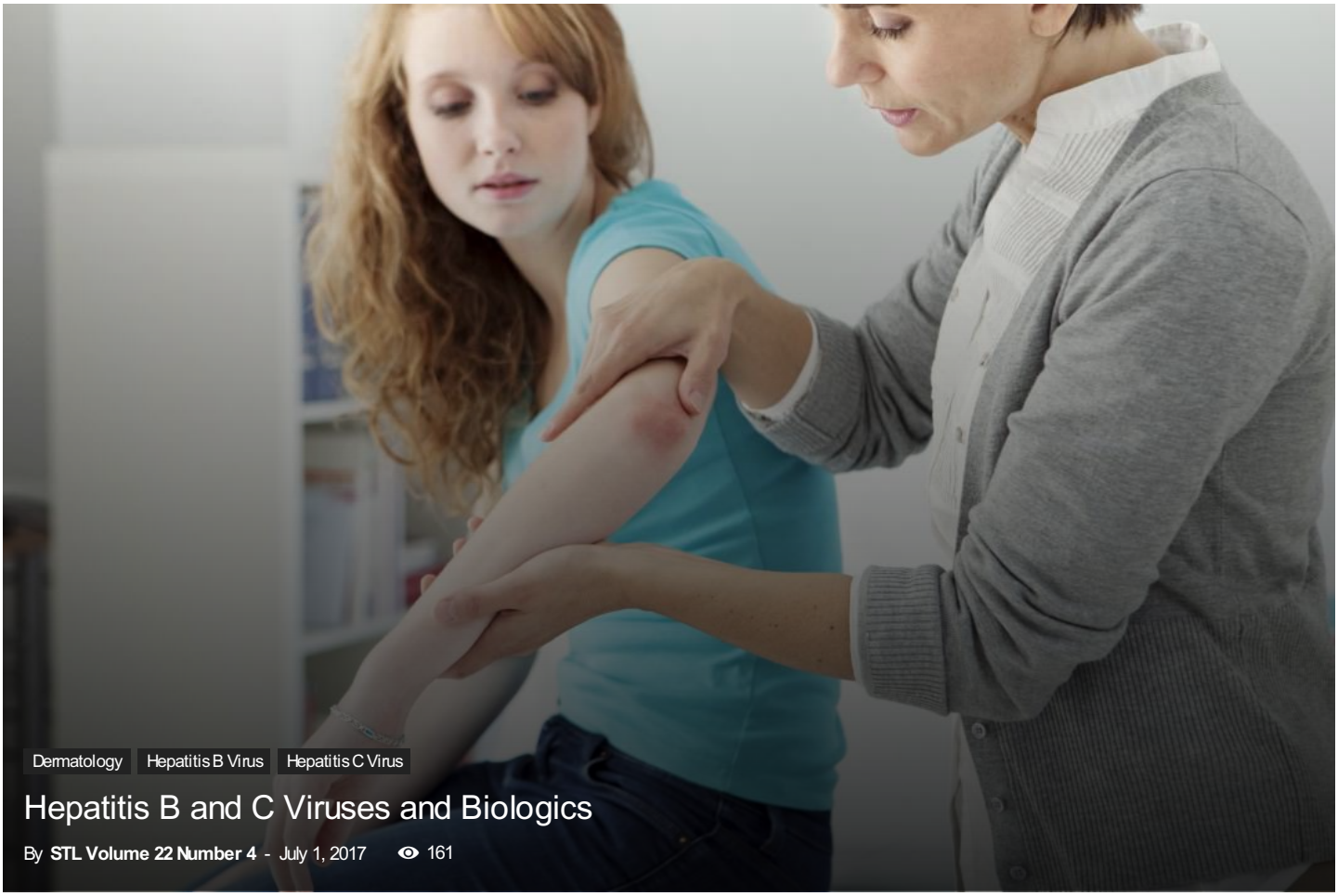

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ABSTRACT

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are common, worldwide viral illnesses that potentially impact the clinician's ability to manage patients with immunosuppressive medications such as biological therapy. In light of recent literature reviews, patients with HBV and HCV should be referred to a hepatologist or infectious disease expert prior to initiation of biological therapy.

Key Words:
adalimumab, biologic, etanercept, hepatitis B virus, hepatitis C virus, infliximab, ustekinumab

Introduction

Hepatitis B virus (HBV) is one of the most common, chronic viral illnesses affecting 370 million people worldwide.[1] Most often it is transmitted during birth or early childhood. Reactivated HBV is characterized by an abrupt increase in serum HBV DNA together with increased alanine aminotransferase (ALT) levels.[1] During

immunosuppressive therapy, HBV DNA in serum often increases by several log10 international units (IU), and this can result in activation of HBV-specific effector cells that target and destroy virally infected hepatocytes. This is particularly relevant in psoriatic patient populations because of the higher incidence of underlying fatty liver and alcoholic liver disease. Reactivation of hepatitis B has a wide clinical spectrum, varying from asymptomatic cirrhosis, to liver failure, to hepatocellular carcinoma, and even death in 15-25% of patients. Standard therapy includes antiviral medications such as lamivudine.[1] HBV has always been a relative contraindication to immunosuppressive or biologic therapy.[1] Table 1 summarizes the serological profiles and suggested management of patients with HBV. [1-3]

HBV infection	HBsAg	Anti-HBsAB	Anti-HBcAB	IgM Anti-HBcAB	Abnormal LFTs and/or symptoms	Additional testing	Treatment
Susceptible	–	–	–	–	–	Not necessary	Consider vaccination, treat with biologic
Immune due to natural infection	–	+	+	–	–		

Not necessary

Treat with biologic therapy

Immune due to HBV vaccine

–

+

–

–

–

Not necessary

Treat with biologic therapy

Acute infection

+

–

+

+

+

Not necessary

Defer biologic therapy, seek hepatologist

Chronic infection

+

–

+

–

+/-

HBeAg+, HBeAb-, HBV DNA

Treat with biologic in conjunction with hepatologist

4 possibilities:

1. Resolved infection
2. False-positive anti-HBcAB, thus susceptible
3. Low level chronic infection
4. Resolving acute infection

–

–

+

–

+/-

HBeAg-, HBeAB+, HBV DNA

Treat with biologic in consultation with a hepatologist

Table 1. Summary of serological profiles and suggested management of patients with HBV
HBsAg = hepatitis B surface antigen; HBsAb = hepatitis B surface antibody; HBcAb = total Hepatitis B core antibody; IgM anti-HBcAb = IgM to Hepatitis B core antibody; HBeAg = hepatitis B envelope antigen; HBeAB = hepatitis B envelope antibody; LFT = liver function tests.

Hepatitis C virus (HCV) is also one of the most common bloodborne viral infectious diseases affecting 4 million people in the US and 200 million people worldwide.[1] Although 30% of patients can experience spontaneous clearance, 70% of affected individuals will progress to a chronic persistent state of HCV. This ultimately leads to cirrhosis, end-stage liver disease, and hepatocellular carcinoma. Standard treatment involves the use of interferon-alpha (IFN-α) and ribavirin, with clearance response rates around 35-45%.[1] Sofosbuvir is a HCV nucleotide analog NS5B polymerase inhibitor indicated for the treatment of genotypes 1, 2, 3 or 4 chronic HCV infection as a component of a combination antiviral treatment regimen. Cure rates as high as 95% have been attained following 12 weeks of therapy.[4] However, due to the prohibitively high cost of such medications, many patients will still have to deal with chronic hepatitis C while on immunosuppressive therapy. Biologics, such as etanercept, infliximab and adalimumab, are considered to be relative contraindications and second-line therapies in moderate to severe psoriasis with co-existent HCV.[5] Interestingly, it has been found that tumor necrosis factor (TNF) levels are elevated in HCV, and higher levels of TNF are associated with more inflammation and fibrosis in the liver as well.[6] Table 2 summarizes the Center for Disease Control's (CDC) recommendations regarding the serological profiles and management of HCV.[7]

Test outcome

Interpretation

Further action

HCV antibody nonreactive

No HCV antibody detected	Sample can be reported as nonreactive for HCV antibody. No further action required. If recent HCV exposure in person tested is suspected, test for HCV RNA.
HCV antibody reactive	Presumptive HCV infection A repeatedly reactive result is consistent with current HCV infection, or past HCV infection that has resolved, or biologic false positivity for HCV antibody. Test for HCV RNA to identify current infection.
HCV antibody reactive, HCV RNA detected	Current HCV infection Provide person tested with appropriate counseling and link them to medical care and treatment.
HCV antibody reactive, HCV RNA not detected	No current HCV infection No further action required in most cases. If distinction between true positivity and biologic false positivity for HCV antibody is desired, and if sample is repeatedly reactive in the initial test, test with another HCV antibody assay. In situations involving recent HCV exposure, clinical evidence of HCV or concerns with specimen storage, follow-up with HCV RNA testing and appropriate counseling.

Table 2. Center for Disease Control's recommendations regarding serological profiles and management of HCV[7]

Discussion

Hepatitis B Virus (HBV)

In a published review of 257 patients treated with anti-TNF agents, there were 42 cases of HBV reactivation reported. This corresponds to a rate of reactivation of 16%, with 80% of cases occurring in hepatitis B surface antigen positive (HBsAg+) carriers, resulting in raised transaminase levels, emerging signs and symptoms of liver disease, the reappearance of serum hepatitis B viral DNA, and a mortality rate of 5%. The authors stated that HBsAg+ carriers with active liver disease and patients presenting with clinical symptoms (e.g., abdominal pain, jaundice, nausea, vomiting, dark urine, pale stools), raised liver enzymes, and/or high viral load should have the HBV infection treated and controlled before initiating therapy. In asymptomatic HBsAg+ carriers, antiviral prophylaxis is recommended and should be started 2-4 weeks prior to anti-TNF therapy and continued for at least 6 months after cessation. In anti-hepatitis B core antibody positive (HBcAB+) persons, routine prophylaxis is not recommended, although individual factors such as the degree of immunosuppression, the length of therapy, and the degree of local HBV endemicity should be taken into account. Regardless, these patients should always be carefully monitored (liver and viral tests every 1-3 months) for the duration of anti-TNF treatment, especially with the use of monoclonal therapy.[8]

In another review conducted between 2007 and 2011, 7 HBV carriers receiving TNF-alpha inhibitors for psoriasis were collected retrospectively. The HBV viral load and aminotransferase levels were regularly monitored. Two of

the 7 patients were inactive HBV carriers, and the other 5 patients had chronic hepatitis B. Only 1 patient received antiviral agents before the anti-TNF-alpha treatment. The mean duration of the anti-TNF-alpha treatment was 26.6 months (range, 14-45 months). These patients were followed from the start of the anti- TNF-alpha therapy for a mean duration of 28.9 months (range, 14-45 months). HBV reactivation was observed in 3 patients, 1 of whom required antiviral treatment. No HBV reactivationrelated hepatitis was observed.[9]

A separate systemic literature review identified 35 HBsAg+ carriers prior to initiation of TNF-alpha inhibitors. Infliximab was used in 17 cases, etanercept in 12 cases, and adalimumab in 6 cases. All 6 cases of clinically symptomatic hepatitis were associated with infliximab therapy. Infliximab was associated with the most cases of a greater than 2-fold increase in alanine aminotransferase (6 of 9 cases) and greater than 1,000-fold increase in HBV DNA load (3 of 4 cases). The 2 deaths due to liver failure occurred with infliximab therapy.[10]

In a retrospective analysis of 62 psoriatic patients with occult HBV infection treated with anti-TNF biological agents over a period of approximately 4 years: 44 subjects were treated with etanercept, 8 with infliximab, and 10 with adalimumab. During the observational treatment period, no signs of HBV activation were observed. In 1 patient the reappearance of HBsAg, without detectable HBV-DNA, was noted before retreatment with etanercept and after 10 months from discontinuation of the previous course. In this patient, etanercept was re-administered in association with lamivudine without any adverse event.[11]

Another case report series followed 7 psoriatic arthritis patients with positive HBcAB who were also on adalimumab for 6 years. Only 1 patient was HbSAg+, and this was the only individual started on prophylactic lamivudine. None of the patients experienced reactivation of hepatitis.[12]

A retrospective analysis was done on 17 patients (13 men and 4 women, aged 36-74 years) with plaque-type psoriasis associated with hepatitis infections (11 with past HBV infection, 5 with chronic HCV infection and 1 affected by both HBV and HCV). Fourteen patients had received etanercept, 2 adalimumab and 1 adalimumab as a second biologic treatment after an unsuccessful trial of etanercept. No changes in serum aminotransferases or viral load were reported in any of these cases.[13]

In regards to ustekinumab, there are sporadic case reports available. One patient with chronic HBV was treated with ustekinumab and had no aggravation of hepatitis after 15 months.[6]Another study of 14 patients was conducted where 11 were HBsAg+. Of these patients, 7 were not given antiviral prophylaxis and 2 patients experienced reactivation, whereas the 3 patients with occult HBV infection had no reactivation.[14]

Hepatitis C Virus (HCV)

There are numerous publications that provide evidence supporting the safe use of biological therapy in the context of HCV. A review of 216 patients with HCV exposed to 1 or more TNFalpha inhibitors over 260 cumulative patient years of exposure revealed only 3 cases of drug withdrawal due to liver issues.[15] In a separate review of 153 patients with HCV infection on TNF-alpha inhibitors, there was only 1 confirmed case of worsening HCV infection.[16] Another retrospective, observational, and multicenter study was carried out in 4 Italian centers. There were 7 patients on adalimumab (40 mg subcutaneously [SC] every 2 weeks) and 8 on etanercept (4 patients at a dosage of 50 mg SC once a week and 4 patients on 25 mg SC twice a week) for a mean of 16 months of therapy (range 12-24 months). During the observation period, these values remained stable and no patients showed reactivation of hepatitis.[17] A prospective open study followed 29 patients with active rheumatoid arthritis that were randomly assigned to receive therapy with methotrexate (MTX) alone, etanercept alone, or a combination of MTX and etanercept, and monitored up to 54 weeks. Aspartate transaminase (AST) and alanine transaminase (ALT) enzyme concentrations did not significantly change in all 3 arms of treatment, nor did the HCV viral load. No patients discontinued the therapy because of worsening liver disease.[18]

Interestingly, Zein et al. conducted a double-blind placebo controlled trial of 50 patients with HCV infection on interferon and ribavirin, and also gave half of the patients concomitant etanercept.[19] The group receiving etanercept actually achieved a higher frequency of viriological and biochemical response and had fewer side effects than the placebo group.[19] A study by Khanna et al. in 2005 reviewed the use of etanercept in 5 clinical studies and also found it to be beneficial when used in combination with standard treatments for HCV.[20]

Very few publications, including Orion et al. and Vigna-Perez et al., provide evidence against the use of TNF-a inhibitors in patients with HCV. They found that adalimumab created a down-regulatory effect on T lymphocytes and, thus, indicated an enhanced risk of bacterial tuberculosis or viral infection reactivation.[21,22]

With respect to ustekinumab, 1 small study of 2 patients treated for 15 months had no aggravation or reactivation of HCV.[6] Another publication showed that 2 of 4 patients had an increase in the HCV copy number and 1 patient fulfilled the HCV reactivation criteria and later developed hepatocellular carcinoma.[14]

Conclusion

All patients with HBV should always be referred to a hepatologist or infectious disease expert prior to biological therapy. Almost all of these patients will require prophylactic antiviral therapy. The only possible exceptions might be those recovering from an acute HBV infection with loss of anti-HBc in serum or patients with chronic HBV with seronegative serum profile. If prophylactic therapy is started, an antiviral should be given pre-emptively, either 2 to 4 weeks before or concomitant with the start of immunosuppressive therapy. Lamivudine has been recommended when immunosuppressive therapy is likely to be less than 6 to 12 months, whereas agents with better resistance profiles such as entecavir and tenofovir are considered preferable when immunosuppressive therapy is continued longer.[1] Although curative treatments are available, affordability may prevent access, therefore, we will still have to manage patients with chronic HCV on concomitant biological therapy.

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