Management of rheumatic disease with comorbid HBV or HCV infection

Dimitrios Vassilopoulos and Leonard H. Calabrese

Abstract | Despite the major advances towards better prevention and treatment of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, these two chronic infections still account for ~500 million infected people and 1 million deaths per year worldwide. Rheumatologists are frequently encountering patients with rheumatic disease who have co-existing HBV or HCV infection in daily clinical practice. Moreover, over the past decade, a number of studies have shown an increased risk of HBV reactivation and liver-related complications in HBV-infected patients treated with biologic agents (especially anti-TNF therapies). In this Review, the basic viral characteristics of HBV and HCV, as well as the natural course of chronic HBV and HCV infection, are outlined. Furthermore, a rational clinical approach for diagnosis and treatment of these comorbid conditions in the context of rheumatic disease is presented.

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Introduction

Chronic infections with hepatitis B virus (HBV) or hepatitis C virus (HCV) remain a global health problem, affecting ~500 million people (~7% of the total world population). Chronic HBV and HCV infection represent the most common cause of cirrhosis and liver cancer worldwide, and account for ~1 million deaths per year globally.[1,2] Widespread vaccination programmes for hepatitis B have markedly decreased the number of new infections (especially in developed countries), whilst newer antiviral therapies can now achieve long-term viral suppression in the majority of patients with chronic hepatitis B (>95%) and cure ~60% of patients with chronic hepatitis C.[3–5]

Despite these major therapeutic advances, the majority of patients with chronic HBV or HCV infection are asymptomatic and remain undiagnosed. Rheumatologists should be aware of the basic facts regarding HBV and HCV infections, including their diagnosis, natural course and treatment. This knowledge is crucial not only from a public health perspective, but also for practical reasons—the administration of traditional immunosuppressive agents or the newer biologic therapies in patients infected with HBV or HCV could lead to serious complications, such as liver failure that can result in liver transplantation or even death. Notably, this risk seems to be much higher with chronic hepatitis B than chronic hepatitis C. In this Review, we will provide basic information on HBV and HCV infection as a guide for rheumatologists, as well as describe a screening and treatment algorithm for patients with rheumatic disease who have co-existing HBV or HCV infection.

Athens University School of Medicine, 2nd Department of Medicine, Hippokration General Hospital, 114 Vass Sophias Avenue, 11527 Athens, Greece (**D. Vassilopoulos**). Department of Rheumatic and Immunologic Diseases, Cleveland Clinic, 9500 Euclid Avenue, Desk A50, Cleveland, Ohio 44195, USA (**L. H. Calabrese**).

Correspondence to: L. H. Calabrese calabrl@ccf.org

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Hepatitis B

HBV characteristics

HBV is a small, partially double-stranded DNA virus that belongs to the family of *Hepadnaviridae* and is classified in 10 different genotypes (A–J; Table 1).[3,6] After viral transmission—either perinatal, sexual or percutaneous[3,6]—the virus enters hepatocytes and its DNA is converted to the covalently closed circular form (cccDNA) in the nucleus of these cells. This form of DNA, which serves as the transcriptional template for a number of different viral mRNAs coding for HBV proteins (hepatitis B core antigen [HBcAg], hepatitis B surface antigen [HBsAg], hepatitis B e antigen [HBeAg], DNA polymerase, HBV X protein [HBx]) has the unique ability to persist in infected hepatocytes for long periods of time, even after viral clearance (spontaneous or treatment-induced). This persisting hepatic reservoir of HBV DNA is responsible for the viral reactivation during immunosuppressive therapy that occurs in a small proportion of patients with past or resolved HBV infection.

In adults infected with HBV, following a short period (lasting weeks) when the virus remains hidden from the host immune system, strong innate (involving natural killer [NK] and natural killer T [NKT] cells) and adaptive (mainly through $CD8^+$ T cells) immune responses are mounted against infected hepatocytes expressing HBV antigens.[7] Noncytolytic and cytolytic immune-mediated mechanisms of viral clearance are engaged in this process, including the action of different cytokines such as interferons (IFN-α, IFN-β and IFN-γ), TNF and IL-6.[7–9] In the majority of adults infected with HBV, host immune responses are able to eradicate the virus (>95%).[1]

Most patients with chronic HBV infection have acquired the virus either through vertical or perinatal transmission (mother to child), as occurs in most Asian countries, or during early childhood through intrafamilial

spread (as is the case in most Mediterranean countries).[1,10] Why the developing immune system of the infant or child is unable to mount an efficient immune response and clear the infected hepatocytes, whereas the opposite occurs during adulthood exposure, is currently unclear.

Natural course of infection

Chronic HBV infection runs through different, usually successive, phases (Figure 1).[1,10,11] During the first, or immune-tolerant, phase (HBeAg-positive)—despite active viral replication in the liver (indicated by high serum HBV DNA levels)—the host immune response against the infected hepatocytes is negligible, with normal levels of aminotransferase aspartate aminotransferase (AST) or alanine aminotransferase (ALT). This phase is usually absent or short-term in adults, but can last for decades in infections acquired perinatally or in early childhood.[1] Random integration of HBV DNA into the host's hepatocyte DNA can occur during this period of high HBV DNA replication.[1] HBV DNA integration into the hosts' chromosomes can increase the risk of hepatocellular carcinoma (HCC) and decrease the likelihood of HBV eradication (either spontaneously or after antiviral treatment).

The second phase, labelled as the immune active or clearance phase, is characterized by a vigorous host immune response against HBV-infected hepatocytes, leading to immune-mediated hepatocyte damage and increased AST or ALT levels (hepatitis). During this HBeAg-positive phase, persistently high or fluctuating HBV DNA levels are associated with marked liver necroinflammation and fibrosis.[1] Eventually, the majority of patients (90%) lose HBeAg spontaneously and develop anti-HBeAg antibodies (HBeAg seroconversion).[1]

The majority of patients (70–90%) who achieve HBeAg seroconversion enter a third phase called the inactive carrier state, which is characterized by low or undetectable serum HBV DNA levels (<2,000 IU/ml), normal AST or ALT levels, minimal liver inflammation or fibrosis and a low risk of liver-related complications (cirrhosis, HCC, death). A proportion of patients who remain in the inactive state for a long period of time eventually lose HBsAg expression at a rate of 0.5–1% per year (Figure 1).[1]

10–30% of HBeAg-negative patients develop chronic hepatitis B,[1,10] either immediately after the immune active phase or years later during the inactive carrier phase.[12] HBV mutant strains with absent or reduced HBeAg secretion, but with intact ability to replicate, predominate during this phase, leading to flares of immune-mediated liver inflammation, which are detected by fluctuating HBV DNA and ALT levels.[12]

Current standard of care

Treatment with antiviral agents is indicated for patients during the immune active stages of the disease (that is, HBeAg positive or negative chronic hepatitis B, which are associated with an increased risk of HBV-related complications such as cirrhosis, HCC or death).[1,13] Although certain differences exist between US and European treatment guidelines,[1,13] in general, therapy is recommended for patients with HBeAg-positive chronic hepatitis B who have elevated ALT (more than one[13] or two[1] times the upper limit of normal values) and/or high HBV DNA (>2,000 IU/ml[13] or >20,000 IU/ml[1]) levels. For patients with HBeAg-negative chronic hepatitis B, therapy is indicated when ALT levels are elevated (more than one[13] or

Key points

- Rheumatologists frequently encounter patients with rheumatic disease who are also infected with either hepatitis C virus (HCV) or hepatitis B virus (HBV)
- Chronic hepatitis B and C can be serious comorbid conditions in patients with rheumatic disease
- HBV reactivation occurs frequently in HBV-infected patients with rheumatic disease who are receiving anti-TNF agents or rituximab without appropriate antiviral prophylaxis
- Oral antiviral therapy can effectively prevent HBV reactivation and is recommended for all HBV-infected patients receiving high-risk immunosuppressive therapy
- Patients with past HBV infection should be carefully screened and monitored during biologic therapy (especially with B-cell-depleting agents) for viral reactivation
- In patients with rheumatic disease who have comorbid chronic hepatitis C, biologic therapy with anti-TNF or B-cell-depleting agents seems to be safe

Table 1 | Comparative virological and clinical features of HBV and HCV infection

Feature	HBV	HCV
Global prevalence	350 million	180 million
Virus (Family)	DNA (*Hepadnaviridae*)	RNA (*Flaviviridae*)
Genotypes	10 (A–J)	6 (1–6)
Clinical significance of genotypes	Clinical course: worse in genotype C	Response to antiviral therapy: worse in genotype 1 than other genotypes
Transmission routes	Intrafamilial Vertical (mother to child) Sexual Injection-drug use	Injection-drug use Transfusion (before 1992) High-risk sexual activity Unknown (15–30%)
Rate of chronicity after viral exposure	<5% (adults); 10–30% (children); 90% (mother to child)	60–85%
Clinical symptoms	Usually asymptomatic	Usually asymptomatic
Lifetime risk of liver complications (cirrhosis, HCC, death)	Up to 40%	15–30%
Factors associated with worse prognosis	Male sex Age >40 years High HBV DNA levels Co-infections (HDV, HIV, HCV) Alcohol intake Genotype C	Male sex Older age at virus exposure (>40 years) Long disease duration Co-infections (HBV, HIV) Alcohol intake
Diagnostic screening	HBsAg, anti-HBc and anti-HBs serum levels	Anti-HCV antibodies: if positive then test for HCV RNA levels
Standard antiviral therapy for chronic hepatitis	Oral nucleos(t)ide analogues indefinitely (HBeAg negative) or 6–12 months after HBeAg seroconversion (HBeAg positive), or PEG-IFN-α2a for 1 year	PEG-IFN-α plus ribavirin for 6–12 months
Reactivation with anti-TNF therapy	Frequency of ~40%	Rare
Need for prophylactic antiviral therapy	Always (oral antivirals)	Only if indicated

Abbreviations: anti-HBc, antibodies against hepatitis B core antigen; anti-HBs, antibodies against HBsAg; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; PEG-IFN, pegylated interferon.

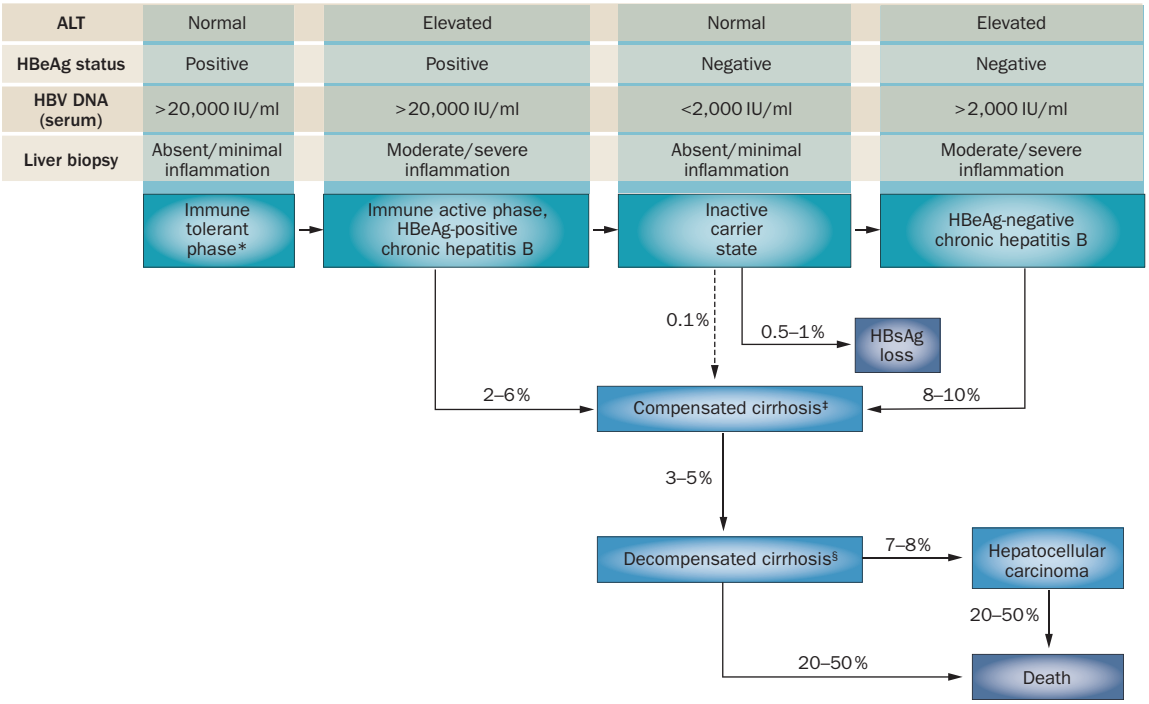

Figure 1 | The natural history of chronic HBV infection. Key features of the natural course of chronic hepatitis B, as well as the most common serological, virological and histological findings in each phase are depicted. Percentages indicate annualized rates of progression.[11,90] *This period can be short or absent in patients infected after birth or during adulthood, but lasts for decades in perinatally acquired infection (especially in patients with genotype C). ‡Liver is heavily scarred, but still functioning. §Liver is heavily scarred and no longer functions properly. Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

two[1] times the upper limit of normal values) and HBV DNA levels are >2,000 IU/ml.[1,13] In doubtful hepatitis B cases, a liver biopsy is helpful for diagnosis and treatment decisions—treatment is indicated when moderate to severe liver inflammation and/or fibrosis is present.[1,13]

Currently available antiviral therapies aim at long-term suppression of viral replication, sustained HBeAg seroconversion (for HBeAg-positive chronic hepatitis B) or HBsAg loss. The goal of long-term viral suppression can now be achieved in >95% of cases with oral antiviral therapies, although HBsAg loss remains a hard to achieve target (<10%).[1] Moreover, successful antiviral therapy can prevent HBV-related complications (cirrhosis) and improve survival.[1,3]

Antiviral agents approved for the treatment of chronic hepatitis B include IFN-α (standard and pegylated-IFN-α2a) and five different oral nucleoside (lamivudine, telbivudine, entecavir) or nucleotide (adefovir, tenofovir) analogues.[1,13] In general, IFN-α-based regimens given subcutaneously for 1 year achieve HBeAg seroconversion in approximately one-third of HBeAg-positive patients and sustained HBV DNA suppression in ~20% of HBeAg-negative patients, whereas HBsAg loss occurs in ~8% of patients.[14] Despite their good efficacy, IFN-α regimens are poorly tolerated, owing to common adverse effects (such as cytopenia or flu-like symptoms), and are infrequently used in daily clinical practice today (<10% in the USA; no data are available for rates in Europe).[15]

Oral antiviral agents have markedly changed the landscape of HBV treatment during the past decade. These agents are efficacious and have an overall safer profile than IFN-α. The first generation of these agents (such as lamivudine) were associated with a high rate of viral resistance during long-term treatment of chronic hepatitis B (~70% after 5 years of treatment) and are not commonly used today.[1,13] New agents with a low rate of viral resistance (such as entecavir and tenofovir) are considered the first-line treatment choices for chronic hepatitis B.[1,13] In contrast to IFN-α, these agents have to be given either indefinitely (HBeAg-negative chronic hepatitis B) or for 6–12 months following HBeAg seroconversion (34–50% after 3–5 years of treatment) in HBeAg-positive chronic hepatitis B.[14,16] As discussed below, these agents are the preferable antiviral agents for prophylaxis in patients infected with HBV receiving immunosuppressive agents. No evidence so far indicates that combination schemes with IFN-α and oral antiviral agents are superior to monotherapy in patients with chronic hepatitis B.[1,13]

HBV reactivation and antirheumatic therapies

Definition

HBV reactivation is described mainly on virological terms as an increase of serum HBV DNA levels by >1 $\log_{10}$ compared with baseline, or a switch in HBV DNA detection from negative to positive.[17] Liver inflammation (hepatitis) indicated by elevated ALT levels usually follows viral reactivation.[17] HBV reactivation can remain subclinical, but in a proportion of patients severe icteric hepatitis and acute liver failure can complicate its course, and death can occur.[17] These life-threatening

complications usually develop in patients with active viral replication (chronic hepatitis B) and advanced fibrosis and/or cirrhosis.[17]

Different immunosuppresive agents (such as corticosteroids), chemotherapeutic drugs and the newer biologic therapies (anti-TNF or B-cell-depleting agents) can cause unopposed HBV replication in the liver by suppressing the host immune response (reflected by increased levels of serum HBV DNA and increased expression of HBV-derived antigens in hepatocytes).[18] Immune-mediated liver inflammation and hepatocyte lysis (hepatitis) can then occur, usually after discontinuation of the immunosuppressive therapy, as a result of the restored immune response.[17–19]

DMARDs

The observation that immunosuppressive therapies can cause HBV reactivation was first made almost three decades ago.[17] Since then, a number of studies in patients with neoplastic (mainly breast cancer) or haematological (mainly lymphomas and leukaemias) diseases have clearly shown that the risk of HBV reactivation is ~50% without antiviral prophylaxis and is associated with a high rate of HBV-related liver mortality (5–30%).[17] Pre-treatment factors associated with an increased risk of reactivation include high levels of HBV viraemia and the inclusion of high-dose corticosteroids in the chemotherapeutic regimen.[19]

Data regarding the rate of HBV reactivation in patients with autoimmune or rheumatic diseases who received traditional immunosuppressive regimens for a short or long period of time are limited. Isolated case reports detail HBV reactivation in patients receiving low-dose corticosteroids or DMARDs (such as methotrexate).[19,20] Nevertheless, if we consider the number of patients who have received such therapies for decades worldwide, we can assume that the risk of HBV reactivation is rather low and certainly less than that seen with chemotherapeutic or biologic agents. On the other hand, treatment with high-dose steroids poses an increased risk of HBV reactivation compared with DMARDs, as has been shown in patients receiving chemotherapeutic regimens that included increased dose of steroids.[21]

Anti-TNF agents

TNF is a pleiotropic cytokine that is specifically involved in host defence against HBV during the acute or chronic phase of infection.[7,9,19] Following the first case reports of HBV reactivation in anti-TNF-treated patients in 2003,[22,23] a number of studies have indicated an increased risk of HBV reactivation during anti-TNF therapy in patients chronically infected with HBV (reviewed in detail elsewhere[24]). In a 2011 review of 89 published cases of HBV-infected patients treated with anti-TNF agents, HBV reactivation was observed in 35 cases (39%);[24] this reactivation rate is close to that observed in patients receiving chemotherapeutic agents (~50%).[17]

Some points with regard to the interpretation of this important data deserve attention. First, in approximately one-third of cases the diagnosis of HBV infection was made during screening or after initiation of anti-TNF treatment, indicating the need for universal HBV screening in patients starting such therapy.[25] Second, in most cases (~75%) viral reactivation was accompanied by biochemical activity (increased AST and/or ALT levels). Furthermore, it should be noted that five patients developed acute liver failure and four died from HBV-related complications.[24] These data are indicative that HBV reactivation can be severe in a proportion of HBV-infected patients without adequate antiviral prophylaxis. Although caution is needed in analyzing this data, being from isolated case reports or small retrospective case series with potential publication bias, they nevertheless strongly indicate an increased risk of HBV reactivation in anti-TNF-treated HBsAg-positive patients.

B-cell-depleting agents

Most data regarding HBV reactivation during B-cell-depleting therapy (rituximab) are from studies in patients with haematological diseases (mainly lymphomas), in whom HBV reactivation has been reported to occur in 27–80% of cases without antiviral prophylaxis.[26–28] It should be mentioned, though, that these patients usually receive combination therapies with high-dose steroids and other chemotherapeutic agents that might contribute to this increased reactivation rate. Only one case report has detailed HBV reactivation in a patient with rheumatoid arthritis (RA) treated with rituximab.[29] Despite the limited data, it is likely that the risk of HBV reactivation is increased during rituximab therapy in patients with rheumatic disease.[30]

Other biologic agents

Data on the effects of the newer biologic agents on HBV reactivation are limited. So far only one case of HBV reactivation in a patient treated with abatacept has been reported,[31] but tocilizumab has been used in combination with antiviral therapy without HBV reactivation according to three reports.[32–34] Interestingly, in one of these patients (HBeAg positive in the immune-tolerant phase), tocilizumab was administered alone for >7 years before antiviral prophylaxis was started, without HBV reactivation.[32]

Patients with resolved HBV infection

Spontaneous HBsAg clearance (HBsAg negative) after acute or chronic HBV infection leads to a state called resolved HBV infection, which is diagnosed by the presence of antibodies against HBcAg (anti-HBc) in the serum (with or without anti-HBsAg antibodies [anti-HBs]).[1] Using sensitive molecular techniques, HBV DNA can still be detected in the liver (and, occasionally, in the serum in low quantities) in a proportion of patients, defining this subgroup as 'occult HBV infection'.[35] The prevalence of resolved HBV infection (HBsAg negative and/or anti-HBc positive) in the general population follows the prevalence of HBV infection in the same population and can range from 5% in countries with a low HBV prevalence (<1%) to 60–70% in countries with a high HBV prevalence.[1]

Data from oncology and haematology literature has shown that HBV reactivation occurs in <5% of patients

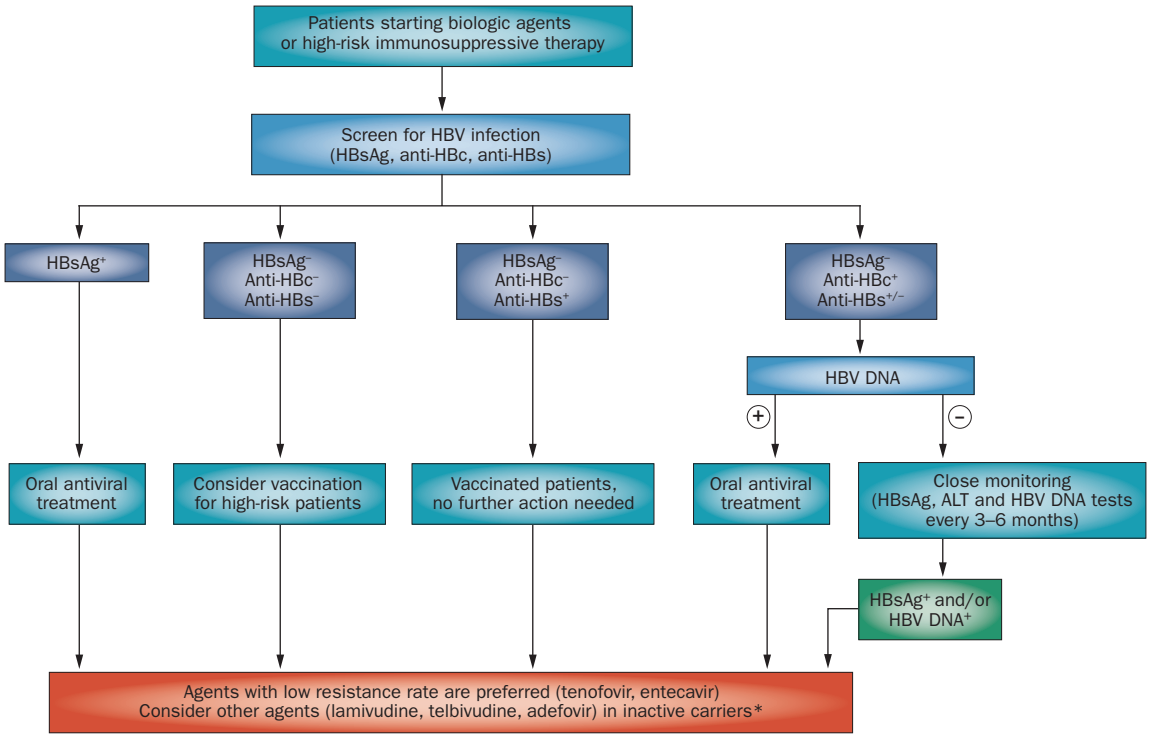

Figure 2 | A screening and treatment algorithm for patients with past or current HBV infection starting biologic immunosuppressive therapies. A screening and treatment algorithm suitable for individuals starting biologic or high-risk immunosuppresive therapy (high-dose steroids, cyclophosphamide, etc) based on available data in the literature is depicted. This algorithm can be applied to patients with rheumatic disease. *Defined as: HBV DNA ≤2,000 IU/ml, normal ALT and absent or minimal inflammation and/or fibrosis in liver biopsy (if performed). Abbreviations: ALT, alanine aminotransferase; anti-HBc, antibody against hepatitis B core antigen; anti-HBs, antibody against HBsAg; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

with resolved HBV infection treated with chemotherapy,[36–38] although this rate seems to be higher in rituximab-treated patients (3-25%).[26,39–41] In patients with rheumatic or autoimmune diseases and resolved HBV infection, the cumulative reported rate of HBV reactivation after anti-TNF therapy is 5%,[24] although major differences exist between studies. In three prospective studies from Southern Europe (France, Italy, Greece), no cases of HBV reactivation among 107 patients with resolved HBV infection treated with anti-TNF agents were noted (anti-HBc positive only; $n = 48$, anti-HBc and anti-HBs positive; $n = 59$),[42–44] and none of these closely monitored patients had occult HBV infection at baseline (all HBV DNA negative). In a retrospective study from Taiwan, Lan *et al.*[45] similarly did not observe HBV reactivation among 58 anti-HBc-positive and anti-HBs-positive patients during anti-TNF therapy. By contrast, of 12 patients positive for anti-HBc, one-third (4 of 12) had occult HBV infection, of whom only one developed HBV reactivation.[45]

Collectively, these data indicate that the risk of HBV reactivation is rather low in patients with anti-HBc and anti-HBs, although this reactivation rate could be higher for patients with true occult HBV infection (anti-HBc positive, anti-HBs negative, HBV DNA positive). Cross-sectional studies investigating the prevalence of occult HBV infection in patients with rheumatic disease starting biologic therapy are needed, as well as prospective studies evaluating the need for prophylactic antiviral therapy versus therapy during reactivation.

Clinical approach

Currently, no formal guidelines exist for the screening, monitoring or treatment of patients with rheumatic disease and current or past HBV infection who start biologic therapies. Our approach for screening and treatment of these patients is based on currently existing recommendations, expert opinion and literature data and are presented in Figure 2.[1,13,19,25]

Initial testing for HBsAg, anti-HBc and anti-HBs should be performed in all patients starting biologic therapies or high-risk immunosuppressive therapies (high-dose steroids, cyclophosphamide, mycophenolate mofetil). HBsAg-positive patients have chronic HBV infection and should receive oral antiviral therapy. The protective role of antiviral therapy has been established in numerous studies over the past decade. For HBsAg-positive patients with haematological or neoplastic diseases who have received chemotherapeutic agents, antiviral prophylaxis with lamivudine has been shown to reduce the rate of HBV reactivation and HBV-related mortality by >80% compared with untreated controls;[46,47] similar results have been obtained with rituximab-containing regimens.[28,48–50] For patients with rheumatic diseases, data so far are limited as prospective controlled trials have not yet been performed. In a prospective study

of 14 HBsAg-positive patients with rheumatic disease who were treated with anti-TNF agents for ~2 years, only one case of HBV reactivation (7%) was reported and that was due to the emergence of a lamivudine-resistant strain after 3 years of treatment with this drug.[44] Furthermore, in a 2011 review of all literature on HBsAg-positive individuals who had received anti-TNF agents, HBV reactivation occurred in 25% of patients who had received antiviral therapy compared with 62% in patients who did not ($P = 0.0005$).[24] No specific data are available regarding the potential protective effect of antiviral therapy in HBV-infected patients with autoimmune or rheumatic diseases who are treated with rituximab, but we can assume that such a protective effect is similar as to that seen in patients with haematological or neoplastic disease.

The choice of the most appropriate antiviral agent should be decided in consultation with a hepatologist and is usually based on additional testing including HBV DNA and ALT levels and, in certain cases, liver biopsy results.[51] In general, considering that most patients with rheumatic disease usually receive long-term, chronic treatment (that is, biologic agents), antivirals with low resistance rates (that is, a reduced chance of the virus developing resistance) such as tenofovir or entecavir are preferred.[1,13] Other agents such as lamivudine, adefovir or telbivudine can be considered for inactive carriers or patients scheduled for short-term therapy (<1 year). Patients who discontinue immunosuppressive therapies should continue antiviral therapy for at least 6–12 months. Frequent monitoring of ALT and HBV DNA levels (every 3–6 months) is crucial to diagnose and treat appropriately any viral reactivation from drug-resistant strains during long-term therapy. The management of patients with proven viral resistance should be made by an experienced hepatologist according to current treatment guidelines.[1,13]

Patients vaccinated against HBV (HBsAg negative, anti-HBc negative, anti-HBs positive) are considered immune and no further action is needed. Anti-TNF therapy has been shown to slightly decrease anti-HBs titres,[42,44,45] but the clinical relevance of this finding is most probably limited. For nonexposed patients (negative for HBsAg, anti-HBc and anti-HBs), a decision to vaccinate should be based on their risk of HBV transmission. Nevertheless, if we consider that HBV vaccination is safe and efficacious, vaccination should probably be offered to all patients with rheumatic disease starting high-risk immunosuppressive therapy.

A number of unresolved issues for patients with resolved HBV infection (HBsAg negative, anti-HBc positive, anti-HBs positive or negative) remain. It is becoming clear that the risk of HBV reactivation is much lower in patients with resolved HBV infection who are HBV DNA negative compared with patients who are HBV DNA positive (have occult infection). Thus, it is desirable to obtain a baseline HBV DNA level for each patient with resolved infection. For patients who are found to be HBV DNA positive, antiviral therapy should be started (as for patients with chronic infection), and for those who are negative, close monitoring is imperative. Taking into account the cost of HBV DNA testing and the large number of patients with resolved infection who need to be tested (especially in endemic, developing countries), this process might not be a realistic option. For such patients, frequent monitoring of HBsAg and ALT levels (every 3–6 months) might suffice to diagnose early HBV reactivation and administer appropriate antiviral therapy.

Hepatitis C

Natural course of infection

HCV should be considered an emerging pathogen in rheumatic diseases,[52] having been only identified through molecular cloning in 1989.[53] Critical to the rheumatologist caring for patients with underlying HCV infection is an understanding of the viral infection itself: its basic epidemiology, microbiology and natural history.

HCV is a global public health problem with ~180 million people now estimated to be infected (Table 1).[2] Although rates of new infection have sharply dropped in the Western world since the development of serological testing (with improved diagnosis as a result of this testing) and advances in sterilization of medical instruments, the rates of HCV infection have remained disturbingly high in areas with poor health-care resources. Confounding the battle against HCV is the fact that most people infected with the virus do not seem to be clinically ill and the treatments, as will be further discussed, are expensive, lengthy and toxic.

In the USA, the estimated prevalence of HCV is ~1.6% of the total population, with 75% thought to be unaware that they are infected.[54] In Europe, the prevalence varies from <0.5% in Northern Europe to >3% in Romania and rural areas.[55] It should be noted, however, that even within a given country the seroprevalence of HCV can differ greatly depending on the demographical features of the population. Thus, a rheumatologist working with patient populations at increased risk (that is, drug users, inner city inhabitants, and so on) might be seeing HCV in their patients with RA at drastically increased rates. In the USA, point prevalence studies performed at several urban Veteran's Affairs Medical Centers have revealed that 11–40% of inpatients and outpatients are HCV seropositive.[56] Collectively, an estimated 350,000 people die annually worldwide as a result of HCV-related liver disease.[57]

A summary of the microbiological, epidemiological and clinical features of HCV is provided in Table 1. HCV is an RNA virus and a member of the *Flaviviridae* family; it is characterized by marked genetic diversity, which has striking effects on treatment response.[2] The virus has a short half-life and turns over an estimated 10–12 billion particles per day.[58] HCV replicates with a low degree of genetic fidelity, leading to the presence of quasispecies that thwart a definitive and curative immune response and complicate vaccine development.[58,59] The high rate of viral turnover also contributes to ongoing immune activation, leading to an array of extrahepatic immunological complications (Box 1).[60] Transmission is primarily parenteral, mainly through injection drug use, although sexual transmission has been well-documented with high-risk activities, especially in men who have sex with men.[4]

Box 1 | Extrahepatic manifestations of chronic hepatitis C

- HCV-associated cryoglobulinaemic vasculitis (small vessel)
- Membranoproliferative glomerulonephritis
- HCV-associated sialadenitis
- HCV-associated arthritis
- HCV-associated medium vessel vasculitis (PAN-like)
- Porphyria cutanea tarda
- Autoantibody formation (rheumatoid factor, anti-nuclear, anti-thyroid, anti-cardiolipin)
- Autoimmune cytopenias

Data from references.[60,64,65] Abbreviations: HCV, hepatitis C virus; PAN, polyarteritis nodosa.

The natural history of HCV is complex; therefore, it is critical for rheumatologists caring for HCV-infected patients to understand where the patients fall in this clinical spectrum (summarized in Figure 3). After infection, an estimated 60–85% of patients become chronically and persistently infected.[2] Depending on numerous factors—including older age, presence of steatosis, male sex, alcohol use and other factors—an estimated 20% of patients develop end-stage liver disease and are likely to die of liver-related complications (Table 1).[2] This progression generally occurs over several decades (Figure 3). Implicit in this natural history is the fact that 75–80% of HCV-infected patients will not die of HCV infection. Identifying who is likely to progress is critical for optimal management of both the rheumatic disorder as well as the attendant HCV infection. Unfortunately, at present, the gold standard for determining prognosis is liver biopsy as no statistically significant correlation exists between liver enzyme levels, or HCV viral load, and prognosis.[2] A number of tests for blood biomarkers and the use of transient elastography have held promise for a more non-invasive approach to determining prognosis,[61,62] although these options have not been extensively investigated in patients with rheumatic diseases.

Extrahepatic complications of HCV infection

An array of extrahepatic complications of HCV have been described including cryoglobulinaemic vasculitis, arthritis and sicca syndrome (reviewed in detail elsewhere[60,63–65]). The main manifestation for which major progress has been observed, particularly with regard to therapy, is that of HCV-associated cryoglobulinaemia. Two therapeutic approaches show promise in this disorder that rheumatologists should be aware of—namely the use of the biologic agent rituximab and the application of antiviral therapy.

In our experience, rituximab, a biologic agent targeting $CD20^+$ B cells, is a logical choice of therapy given the underlying problem of cryoglobulinaemia is hyperactive B cells producing immunoglobulins, often monoclonal, with the physiochemical property of being cryoprecipitable. Traditional therapies, which in the pre-HCV era consisted of aphaeresis, cyclophosphamide and glucocorticoids, are suboptimal yet might be useful in the treatment of patients with fulminant disease.[65] Although rituximab is not approved for HCV-related cryoglobulinaemia, substantial off-label experience has been generated with promising results. Rituximab has been used in a variety of patients—those naive to antiviral therapy; those intolerant or for whom antiviral therapy is contraindicated; and for those who have failed antiviral therapy[66–75]—and has been recommended as part of the therapeutic armamentarium by an Italian consensus panel.[76] Two phase III randomized controlled trials have clearly demonstrated the efficacy of rituximab in HCV-associated cryoglobulinaemia.[74,75] In general, both clinical and immunological effects have been observed and in one of the larger studies rituximab seemed superior to antiviral therapy alone.[77] At the present time, however, rituximab should be used with caution. Clinicians using this approach should be aware of toxicities and adverse effects, including infection and possible flare of vasculitis from rapid immune complex formation, in those with the highest levels of cryoglobulins.[78] The use of low-dose IL-2 has been demonstrated to have impressive efficacy in patients infected with HCV who are refractory to antivirals,[79] and deserves further investigation.

Rheumatologists should also be aware that antiviral agents alone might be the optimal therapy for patients' with milder forms of the disease (skin manifestations limited to inflammatory purpura, mild neuropathy and no life-threatening complications).[65,80] Over the past two decades, major advances in antiviral therapy for HCV have occurred; these advances have been reviewed elsewhere[2,81] and are summarized in Figure 4. The suggestion is that we can now expect virological cure in up to 75% of patients who are candidates for such therapy.[2,81] Numerous studies have documented the effectiveness of a combination of pegylated interferon and ribavirin,[82] and studies incorporating the newly approved direct protease inhibitors have yet to be reported but are in progress (Patrice Cacoub, personal communication).

Unfortunately, many patients are not candidates for antiviral therapy based on comorbidities including renal failure, uncontrolled mood disorders and other factors. In addition, interferon-based therapies can exacerbate underlying autoimmune diseases (including psoriasis, inflammatory arthritis and various vasculitic manifestations such

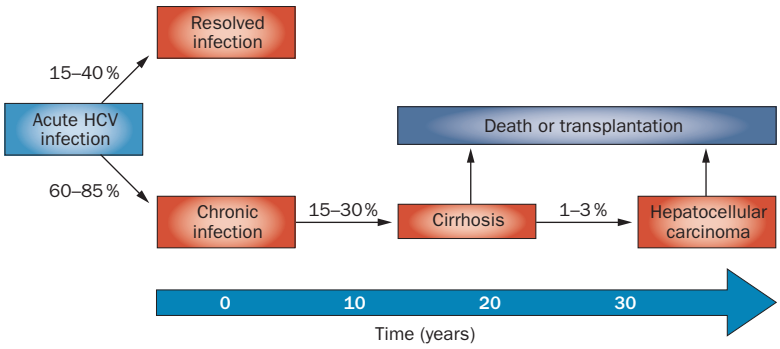

Figure 3 | The natural history of HCV infection. Key features of the natural course of chronic hepatitis C are depicted. The rate of progression to cirrhosis in those infected with HCV, in general, is accelerated by a long duration of infection, viral exposure after the age of 40, daily alcohol use (>50 g per day), male sex and co-infections due to HBV and/or HIV. Data presented from references.[2,58] Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus.

as ischaemic skin lesions, neuropathy, nephropathy, and so on) and must be carefully monitored.[83,84]

Rheumatic disease and associated HCV infection

For patients with established autoimmune and autoinflammatory disease, associated HCV infection poses a series of special challenges. For patients with RA, clear guidelines on long-term management of chronic viral hepatitis with minimal parenchymal disease are lacking, with adequate guidance only for patients with advanced liver disease.[85] Although conventional wisdom suggests that avoiding hepatotoxic drugs (such as methotrexate and leflunomide) is logical and less potent agents (such as antimalarials and sulfsalazine) are safer, there is a paucity of data for all nonbiologic DMARDs in terms of their contributions to hepatic fibrosis (as assessed by serial liver biopsies). On the other hand, the published experience in multiple inflammatory disease states—including RA, inflammatory bowel disease and psoriasis—is growing, suggesting TNF inhibitors are safe according to the reported experience, as summarized in a 2011 systematic review.[86] Of 153 patients with chronic HCV infection who had been treated with different anti-TNF agents (etanercept, $n = 110$; infliximab, $n = 34$; adalimumab, $n = 9$), only two cases (1.3%) of confirmed or possible HCV-related liver worsening were recorded.[86] In addition, data from one small trial indicate that etanercept might actually enhance the effect of IFN-based antiviral therapy.[87] Moreover, a multicentre trial of infliximab as an adjunct for HCV therapy, which will include pre-therapy and post-therapy liver biopsies, is now completely enrolled;[88] this trial promises to provide the first large study examining the effects of an anti-TNF agent on liver histology.

As discussed above, rituximab is a safe option in patients with chronic HCV infection and cryoglobulinaemia and can thus be used in patients with co-existing RA,[85] although efficacy data in such patients are lacking. The safety of more potent immunosuppressive drugs (such as cyclophosphamide) and antimetabolites (such as mycophenolate mofetil or azathioprine), which can be used to treat other forms of connective tissue disease, have not been systematically investigated. However, the safety of these immunosuppressive drugs can be inferred from their extensive use in the setting of liver transplantation and in treatment of HCV cryoglobulinaemia in the pre-antiviral[89] and antiviral era.[75]

Clinical approach

In the absence of more formal guidance on co-management of HCV infection in patients with rheumatic disease and the existing gaps in evidence, we believe the following represents a reasonable clinical approach. Rheumatologists should strongly consider screening for HCV infection (that is, initial test for HCV antibodies and follow-up testing for HCV RNA) in all patients with rheumatic diseases initiating long-term immunosuppressive therapy with biologic agents, nonbiologic agents or conventional immunosuppressive therapies. All viraemic patients should be referred to a hepatologist for co-management, which includes consideration for baseline liver biopsy and determination of whether the patient warrants HCV antiviral therapy. For patients with underlying autoimmune or autoinflammatory disease initiating IFN-α-based therapies, the rheumatologist should remain vigilant for exacerbation of, or newly developed, autoimmune sequelae. For those initiating long-term immunosuppression (especially with biologic agents), serial assessments for progression of hepatic fibrosis are warranted. Above all, the optimal treatment of patients with rheumatic diseases and comorbid HCV requires a close and open relationship between the rheumatologist and interested hepatologist. Neither specialist can be considered most important in these cases when evidence-based data on management are often lacking. As always, shared and informed decision-making with the patient is of the utmost priority.

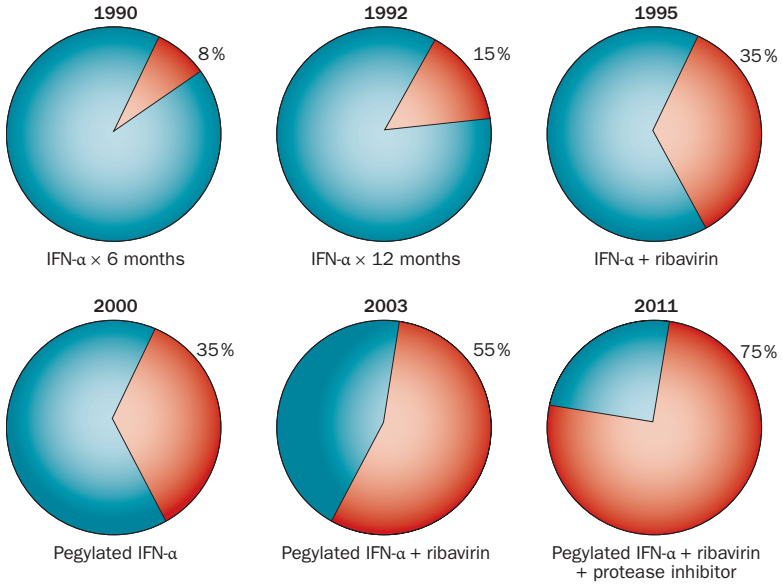

Figure 4 | The evolution of antiviral therapies for chronic hepatitis C. Over the past two decades, major advances have been made in the treatment of chronic hepatitis C, with up to 75% of patients treated with antiviral therapy achieving a virological cure (that is, undetectable levels of HCV RNA). Percentages of patients achieving a virological cure are shown in red; the proportion who did not achieve this cure is shown in blue.

Conclusions

The widespread experience with the use of biologic agents in patients with autoimmune or autoinflammatory diseases over the past decade has revealed the serious threat of HBV reactivation in patients receiving these agents (such as anti-TNF agents or rituximab), whilst, at the same time, has shown that their use in patients with well-compensated chronic hepatitis C is fairly safe in the short term. The potential life-threatening complications of HBV reactivation emphasize the need for appropriate screening of all patients with rheumatic disease starting high-risk immunosuppressive therapy by the caring rheumatologist. Furthermore, the encouraging results of successful prevention of HBV reactivation with appropriate oral antiviral therapy demonstrate that antirheumatic treatment with biologic agents should not be withheld in

these patients, given that proper pre-treatment evaluation and on-treatment monitoring in collaboration with a hepatologist is provided. For patients with chronic hepatitis C and associated cryoglobulinaemic vasculitis, the use of antiviral therapy (either alone or in combination with rituximab) has markedly improved the outcome of these difficult to treat patients.

Review criteria

Relevant articles for this Review identified by searching PubMed using different combinations of the MeSH terms "hepatitis B", "hepatitis C", "tumor necrosis factor-alpha", "rheumatic diseases", "Biological Control Agents", "antibodies, monoclonal" and "TNFR-Fc fusion protein" was performed.

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Author contributions

Both authors contributed equally to all aspects of this manuscript.