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LAVORO ORIGINALE

Prophylaxis and therapy of HBV infection in 20 patients treated with disease modifying antirheumatic drugs or with biological agents for rheumatic diseases*

Profilassi e terapia dell'infezione da HBV in 20 pazienti con malattie reumatiche trattati con farmaci "di fondo" o agenti biologici

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RIASSUNTO

La nostra esperienza in 20 pazienti consecutivi documenta la possibilità di effettuare una profilassi o terapia dell'infezione da HBV in pazienti con malattie reumatiche in cui è necessaria una terapia immunosoppressiva con farmaci "di fondo" tradizionali o con agenti biologici. Tale comportamento permette di utilizzare al meglio le terapie antireumatiche e di ridurre il rischio di riaccensioni dell'epatite virale.

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INTRODUCTION

Hepatitis B virus (HBV) is a DNA virus transmitted predominantly by sexual contact or percutaneous exposure. HBV infection is by far the most common chronic viral infection affecting the liver in the world, and a leading cause of cirrhosis and hepatocellular carcinoma. Reactivation of HBV replication in patients undergoing immunosuppressive therapy is a well recognised and frequently reported complication of considerable clinical importance. The consequences of hepatic injury in these patients may range from asymptomatic liver function disturbances to massive hepatic necrosis, liver failure, and death (1-2).The frequence of viral reactivation in HBV carriers with onco-haematological disorders undergoing immunosuppressive therapy ranges from 14% to 50%, associated with 5% to 12% mortality (3-4).

An unrecognised HBV infection may expose patients with rheumatic diseases to the same risks. In fact, viral reactivation leading to serious complications has been reported also in patients undergoing therapy with traditional disease modifying antirheumatic drugs (DMARDs) and/or biological agents, including anti-tumour necrosis factor (TNF) and anti-B cell therapy (5-15), indicating the need for an accurate screening in patients candidate to these treatments.

On the other hand, the presence of HBV infection may induce to delay or to avoid the use of these drugs, with the risk to undertreat rheumatic patients who need such therapy.

However, it has been suggested that prophylactic treatment with antiviral agents can reduce the rate of reactivation and the mortality associated with flares. Lamivudine, the agent of choice, is a potent inhibitor of HBV replication in patients with chronic infection, by causing chain termination of an RNA-dependent HBV polymerase. Although no randomised trial have been completed, most reports to date have demonstrated the benefit of

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lamivudine given prophylactically to patients with cancer undergoing chemotherapy (16-19). It has been suggested that lamivudine should be given throughout the course of treatment and extended for 6 months after completion of the chemotherapy regimen, because HBV flares my occur days or weeks after chemotherapy has stopped. Short term lamivudine is safe and, usually, free of toxicity, with a risk-benefit ratio that flavours prophylaxis. Analogously, in a small number of patients with rheumatic disease who had reactivation of HBV during an immunosuppressive regimen, lamivudine was successfully employed to suppress HBV replication, allowing successful reinstitution of treatment. Moreover, in few cases, the drug was used as prophylaxis in HBV inactive carriers considered at high risk of reactivation (12, 13, 20-22). The benefit versus risk of prophylactic antiviral therapy to prevent HBV flares is less certain in those patients requiring an extended course of immunosuppressive therapy, since long-term lamivudine administration is associated with the emergence of lamivudine-resistant HBV (23, 24). Limited information is available on the rate of lamivudine resistance in immunosuppressed subjects (23, 25).
We refer here on a series of 20 consecutive patients who received lamivudine as prophylaxis of HBV reactivation, or therapy of active infection, when treated with high-risk traditional DMARDs or with biological agents for rheumatic diseases.

PATIENTS AND METHODS

At our Department, since January 2004, all consecutive patients with rheumatic diseases receiving, or planned to receive, either immunosuppressive DMARDs or biological agents (TNF-alpha- or IL-1-blocking agents, anti B-cell marker antibodies) underwent a revaluation of HBV markers, including HBsAg, HBsAb, HBcAb.
Patients were classified as: active carriers; inactive carriers (HBsAg positive, aminotrasferase persistently normal; HBV-DNA <2,000 copies/ml); potential occult carriers (HBsAg negative, HBcAb positive).
Antiviral treatment was recommended in all the active carriers.
As far as the inactive carriers, according the suggestions of the Italian Association for the Study of the Liver (A.I.S.F.) (26), patients were divided into two risk categories with regard to the type and to the degree of immunosuppression:

a) high risk of HBV reactivation, in patients undergoing the following therapy: biological agents, medium to high dosage steroids (>7.5 mg/die) for prolonged periods (27), immunosuppressors such as cyclophosphamide, methotrexate, leflunomide, calcineurin antagonists, azathioprine and mycophenolate mofetil;
b) low risk of HBV reactivation, in patients treated with steroids at <7.5 mg/die, sulfasalazine or hydroxychloroquine. Antiviral prophylaxis was started in patients of the first risk category.

Antiviral treatment was recommended even in patients classified like potential occult carriers (HBsAg negative, HBcAb positive), with the prescription to a treatment with rituximab, a chimeric monoclonal anti-CD20 antibody, in relation with the particular risk of viral reactivation during this treatment (15).
Twenty patients with chronic HBV infection and with rheumatic disease who were receiving immunosuppressive therapy, or were candidates for it, in which antiviral treatment was needed, were identified, and are the object of this analysis. Their main demographic and clinical data are shown in table I. Immunosuppressive treatment was performed according the rheumatologist decision and is indicated in Table I, while antiviral treatment was performed according to the infectious diseases specialist: Lamivudine 100mg/die was prescribed to all patients, and in 3 patients, adefovir dipivoxil was associated. Data were censored at October, 30, 2007. HBV-DNA was measured by branched-DNA PCR assay (HBV-DNA 3.0, Syemens). Sensibility limit is 2,000 copies/ml.

RESULTS

Twenty consecutive patients with HBV infection needing immunosuppressive treatment for rheumatic diseases in which antiviral treatment was started are the object of this study. Mean age was 62 years (Table I), with a range from 42 to 80. They suffered from different rheumatic diseases: 9 with rheumatoid arthritis (RA), 5 with polymyalgia rheumatica (PMR), 2 with psoriasic arthritis, 1 each with systemic lupus erythematosus, systemic sclerosis, Sjögren syndrome, Behcet's Disease.
No patient had co-infection with HDV. Patient 20 had HBV and HCV co-infection. On presentation, serum HBsAg positivity was detectable in nineteen patients, with negative anti-HBs. One patient (number 1 in Table I), was HBsAg negative and an-

Table 1 - Main clinical characteristics of 20 rheumatological patients treated with lamivudine.

Patient	*Sex*	*Age*	*Rheumatic disease*[1]	*Disease duration (years)*	*Immuno-suppressive therapy for Rheumatic disease*[2]	*HBV-DNA*[3]	*HBsAg*	*HBsAb*	*HBcAb*	*HBeAg*	*HBeAb*	*AST*	*ALT*	*HBV status*[4]
1	F	58	RA	19	Pred 6 mg/die, HCQ, RIT	NA[5]	NEG	POS	POS	NA	NA	23	32	POC
2	M	56	RA	7	Pred 20 mg/die, SSZ, ADA	<2000	POS	NEG	POS	NEG	POS	17	16	IC
3	F	60	RA	3	Pred 10 mg/die, MTX, HCQ	<2000	POS	NEG	NEG	NEG	POS	12	14	IC
4	F	73	RA	19	Pred 4 mg/die, ETA	<2000	POS	NEG	POS	NEG	POS	22	15	IC
5	M	44	PsA	3	Pred 4 mg/die, MTX, HCQ	<2000	POS	NEG	POS	NEG	POS	27	20	IC
6	F	66	RA	2	Pred 4 mg/die, MTX, INFL	<2000	POS	NEG	NEG	NEG	POS	15	15	IC
7	F	60	RA	0	Pred 5 mg/die, MTX, HCQ	NA	POS	NEG	POS	NA	NA	14	10	IC
8	M	78	PMR	0	Pred 37.5 mg/die	NA	POS	NEG	POS	NA	NA	14	18	IC
9	F	80	PMR	0	Pred 25 mg/die	<2000	POS	NEG	NEG	NEG	NEG	18	20	IC
10	F	68	SSc	6	CYC	<2000	POS	NEG	POS	NEG	POS	9	25	IC
11	M	53	PsA	1	Pred 4 mg/die, MTX, SSZ	61.745	POS	NEG	POS	NEG	POS	21	22	AC
12	F	71	RA	33	Pred 4 mg/die, MTX	7.371	POS	NEG	POS	NEG	POS	18	20	AC
13	F	71	PMR	1	Pred 15 mg/die	30.691	POS	NEG	NEG	NEG	NEG	27	20	AC
14	F	58	pSS	1	Pred 5 mg/die	292.400	POS	NEG	POS	NA	NA	42	48	AC
15	M	56	PMR	0	Pred 15 mg/die	738.248	POS	NEG	POS	NA	NA	26	34	AC
16	F	47	SLE	19	Pred 10 mg/die, HCQ	49.267	POS	NEG	POS	NEG	NEG	360	462	AC
17	F	67	RA	17	Pred 5 mg/die, MTX	57.857.484	POS	NEG	POS	NEG	POS	138	172	AC
18	M	58	RA	15	Pred 4 mg/die, MTX, SSZ	8.500	POS	NEG	POS	NEG	POS	35	31	AC
19	M	69	PMR	1	Pred 10 mg/die	6.715.556	POS	NEG	POS	NEG	POS	109	225	AC
20[6]	M	42	Behcet	2	Pred 25 mg/die	<2000	POS	NEG	POS	POS	NEG	27	67	AC

[1]RA = Rheumatoid Arthritis; PsA = Psoriatic Arthritis; SSc = Systemic Sclerosis; PMR = Polymyalgia Rheumatica; pSS = primary Sjögren's syndrome; SLE = Systemic Lupus Erythematosus. [2]Pred = Prednisone (mg/d); MTX = Methotrexate; HCQ = Hydroxychloroquine; ETA = Etanercept; INFL = Infliximab; CYC = Cyclophosphamide; ADA = Adalimumab; SSZ = Sulfasalazine; RIT = Rituximab. All patients receiving MTX were supplemented with Folic Acid. [3]Data are expressed as copies/mL. [4]POC = potential occult carrier; IC = inactive carrier; AC = active carrier; [5]NA = not available; [6]Patient 20 was co-infected by HCV, for which received interferon alpha.

ti-HBc positive. Antiviral prophylaxis was advised during a course of treatment with rituximab.

Nine patients (number 2-10 in Table I) were inactive carriers, with undetectable viremia and normal liver function test, in which antiviral prophylactic therapy was started for a high risk of HBV reactivation when receiving immunosuppressive treatment. In three of them (patients 2, 4, 6), therapy with TNF blocking agents was started shortly after antiviral therapy.

Ten patients (number 11-20 in Table I) had active viral replication. In one case (patient 17), a clear HBV reactivation had been observed during a course of treatment with MTX without HBV prophylaxis. The other patients had persistent positive viremia and, in some cases, increased aminotransferases.

Lamivudine was given at the planned dose of 100 mg daily in all cases, and was well tolerated. In three patients adefovir was associated to lamivudine. In all cases, immunosuppressive treatment was given for the planned duration of therapy, with good results on the rheumatic diseases. In one patient, lamivudine was discontinued 6 months after having completed the planned 6-month long therapy with pulse Cyclophosphamide, without rebounds of HBV infection. Lamivudine discontinuation is programmed also for other patients who will discontinue immunosuppressive treatment (e.g., those with PMR).

At the moment of the last visit of follow up (median: 19 months after the start of antiviral treatment; range 3-41, for a total of 386 month/person), ALT and AST levels normalized and viremia was negative in all the patients. Patient 16, with serum HBeAb negative at the beginning of the therapy with lamivudine, had serum HBeAb positive at the follow up.

DISCUSSION

Reactivation of HBV replication or clinical hepatitis, or both, is a well known complication that may arise during the administration of immunosuppressive drugs, or after its discontinuation, in oncological and haematological disorders (28,29), but limited information is available on the effect of the different immunosuppressive regimens in patients with rheumatic diseases and chronic HBV infection, in which, typically, these agents are given for longer periods of time in lower doses. Moreover, some anti-cytokine agent such as TNF-alpha- or IL-1-blocking drugs are specifically used in rheumatic diseases or other immune-mediated disorders, but not in cancer.

Few case reports have described fatal HBV reactivation in inactive carriers (HBsAg+, HBV-DNA negative), treated with low-dose MTX (4-10 mg/wk) and steroids for RA, shortly after discontinuation of the treatment (5, 6, 8-11). It has been suggested that in these cases, after discontinuation of immunosuppression, T-cells might recover their immunocompetence and destroy infected hepatocytes.

On the other hand, there are case reports of viral reactivation during the course of immunosuppressive therapy with Azatioprine (7), or high doses of steroids plus chloroquine (30). The use of cyclophosphamide, a drug with several indications for rheumatic diseases, has also been associated with viral reactivation in patients with nephrological or haematological diseases.

As far as biological agents, in two inactive HBV carriers treated with the anti-TNF alpha monoclonal antibody infliximab plus low-dose MTX for RA, a reactivation of viral infection was observed (12,14), that was controlled with lamivudine, and discontinuation of the immunosuppressive treatment. A further HBsAg+ HBV-DNA-negative suffered from fulminant hepatitis after the start of infliximab therapy for adult-onset Still's disease, but the viral etiology of the hepatitis was not demonstrated (10).

Interestingly, in a series of 80 patients with Crohn's disease treated with infliximab, 2 were inactive carriers of HBV, and in both viral reactivation was observed, whereas in one patient that was already receiving lamivudine at the moment of the start of infliximab, for signs of viral replication, no increase in viral replication or exacerabation of chronic hepatitis was observed thereafter (13).

Although there are also reports of patients with RA or Crohn's disease and HBV infection treated with infliximab without complications (31-35), these observations clearly indicate the risk of HBV reactivation during treatment with TNF-blocking agents.

On the contrary, no reactivation of HBV infection was observed in a small number of patients receiving different anti-TNF agents for rheumatic disorders and concomitantly treated with lamivudine (12, 20, 22).

These observations led the Italian Association for the Study of the Liver (A.I.S.F.) to suggest that antiviral therapy is indicated in HBV+ active carriers, whereas antiviral prophylaxis is suggested in all HBsAg positive inactive carriers undergoing treatments considered at high-risk of reactivation (26). These include anti-TNF antibodies, medium to high dosage steroids (>7.5 mg/die) for prolonged periods, immunosuppressive DMARDs such as cyclophosphamide, methotrexate, leflunomide, calcineurin antagonists, azathioprine and mycophenolate mofetil. Prophylaxis should be started 2–4 weeks before the immunosuppressive therapy if possible and continued for at least 6–12 months afterwards (i.e. after immunosuppressive therapy has been suspended).

Our experience demonstrate the feasibility of such an approach, that can reduce the risk of viral reactivation and allows the choice of the optimal immunosuppressive treatment in rheumatic patients. A series of 20 consecutive individuals with different rheumatic disorders could receive with success the planned therapy, together with antiviral treatment. Antiviral therapy was well tolerated and efficacious, since no cases of viral reactivation were observed after a median follow-up of 19 months, for a total of 386 month/person. Using such an approach, therapy with TNF-blocking agents could be started in three patients and was given without complication.

It should be underlined that longer follow-up is needed in order to determine the real incidence of viral reactivation in these patients, and the clinical and virological predictors of it. In particular,

although we did not observe any case of lamivudine resistance, information on the rate of resistance is not available in rheumatic patients, whereas among 32 HBV carriers treated with chemotherapy for haematologic malignancies, the emergence of HBV mutant occurred in 3.1% of prophylactic lamivudine courses and was of little clinical relevance (25). In lamivudine resistant HBV mutants, adefovir dipivoxil is a therapeutic option and should be taken into account when long term immunosuppressive therapy is foreseen (36).

SUMMARY

Object of the study: To evaluate the safety and tolerability of lamivudine in patients with HBV infection needing immunosuppressive treatment for rheumatic diseases.

Patients and methods: Twenty patients with rheumatic diseases planned to receive immunosuppressive DMARDs or biological agents were screened for HBV markers. In all active carriers antiviral treatment was recommended. Inactive carriers (HBsAg positive, aminotrasferase and viremia persistently normal) were divided into two risk categories according to the type and the degree of immunosuppression, and antiviral prophylaxis was started only in patients of the high risk category. Antiviral treatment was recommended also in potential occult carriers (HBsAg negative, HBcAb positive) treated with rituximab. In twenty patients antiviral treatment was started: 1 was a potential occult carrier planned to receive rituximab; 9 were inactive carriers, in which prophylactic therapy was needed for a high risk of HBV reactivation (in 3, for the use of TNF blocking agents); 10 were treated for active viral replication. Prophylaxis and therapy were performed with lamivudine. In three patients adefovir was associated.

Results: Antiviral drugs were well tolerated. In all cases, immunosuppressive treatment was given for the planned duration of therapy, with good results on the rheumatic diseases. Median duration of antiviral treatment was 19 months (for a total of 386 month/person). No cases of viral reactivation were observed.

Conclusion: Our experience demonstrates the feasibility of a prophylaxis and therapy of HBV infection in patients with rheumatic diseases. This approach reduces the risk of viral reactivation and allows the choice of the optimal immunosuppressive treatment in rheumatic patients.

Parole chiave - HBV, lamivudine, biological agents, DMARDs.
Key words *- HBV, lamivudina, farmaci biologici, DMARDs.*

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