivirals in patients with recurrent HSV</td>
</tr>
<tr>
<td>BSR and BHPR Rheumatoid Arthritis Biologics Draft Guidelines (2009)\textsuperscript{51}</td>
<td>HBV: screen for risk factors, assess serology if felt to be appropriate HCV: screen for risk factors, assess serology if appropriate HIV: screen for risk factors, assess serology if appropriate VZV: confirm previous infection or immunization</td>
<td>Confirm routine vaccinations received HBV vaccine if considered at risk Influenza (annual) and pneumococcal vaccination Live viruses contraindicated up to 3 months after anti-TNF Avoid live oral polio vaccine in family members also Consider IV immunoglobulin if significant exposure to VZV or measles</td>
</tr>
<tr>
<td>Medical Board of the National Psoriasis Foundation: monitoring and vaccinations in patients treated with biologics for psoriasis (2008)\textsuperscript{52}</td>
<td>No clear consensus on testing for HBV or HCV. Notable variation in practice and recommendation by expert panel. Some advocate universal testing, others reserve for those with deranged liver function tests or risk factors. HBV: assess serology before commencing anti-TNF HCV: assess serology before commencing anti-TNF HIV: pre-treatment testing if risk factors present</td>
<td>Routine vaccines (given at baseline if possible). Variation in recommendation of influenza, HBV or pneumococcal vaccination amongst expert panel. Anti-viral prophylaxis if HBV positive</td>
</tr>
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</table>
Testing for serological status with regard to common herpes viruses or JC virus is not supported by the literature. The possible exception to this is testing for varicella zoster status, since primary infection in non-immune adult patients on anti-TNF therapy has been associated with fatal outcomes, and effective immunization exists. Many authors have recommended simply questioning patients about previous chickenpox to assess probable immunity, although this relies upon the accuracy of recall, and a number of cases of primary varicella infection occurred in patients who had reported previous chickenpox.\textsuperscript{50–52}

HPV testing is similarly not supported by the literature, although clearly all female patients should be encouraged to participate in the national cervical cytology screening programs. It is likely that immunization against HPV should be advocated once this is more widely available.

Although confirmation that patients have received standard vaccinations according to local and national schedules is good practice, whether specific additional vaccination is indicated in patients with IBD, particularly prior to anti-TNF therapy, is unsettled. Universal hepatitis B immunization in non-immune patients is recommended by ECCO, although there is little evidence that patients with IBD represent a high-risk group for the acquisition of HBV infection.\textsuperscript{50}

When administered, vaccine responses may be reduced in patients treated with anti-TNF drugs, but are still generally adequate to provide immunity. It is important to note that live vaccination (e.g. varicella zoster, MMR, yellow fever, vaccinia, oral polio vaccine) is contraindicated in patients receiving immunosuppressive therapy, including anti-TNF. Notably, live vaccines may also be relatively contraindicated in close contacts (e.g. children) of patients treated with anti-TNF. Studies have demonstrated that rates of immunization against preventable disease remain low in patients with IBD, and leave considerable room for improvement.\textsuperscript{53}

\textbf{Conclusions}

Despite numerous case reports of complications related to viral infection in patients treated with anti-TNF, until recently the subject has received limited attention. The recent formulation of guidelines and consensus statements concerning prevention of opportunistic infection in patients treated with anti-TNF therapy has partially addressed this issue, although as discussed above, some uncertainties persist. Specific risks associated with the use of anti-TNF drugs have been described in patients with chronic hepatitis B virus infection, and related to primary and reactivated varicella zoster infection. Despite their therapeutic
potency as immunosuppressive agents, and the theoretical risks of inhibition of TNF on the course of viral infection, a generally reassuring safety profile is emerging. However, further studies are required to fully define the long-term safety of anti-TNF treatment in chronic infections such as HCV, and in relation to potentially oncogenic viruses such as EBV or HPV.

With the availability of effective vaccines and anti-viral drugs, viral complications occurring in the setting of therapy for IBD can largely be effectively managed. Assessment of patients for latent tuberculosis has become standard practice prior to initiation of anti-TNF therapy, and in a similar manner, clinical and serological assessment of relevant vaccination and viral status should become routine.

Finally, severe infection with viruses including CMV, varicella or HSV has been reported, often with atypical features. Physicians managing patients receiving anti-TNF therapy for IBD or other conditions should remain vigilant for a viral aetiology in any such patient becoming unwell.

References


