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2. Inhibition of Hepatitis B Viral Replication by Lymphoblastoid Interferon [and Discussion]

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2. Inhibition of hepatitis B viral replication by lymphoblastoid interferon

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Introduction

Human leucocyte interferon has been used to treat chronic hepatitis B virus (HBV) infection. In uncontrolled studies along or in combination with adenine arabinoside (Ara-A) it has been shown, in a minority of patients, to produce permanent inhibition of viral replication: loss of HBV–DNA polymerase activity (DNAp), seroconversion from HBeAg to anti-HBe and a decrease in HBsAg concentration (Scullard *et al.* 1981). Loss of HBsAg is uncommon and probably reflects the presence of clones of hepatocytes containing integrated HBV–DNA (Brechot *et al.* 1981; Shafritz *et al.* 1981). A controlled study in which human leucocyte interferon was given in lower total doses failed to produce a permanent effect (Weimar *et al.* 1980). Human fibroblast interferon has been shown to have no significant antiviral effect in chronic HBV infection (Weimar *et al.* 1979).

Ara-A in a controlled study and its monophosphate ester (Ara-AMP) in an uncontrolled study, have been shown to produce permanent inhibition of HBV replication (Bassendine *et al.* 1981; Weller *et al.* 1982).

Patients and methods

Three patients with histologically proven HBsAg-positive chronic liver disease have been treated with human lymphoblastoid interferon. All were HBeAg and HBV–DNAp positive. Case and treatment details are shown in table 1. Serum HBsAg and HBeAg were detected by radioimmunoassay (Abbott Labs). HBV–DNAp was measured by the method of Marion *et al.* (1981): the upper limit of our normal range is 850 disintegrations per minute per 200 µl (2 s.d. above the mean of 50 negative controls). Serum HBV–DNA was measured by molecular hybridization with ^{32}P-labelled cloned HBV–DNA (Weller *et al.* 1982).

Results

All three patients have shown a marked decrease in HBV–DNAp and HBV–DNA during treatment (figure 1). In case 1 this has been prolonged and accompanied by a transient 4–5-fold increase in aspartate transaminase activity after the treatment period. A smaller increase was seen during therapy in cases 2 and 3 treated with higher doses and was more marked in case 3 who received the higher i.v. dose initially. HBsAg and HBeAg have remained positive in each case for the period of follow-up. Predictable and manageable interferon side effects were seen: fever, headache, rigors, myalgia, mild thrombocytopenia ($90–100 \times 10^9$/l) and leucopenia ($2.0–2.5 \times 10^9$/l). Purpura occurred in cases 1 and 3, which resolved by continuing interferon and substituting paracetamol for aspirin to control side effects. Cases 1 and 2 complained of

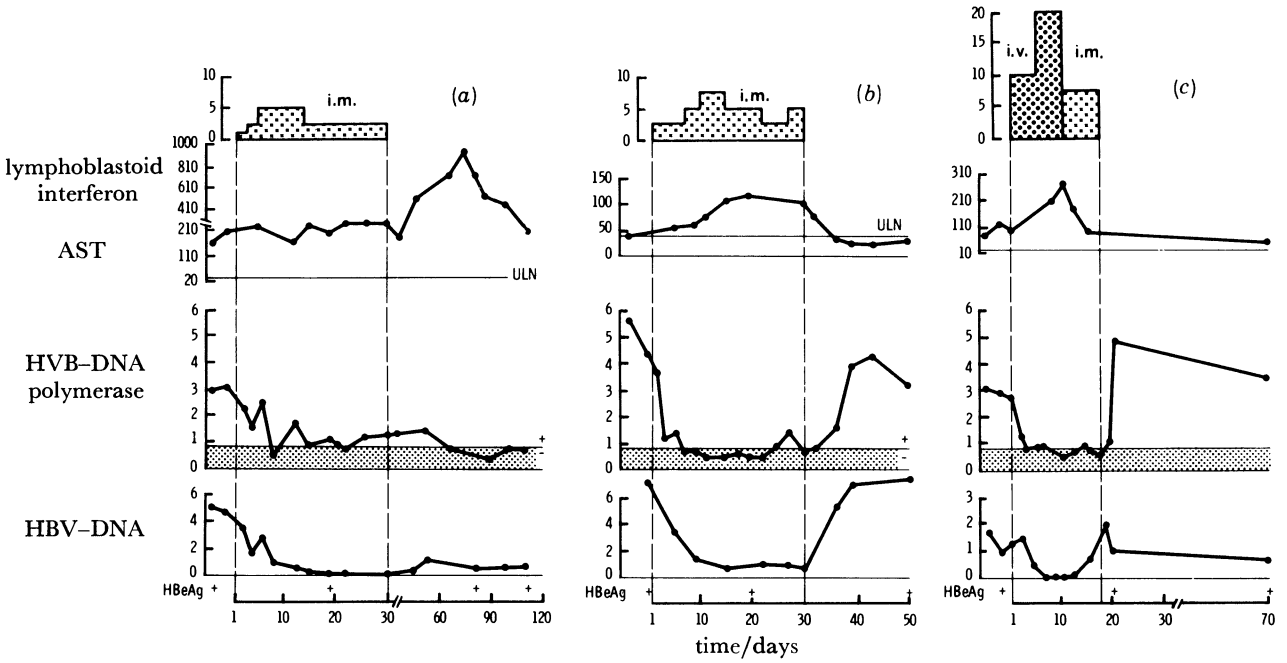

FIGURE 1. Effect of lymphoblastoid interferon on HBV replication and aspartate transaminase (AST). (*a*) Case 1; (*b*) case 2; (*c*) case 3. Interferon is expressed as megaunits per square metre, AST as i.u. per litre, HBV–DNA polymerase as thousands of disintegrations per minute per 200 µl and HBV–DNA as area under peak in arbitrary units after 26–36 h of exposure. Interferon units are with reference to the international standard.

TABLE 1. CASE AND TREATMENT DETAILS

case no.	sex	age	histology	interferon dose Mu m^{-2}	route	duration days
1	F	11	c.a.h.	1.25–5	i.m.	30
2	M	48	c.a.h.	2.5–7.5	i.m.	30
3	M	31	c.p.h./c.a.h.	10–20	i.v.	11
				7.5	i.m.	7

Abbreviations: c.a.h., chronic active hepatitis; c.p.h., chronic persistent hepatitis; i.m., dose given as single intramuscular injection; i.v., dose given as 24 h intravenous infusion.

transient hair loss after therapy. Side effects in case 3, treated with the high i.v. dose, seemed no greater than in the other cases. I.v. therapy was stopped because of lack of easy venous access.

DISCUSSION

Human lymphoblastoid interferon as a single daily intramuscular injection or as a continuous i.v. infusion inhibits HBV replication in patients with HBsAg-positive chronic liver disease. In one female patient this has been prolonged and associated with a transient increase in aspartate transaminase activity. This increase after therapy has been described in HBsAg-positive patients treated with ARA-AMP (Weller *et al.* 1982), after withdrawal of immunosuppressant drugs (Scullard *et al.* 1981; Weller *et al.* 1982) and during immunostimulant therapy with BCG (Thomas *et al.* 1981) and suggests that there may be increased lysis of infected hepatocytes because of enhancement of the immune response to the virus during the phase of

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seroconversion of HBeAg to anti-HBe. Loss of HBeAg, development of anti-HBe and a decrease in HBsAg concentration may be delayed for 6 months after DNAp has become negative.

Interferon side effects were well tolerated. The purpura that occurred in two patients appears to have been related to a combination of mild thrombocytopenia and the functional platelet abnormalities induced by aspirin since the purpura resolved when paracetamol was used to control side effects.

Although further studies and follow-up are needed, lymphoblastoid interferon seems to be another candidate for use in controlled trials in the treatment of chronic HBV infection.

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