Original Article

Outcomes of Chronic Hepatitis B Infection in Oriental Patients with Rheumatic Diseases

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Abstract

Introduction: The aim of this study was to ascertain the outcomes of chronic hepatitis B (CHB) infection following immunosuppressive therapy in 38 consecutive oriental patients with systemic rheumatic diseases. Materials and Methods: This is a retrospective consecutive, non-comparative study. Results: The majority of patients were female (26, 68.4%), predominantly Chinese (92.1%), with a mean age 54 ± 14 years (range, 16 to 87). The mean duration of rheumatic disease was 9 ± 11 years (range, 0.1 to 48), with rheumatoid arthritis (52.6%) and systemic lupus erythematosus (23.7%) being the most common. The mean duration of CHB infection was 6 ± 5 years (range, 0.1 to 17), with the majority diagnosed during pre-methotrexate screening (50.0%) and asymptomatic transaminitis following initiation of immunosuppressive therapy (23.7%). Upon diagnosis of rheumatic disease, all patients had normal alanine aminotransferase (ALT). Of these, 18.2% were positive for hepatitis B e antigen (HBeAg) and 78.1% were positive for anti-HBe antibody. Twenty (52.6%) developed ALT elevation, which was more than twice the upper limit of normal in 12 patients. ALT normalised spontaneously in 12 patients without hepatic decompensation or change in therapy. Seven (18.4%) patients received lamivudine for 18 ± 22 months (range, 2 to 61). Two patients developed YMDD mutation subsequently treated with adefovir (1) and adefovir/lamivudine (1). There were 3 (7.9%) hepatitis B virus (HBV)-unrelated deaths [infection (2), genitourinary malignancy (1)], and 1 from HBV-reactivation complicated by septicaemia. None have developed hepatocellular carcinoma. Conclusion: Elevated ALT occurred in 52.6% of patients, with only 18.4% requiring anti-viral therapy for HBV reactivation. HBV-related mortality was low. With the appropriate precautionary measures, prednisolone and immunosuppressants (except methotrexate and leflunomide) may be used safely in patients where clinically indicated.

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Key words: Ankylosing spondylitis, Lamivudine, Rheumatoid arthritis, Spondyloarthropathies

Introduction

More than 75% of patients with chronic hepatitis B virus (HBV) infection are found in Asia, where hepatitis B is the leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC).[1] A hepatitis B seroprevalence survey conducted in 1999 showed that the overall prevalence of chronic hepatitis B (CHB) virus infection was 4.1% among Singapore residents aged between 18 and 69 years.[2] The level of immunity to HBV virus was also lowest in the 18 to 29 years age group. Up to 50% of patients with chronic HBV infection in Singapore have chronic hepatitis, with raised serum alanine aminotransferase (ALT) and histologic changes, and about 20% have cirrhosis.[3]

The relationship between HBV and rheumatic disorders include rheumatic manifestations of CHB infection,[4] hepatitis B vaccination triggering autoimmune diseases,[5] and CHB reactivation following initiation or withdrawal of corticosteroid and non-corticosteroid-based immunosuppressive therapies, more commonly described in the treatment of cancer than rheumatic diseases.[6] To our knowledge, there has been no study to date on the outcomes of CHB

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infection in a large cohort of oriental patients with systemic rheumatic diseases treated with immunosuppressive therapies.

Materials and Methods

This was a retrospective, non-comparative case series of all consecutive patients with CHB seen in the inpatient and outpatient services of the Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital during the 6-year study period from 1 August 2000 to 31 July 2006. The clinical records of all patients were retrospectively evaluated for their demographic profile, types of rheumatic disease, hepatitis B serologies, name and doses of immunosuppressive therapies used, anti-viral therapies and outcome, and outcome of CHB infection and rheumatic disease activity at last review. The data was analysed using EXCEL (Microsoft) and SPSS 10.0 (SPSS Inc) softwares.

Results

There were 12 (31.6%) male and 26 (68.4%) female patients. The racial distribution comprised of Chinese (92.1%), Malays (5.3%) and other races (2.6%). The mean age of all patients was 54 ± 14 years (range, 16 to 87). The mean duration of rheumatic disease from diagnosis was 9 ± 11 years (range, 0.1 to 48), with rheumatoid arthritis (RA) (52.6%), systemic lupus erythematosus (SLE) (23.7%) and psoriatic arthritis (10.5%) being the most common. The distribution of the various types of rheumatic diseases is shown in Table 1.

Table 1. Distribution of Types of Rheumatic Diseases (n = 38)

Types of rheumatic diseases	No. of patients	%
Rheumatoid arthritis	20	52.6
Systemic lupus erythematosus	9	23.7
Psoriatic arthritis	4	10.5
Ankylosing spondylitis	3	7.9
Sjogren's syndrome	1	2.6
Dermatomyositis	1	2.6

Table 2. Immunosuppressive Therapies in 8 Patients Receiving Anti-viral Therapy

Types of immunosuppressive therapies	Rheumatic disease	No. of patients	%
Sulfasalazine	PsA	1	12.5
Prednisolone	SLE	1	12.5
Prednisolone + azathioprine	SLE, DM	2	25.0
Prednisolone + hydroxychloroquine	SLE, RA	2	25.0
Prednisolone + sulfasalazine	AS	1	2.5
Prednisolone + methotrexate + sulphasalazine + hydroxychloroquine	RA	1	12.5

AS: ankylosing spondylitis; DM: dermatomyositis; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus

CHB infection, mean duration 6 ± 5 years (range, 0.1 to 17) from diagnosis, was diagnosed during pre-methotrexate screening (19, 50.0%), asymptomatic elevation of liver enzymes (9, 23.7%), routine health screening (7, 18.4%), evaluation of cutaneous vasculitis associated with the underlying rheumatic disease (2, 5.3%), and evaluation for cirrhosis (1, 2.6%). Upon diagnosis of their rheumatic disease, all patients had normal ALT. 18.2% of patients were positive for hepatitis B e antigen (HBeAg), 78.1% were positive for anti-HBe antibody and 54.5% with elevated HBV DNA.

Following immunosuppressive therapy, 20 (52.6%) patients developed ALT elevation, which was more than twice the upper limit of normal in 12 patients. Seven (35%) patients had ultrasonographic evidence of non-alcoholic fatty liver disease. HBV DNA was elevated in 8 (40.0%), negative in 6 (30.0%) and not tested in 6 patients (30.0%). ALT normalised spontaneously in 12 patients without hepatic decompensation or change in therapy, including in those where HBV DNA was negative or not tested.

Eight (21.1%) patients received lamivudine, among whom 7 received lamivudine therapeutically for HBV reactivation (elevated ALT and HBV DNA), and 1 prophylactically for normal ALT with elevated HBV DNA. Among the 7 patients treated for HBV reactivation, 3 (37.5%) had HBeAg-negative viraemia. The various types of immunosuppressive therapies patients with HBV reactivation had received prior to the initiation of lamivudine are summarised in Table 2. Of note, HBV reactivation occurred following the use of high dose (0.5 to 1 mg/kg/d) prednisolone in 2 patients, and low dose (<10 mg/d) in 4 patients, where prednisolone was being gradually tapered at a rate of 1 to 5 mg every 2 to 4 weekly in 3 patients. These 6 patients also concomitantly received azathioprine (2), hydroxychloroquine (2), sulfasalazine (1), and a combination of hydroxychloroquine, sulfasalazine and methotrexate (1). Only 1 patient who had psoriatic arthritis developed HBV reactivation while receiving sulfasalazine alone. Four patients had liver biopsies done, among whom all had active necroinflammation, and 3 had histological evidence of fibrosis. All 7 patients treated for HBV reactivation received lamivudine over 18 ± 22 months (range, 2 to 61). Two of these patients developed treatment-resistant YMDD mutation of HBV. One was a patient with SLE who received adefovir for 20 months after having been on lamivudine for 25 months. The other patient with RA with histological evidence of cirrhosis received adefovir and lamivudine for 3 months after having been on lamivudine for 61 months.

HBV-related mortality was low. There were a total of 4 deaths, of which 3 (7.9%) were HBV-unrelated deaths

Table 3. Types of Therapy as at Last Review (n = 38)

Arthritides	**RA (n = 20)**	**PsA (n = 4)**	**AS (n = 3)**
Nil	1	0	1*
PNL	2	1	0
SSZ	2	3 (1*)	2
PNL + SSZ	3	0	0
PNL + CsA	1	0	0
SSZ + AZA	1*†	0	0
SSZ + IM Gold	1	0	0
PNL + SSZ + D-Pen	2	0	0
PNL + SSZ + AZA	1	0	0
PNL + SSZ + HCQ	4 (1*)	0	0
HCQ + SSZ + D-Pen	1	0	0
PNL + HCQ + SSZ + D-Pen	1	0	0
Connective tissue diseases	**SLE (n = 9)**	**pSS (n = 1)**	**DM (n = 1)**
PNL	1	1	0
HCQ	1*	0	0
AZA	1	0	0
PNL + AZA	1	0	0
PNL + HCQ	2	0	0
PNL + CYP	1*†	0	0
PNL + CsA	0	0	1*
HCQ + AZA	1	0	0
PNL + HCQ + MMF	1	0	0

AS: ankylosing spondylitis; AZA: azathioprine; CsA: cyclosporine; CYP: cyclophosphamide; DM: dermatomyositis; D-Pen: D-penicillamine; HCQ: hydroxychloroquine; IM: intramuscular; MMF: mycophenolate mofetil; PNL: predisolone; PsA: psoriatic arthritis; pSS: Primary Sjogren's syndrome; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSZ: sulfasalazine

* HBV reactivation treated with anti-viral therapy

† Lamivudine-related YMDD mutation

from pyogenic infection (2) and metastatic transitional cell carcinoma of the ureter (1). There was 1 death from HBV reactivation associated with *Proteus mirabilis* septicaemia and multi-organ failure in a patient with SLE. None of the patients developed hepatocellular carcinoma (HCC).

Upon last review, 22 (57.9%) patients, of whom 16 (72.7%) had inflammatory arthritis and 6 (27.3%) had connective tissue diseases, were deemed to still have active systemic rheumatic disease requiring a median of 2 (IQR, 1 to 3) immunosuppressive therapies. The types of immunosuppressive therapies at last review are summarised in Table 3.

Discussion

Reactivation of HBV infection is a well recognised complication in infected patients who undergo cytotoxic chemotherapy for cancer and other forms of immunosuppressive therapies.[6] The clinical manifestations range from asymptomatic self-limiting anicteric hepatitis to severe, progressive decompensated hepatitis. Risk factors for HBV reactivation from studies in cancer patients undergoing chemotherapy include being male, being of a younger age and having pre-chemotherapy ALT elevation. HBeAg positivity and pre-chemotherapy HBV DNA viral load were not consistently found to be risk factors in most studies. As for the treatment factors, corticosteroids and anthracyclines have been most frequently associated with HBV reactivation.[6] From our study, there were no particular clinical or virological features that were more commonly seen in patients with HBV reactivation. The majority of patients requiring anti-viral therapy developed HBV reactivation while on prednisolone regardless of whether they were on a high or low dose, and no matter what the rate of prednisolone taper. There did not appear to be any correlation between HBV reactivation with any other specific disease-modifying anti-rheumatic drug (DMARD). This was partly because of the variety of combinations of DMARD used, with relatively few patients for each type of DMARD precluding meaningful statistical comparison.

Immunosuppressive therapy resulting in reactivation of HBV infection has been reported in the rheumatology literature mainly in the form of case reports or case series. To our knowledge, this is the largest cohort of patients where long-term outcomes of patients with various rheumatic diseases and CHB following long-term immunosuppressive therapy were studied. CHB reactivation has been reported following the use of chloroquine,[7] azathioprine,[8] methotrexate,[9,10] pulse methylprednisolone/cyclophosphamide plus hydroxychloroquine and combination of hydroxychloroquine, sulphasalazine and methotrexate in the treatment of various rheumatic diseases.[11] There have been no reports of HBV reactivation with other DMARD – like intramuscular gold and D-penicillamine. In our series, intramuscular gold and D-penicillamine were in fact not uncommonly used in the treatment of active RA in the presence of CHB infection where methotrexate and leflunomide are contraindicated. With the advent of biologic DMARDs, reports of reactivation following the use of the anti-tumour necrosis factor (TNF) agent infliximab[12-16] (but not etanercept and adalimumab) have been reported in cases of RA,[12,15] spondyloarthropathy,[16] ankylosing spondylitis (AS)[14] and adult onset Still's disease.[13] Although CHB reactivation has been reported following the use of anti-CD20 monoclonal antibody, rituximab, in combination with prednisolone, cyclophosphamide, doxorubicin and vincristine in the treatment of lymphoma,[6] there have been no reports of reactivation when used in the treatment of systemic rheumatic diseases like SLE and RA. The use of mycophenolate mofetil has been reported to result in HBV reactivation in HBV-associated membranous nephropathy and following renal transplantation.[17,18] This has not been reported in rheumatic diseases to date, in

particular in SLE where this is now increasingly used in the induction and maintenance treatment of proliferative lupus nephritis.[19,20] Our only patient with SLE who received prednisolone, mycophenolate mofetil and hydroxychloroquine did not develop CHB reactivation.

In our clinical practice since the mid-1990s, all patients are routinely tested for HBsAg and hepatitis C antibody positivity prior to initiation of methotrexate or leflunomide,[21] given the endemicity of CHB in Singapore and the risk of hepatotoxicity with these 2 drugs. These drugs are not initiated in CHB patients, and methotrexate is withdrawn and replaced with alternative DMARDs in patients who are subsequently found to have CHB. We do not routinely screen all patients for HBsAg prior to the initiation of all other immunosuppressive drugs, although serum ALT is periodically tested in the majority of patients. Thus, 23.7% of our cohort was diagnosed with CHB following evaluation for asymptomatic elevation of liver enzymes.

Various mechanisms have been proposed to explain how CHB reactivation might occur following immunosuppressive therapy. CHB infection is a dynamic state of interactions between the virus, hepatocytes and the host immune system as HBV is usually not cytopathic by itself. Acute exacerbation of CHB secondary to any form of immunosuppressive treatment is usually accompanied by enhanced viral replication, as reflected by increases in the serum levels of HBV DNA, HBeAg, HBV DNA polymerase and infection of naive hepatocytes with HBV initially. The second stage is related to restoration of immune function following withdrawal of cytotoxic or immunosuppressive therapy, which causes rapid immune-mediated destruction of infected hepatocytes, with upregulated host immune responses including HLA-class I antigen restricted, cytotoxic T lymphocyte (CTL) mediated responses against HBV antigens expressed on hepatocytes, culminating in apoptosis.[22] HBV-specific CTL also secrete TNF-alpha, resulting in elevated levels of TNF-alpha in the serum and hepatocytes of CHB patients.[23-25] Consequently, different TNF-alpha promoter polymorphisms have been shown to be associated with different outcomes of CHB infection.[26] Although lysis of HBV-infected hepatocytes is mainly mediated by CD8 cytotoxic T cell immunity, B cells may also act as antigen-presenting cells and prime cytotoxic T lymphocyte-specific responses in HBV infection.[27]

In vitro studies using HBV DNA-transfected hepatoma cells incubated with prednisolone, azathioprine and cyclosporine have demonstrated increased intracellular viral DNA and RNA levels by approximately 2-fold and 4-fold with prednisolone and azathioprine respectively, but no change in the levels of viral RNA or DNA with cyclosporine.[28] The mechanism by which corticosteroids mediate HBV reactivation and replication has been shown to be likely to be via the specific glucocorticoid-respone element in the HBV genome.[29,30] The role of TNF-alpha in promoting viral clearance in HBV infection may be a possible mechanism resulting in reactivation with anti-TNF alpha therapies.[31] Similarly, down-regulation of TNF-alpha with chloroquine may also be a mechanism leading to reactivation following the use of hydroxychloroquine.[32] However, not all immunosuppressive therapies appear to promote HBV replication. Studies have shown that mycophenolic acid and cyclosporine, but not tacrolimus inhibit HBV replication in vitro.[33-35] In our series, apart from prednisolone being associated with HBV reactivation, the use of azathioprine and hydroxychloroquine were not consistently associated with HBV reactivation. There were only 2 patients treated with cyclosporine and 1 with mycophenolate mofetil, making it difficult to draw any conclusions on the effects of these on HBV reactivation.

The indications for anti-viral therapy in CHB infection include persistent elevation of serum ALT, defined as 3 or more readings of serum ALT at levels above twice the upper limit of normal within a period of 6 months, and HBeAg positive and/or HBV DNA (as measured by non-PCR technique) positive. Pre-treatment liver biopsy, although not mandatory, may be useful in excluding other causes of elevated serum ALT, e.g. non-alcoholic fatty liver disease and drug-induced hepatitis, and to prognosticate the extent of HBV-related hepatic necroinflammation and/or cirrhosis. The goals of treatment are sustained virological suppression, thus decreasing the risk of cirrhosis, liver failure and HCC.[36,37]

In patients with systemic rheumatic disease and in kidney transplant recipients, the duration of immunosuppressive therapy is usually long-term, and possibly life-long. In such patients, nucleoside analogue (NA) is the current treatment of choice as interferon-alpha will be contraindicated since it may augment the patient's immune response, thus aggravating the underlying rheumatic disease or inducing allograft rejection. Lamivudine, the first available NA, is well tolerated and gave rise to a HBeAg seroconversion rate of up to 40% after 3 years and 47% after 4 years of treatment in a non-immunosuppressed host.[38,39] It has also been shown to be effective in delaying clinical progression in CHB-related cirrhosis by reducing the incidence of hepatic decompensation in non-immunosuppressed hosts.[40]

The main limitations are the development of YMDD mutation with long duration of NA therapy and potential acute exacerbation of CHB following withdrawal of NA treatment. Newer antiviral agents like adefovir and entecavir have been used as second-line antiviral therapy in patients who developed lamivudine resistance.[41-43] Nevertheless, it should be noted that lower incidence of drug resistance, compared to lamivudine, for these agents were best seen in

treatment-naïve patients.[44,45] Entecavir resistance was most commonly seen in patients with pre-existing or co-existing lamivudine resistance.[46] Among our patients, the majority with HBV reactivation received lamivudine over an average of 24 months, with YMDD mutation developing in 2, who were subsequently treated with either adefovir alone or a combination of adefovir and lamivudine.

The role of prophylactic antiviral therapy remains controversial in patients with rheumatic diseases requiring long-term immunosuppressive therapy,[47] in contrast to patients who receive cytotoxic therapy for cancer who require a more finite period of cancer chemotherapy, where prophylactic lamivudine has been shown to be effective.[6,48]Although prophylactic use of lamuvidine was deemed to be effective in preventing the exacerbation of CHB in 3 patients with RA, 1 with spondyloarthropathy and 1 with AS in recent studies on patients who received etanercept, infliximab or adalimumab,[12,14,49] there were no comparable or placebo groups in these series to support the effectiveness of lamivudine "prophylaxis".

Patients with CHB who require long-term immunosuppressive therapy require periodic monitoring of serum ALT for CHB flares, in particular following the initiation and withdrawal of therapy. In addition, liver function tests should be monitored when patients are maintained on the maximum dose of immunosuppressive therapy, especially over a substantial period of time. For the present, NA appears to be the treatment of choice for the exacerbation of CHB. Adefovir and entecavir should be considered in patients who have developed YMDD mutation following lamivudine treatment. The prophylactic use of lamivudine for rheumatic diseases, although advocated by some,[47,49] remains controversial.

Elevated ALT occurred in 52.6% of patients in our study, with only 18.4% requiring anti-viral therapy for HBV reactivation. HBV-related mortality was low. With the appropriate precautionary measures, prednisolone and immunosuppressants (except methotrexate and leflunomide) may be used safely in patients where clinically indicated.

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