Treatment of polyarteritis nodosa related to hepatitis B virus with interferon-alpha and plasma exchanges

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Abstract

Objectives—To test the effectiveness of and tolerance to interferon-alpha 2b (INFa2b) in association with plasma exchanges for the treatment of polyarteritis nodosa (PAN) related to hepatitis B virus (HBV).

Methods—A prospective, non blinded, multicentre trial was carried out in which patients with multisystemic HBV-related PAN were included. Each patient received the association of INFa2b and plasma exchanges. The end point of the study was control of the disease (recovery or remission) or death.

Results—Six patients were included in the study. Each patient had histopathological or arteriographic evidence of vasculitis and was infected with actively replicating HBV. All patients were alive at the end of the study and no longer presented clinical or laboratory evidence of systemic vasculitis. HBeAg/anti-HBeAb seroconversion was observed in four patients (66.6%) and HBsAg/anti-HBsAb in 3/6 (50%). Two patients are still being treated with INFa2b because of chronic active hepatitis.

Conclusions—It is considered that this new therapeutic approach to HBV-related PAN effectively cured systemic vasculitis and was associated with control of HBV infections. Antiviral therapy may have a role to play as the first line treatment regime of virus-induced vasculitis.

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Polyarteritis nodosa (PAN) is a well-known form of necrotising angiitis. The association of PAN with hepatitis B virus (HBV) was described in 1970³ and has been confirmed by many previous reports.^{2 3} In our experience,⁴⁻⁶ the evolution of PAN and HBV infection were usually dissociated in patients with HBV-related PAN treated with steroids and immunosuppressive drugs such as cyclophosphamide. Most of the patients who recovered from PAN had chronic HBV infections and in some cases we observed a progression to cirrhosis. In a previous study,⁷ we reported the effectiveness of the association of a short term steroid treatment followed by the combination of vidarabine (Vira A), plasma

exchanges in the treatment of HBV-related PAN. The purpose of this study was to test a new antiviral agent, INFa2b, in association with plasma exchanges as the first-line treatment of HBV-related PAN.

Patients and methods

PATIENTS

Criteria for entry into the study were similar to those previously described.⁷ All patients had PAN with multiple system involvement; histological or angiographic evidence of vascular lesions indicative of a diagnosis of vasculitis; HBV infection with active viral replication. Previous treatment with steroids, cyclophosphamide and Vira A were considered exclusion criteria. Patients were consecutively enrolled in the trial. Recruitment began in January 1988. The end point of the study was control of the disease (recovery and remission, as defined below) or the patient's death. The study protocol was approved by the Biomedical Ethics Committee of the University of Paris-Nord.

TREATMENT PROTOCOL

Prednisone. Administration of prednisone was optional and given only in the case of severe or life-threatening manifestations of PAN. When given, every patient took prednisone at a dose of 1 mg/kg/day during the first week of treatment. The prednisone dose was rapidly tapered and steroids were stopped at the end of the second week. In the case of failure of the assigned treatment (lack of clinical improvement or relapse), prednisone was given again at a dose of 1 mg/kg/day.

Interferon-alpha 2b (INFa2b). INFa2b was started just after the patient's inclusion in the study. It was initiated at a dose of 3 million units, three times a week. The treatment duration depended on the results of HBV replication tests. In the case of seroconversion within the weeks following INFa2b, the antiviral treatment was stopped. If HBe antigenaemia remained positive, INFa2b was administered for one year and additional treatments could be given later on, depending on the patient's liver function status.

PLASMA EXCHANGES⁸

Every patient had plasma exchanges, which were started just after the patient's inclusion in

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the study. Each patient had nine to 12 plasma exchanges during the first three weeks of treatment with INF α 2b. During this period, the number of plasma exchanges depended on vascular access and the level of clotting factors before plasma exchanges. After this period, plasma exchanges were performed two or three times a week, depending on the clinical results observed, and then stopped. The amount of plasma scheduled to be exchanged during each session was 60 ml/kg of body weight. The replacement fluid consisted of 500 ml of fluid gelatin and 4% albumin.

SEROLOGICAL ASSAYS

Patients' sera were tested with commercial radioimmunoassays (Abbott) for the presence of HBsAg, anti-HBsAb and anti-HBcAb and, when HBsAg positive, for HBeAg and anti-HBeAb. The presence of HBV DNA in the sera was assayed using a spot hybridisation technique and HBV DNA polymerase as previously described.⁹

EVALUATION OF DISEASE ACTIVITY

The disease was controlled when the patient's general condition improved; no new clinical manifestations related to PAN developed; the erythrocyte sedimentation rate (ESR) became normalised. Stabilisation or improvement (partial or total) of peripheral neuropathy and renal and cardiac function (if abnormalities existed previously) was also necessary. The patient was considered to be completely recovered from PAN when the required criteria for control of the disease were met and maintained for at least 12 months after discontinuation of treatment, or when HBeAg/anti-HBeAb seroconversion had also been obtained six months after discontinuation of treatment. Clinical remission was achieved when clinical symptoms became attenuated or improved and laboratory abnormalities returned to normal under constant treatment. If there was no evidence of control of the disease activity under the assigned treatment or if a relapse (new systemic manifestations of PAN or worsening of the initial manifestations of the disease) occurred, the trial was stopped, and the patient was withdrawn from the study. Withdrawal from the study because of assigned treatment failure was recorded by the coordinating committee.

FOLLOW UP EVALUATIONS

The clinical and laboratory data were collected at the time of inclusion in the study, 15 and 30 days later (45 days after study entry), then every month for six months, every three months for one year, and every six months for the next five years. In case of a relapse or incomplete control of the disease, additional tests were performed.

Results

Between January 1988 and June 1992, six patients were eligible for the study.

CLINICAL FINDINGS

The clinical manifestations of PAN in the six study patients are summarised in the table. Of the six patients, four were men and two were women; their mean (SD) age at inclusion was 56.5 (14.1) years (range: 36–72 years). In four of six patients it was possible to determine the origin of the contamination with HBV: blood transfusion in patient 6; homosexual contact with serum HBsAg-positive partners (in cases 1 and 3); dental treatments were the only suspected risk factor in patient 4. Three patients presented clinical signs of acute viral hepatitis before developing PAN within 15 days, one and 37 months (respectively cases 1, 4 and 6).

Histopathological or angiographic evidence of vasculitis was found in all six patients. All our six patients met the diagnostic criteria defined by the American College of Rheumatology.³

LABORATORY FINDINGS

Renal failure, present in one case (serum creatinine: 2.4 mg/dl) was the result of membranous glomerulonephritis associated with renal vasculitis. Antineutrophil cytoplasmic antibodies were not found in any patient. HBsAg and HBeAg were always present and IgM anti-HBc was positive in patient 1. Viral DNA and/or DNA polymerase was obtained in five of six patients and the replication level was high in every case. Transaminases were elevated in three patients.

During the weeks after the onset of treatment, transaminases decreased when they had previously been high and, conversely, no increase in transaminases was noted. After treatment, 4/6 patients (66.6%) seroconverted to anti-HBeAb and three (50%) to anti-HBsAb. When obtained, HBeAg/anti-HBeAb and HBsAg/anti-HBsAb seroconversions occurred one, five, eight and 11 months after the beginning of treatment.

LIVER BIOPSIES

At the time of diagnosis, a liver biopsy was performed in 5/6 patients. Histological evidence of persistent chronic hepatitis was present in one and chronic active hepatitis in four. The biopsy did not demonstrate hepatitis in one case but revealed necrotising vasculitis.

RESULTS OF PLASMA EXCHANGES

Ninety one plasma exchanges were performed. The mean number of plasma exchanges per patient was 15 (range: 5–35). The mean (SD) volume exchanged was 3825 (400) ml. The side effects and complications of plasma exchanges were mild and transient.

OUTCOME

The mean (SD) follow up period was 19.1 (20.1) months (range: 10.5–59.8 months). Disease activity was controlled in every patient during the first weeks of treatment. All six

Clinical manifestations, laboratory data, histopathological and angiographic evidence of vasculitis, follow up in six patients with HBV related PAN

Number	Sex	Age	Symptoms	Abnormal laboratory data at inclusion	Pathology*	Liver histology	Angiogram	HBeAg/anti-HBeAb HBsAg/anti-HBsAb seroconversion	Outcome HBV/PAN
1	F	36	weight loss, hypertension, retinal vasculitis, CNS involvement	ASAT: 120 IU/I ALAT: 110 IU/I	neuromuscular biopsy	aggressive hepatitis	normal	no no	remission/ recovered
2	F	72	cholecystitis, mononeuritis multiplex	ASAT: 80 IU/I ALAT: 70 IU/I	liver and gall bladder biopsies	no hepatitis vasculitis	ND	yes (5 mo) yes (5 mo)	recovered/ recovered
3	M	47	fever, weight loss, myalgias malignant hypertension, mononeuritis multiplex		rectal biopsy	aggressive hepatitis	MAM, RI	no no	remission/ recovered
4	M	51	weight loss, myalgias, polyarthritides, mononeuritis multiplex	ASAT: 120 IU/I ALAT: 280 IU/I	neuromuscular biopsy	aggressive hepatitis	ND	yes (8 mo) yes (8 mo)	recovered/ recovered
5	M	63	weight loss, fever, Raynaud's phenomenon mononeuritis multiplex		neuromuscular biopsy	persistent chronic hepatitis, vasculitis	normal	yes (1 month) no	recovered/ recovered
6	M	70	myalgias, nephrotic syndrome	creatinine: 2.4 mg/dl	renal biopsy	aggressive hepatitis	normal	yes (11 mo) yes (12 mo)	recovered/ recovered

MAM: mesenteric artery microaneurysms, RI: renal infarcts. ND: not done* tissues with biopsy proven vasculitis.
ASAT: aspartate aminotransferase, ALAT: alanine aminotransferase, CS: corticosteroids.

patients were alive at the end of the study and had recovered completely from PAN; four of them had recovered from HBV as well and the remaining two are still being treated with INFa2b because of chronic active hepatitis but do not present any symptoms of PAN.

Sequelae of polyarteritis nodosa were present in three patients. One is handicapped by peripheral neuropathy, one (case 6) by renal failure (serum creatinine: 2.4 mg/dl) and one by hypertension requiring treatment with a converting enzyme inhibitor (case 3).

Discussion

Hepatitis B virus is an aetiological factor of polyarteritis nodosa^{1 2 10} and it has been suggested that circulating hepatitis B Ag/Ab immune complexes have an important role in the pathogenesis of vasculitic lesions.¹¹ On theoretical grounds, the existence of a chronic HBV infection with a high level of virus replication should require a specific approach because steroids are known to enhance viral replication, favour the exacerbation of chronic hepatitis¹² and ultimately the progression towards liver cirrhosis. We proposed a new therapeutic sequence to obtain the following effects: initial administration of steroids to rapidly control the most severe, life-threatening manifestations of polyarteritis nodosa which are common during the first weeks of the disease; rapid discontinuation of steroids to trigger a rebound of immunological clearance of HBV-infected hepatocytes and favour seroconversion from HBeAg to anti-HBeAb as documented for chronic hepatitis B;¹³ plasma exchanges to remove pathogenic circulating immune complexes⁸ and prevent further damage especially after steroid withdrawal; administration of an antiviral agent (Vira A, INFa2b) to induce HBeAg/anti-HBeAb seroconversion.

At the time of our first study,⁷ Vira A was the most effective antiviral agent available against HBV. The overall therapeutic results obtained were excellent: 24 of 33 patients (72.7%) no longer had any symptoms of vasculitis following therapy and none relapsed during the prolonged follow up period. Seventeen of the 33 patients (51.5%) no longer exhibited

serological evidence of HBV replication. Considering the favourable results obtained with Vira A, we decided to test new antiviral agents, such as INFa2b, in the treatment of HBV-related PAN. Until 1988, HBV-related PAN accounted for one third (36%) of all cases of systemic PAN⁴ studied in France by our group. Since 1987, its frequency progressively decreased and represented less than 10% of all cases of PAN we observed between 1990–92. Although only a small number of patients has been included in the study, the therapeutic results obtained are promising. All the patients recovered completely from PAN and are still alive at the end of the study. The combination of INFa2b and plasma exchanges is well tolerated by patients and only minor side effects were observed. HBeAg/anti-HBeAb seroconversion was observed in four patients (66.6%) and HBsAg/anti-HBsAb seroconversion occurred in three (50%). Our results lead us to think that antiviral therapy will have a role to play in the treatment of virus induced vascular disease and HBV-related PAN, as recently described for cryoglobulinemia associated with hepatitis C virus.¹⁴ It has been feared that INFa2b would worsen immune complex-mediated diseases by depressing suppressor T-cell function and enhancing HLA expression.¹⁵ We did not observe such effects.

In HBV-related PAN, the association of INFa2b and plasma exchanges is effective, and facilitates recovery from the vasculitis and HBeAg/anti-HBeAb seroconversion.

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