Randomised controlled trial of interferon alfa 2A (rbe) (Roferon-A) for the treatment of chronic hepatitis B virus (HBV) infection: factors that influence response

MG BROOK, J A MCDONALD, P KARAYIANNIS, L CARUSO, G FORSTER, J R W HARRIS, AND H C THOMAS

From the Academic Department of Medicine and Department of Genitourinary Medicine, St Mary's Hospital Medical School, London

SUMMARY In a randomised controlled trial recombinant interferon alpha 2A (Roferon-A, rIFN alfa A) given at a dosage of 10 million units (MU)/m² thrice weekly for six months was significantly better (p<0.02) than no treatment in producing a sustained loss of hepatitis B antigen (HBeAg) in hepatitis B virus (HBV) chronic carriers. Although lower doses (5 MU/m² and 2.5 MU/m²) also produced some responses, the seroconversion rate was not significantly greater than that observed in the control group. Sixteen of the 45 patients receiving interferon were human immunodeficiency virus (HIV) antibody positive: none of these responded. Forty one per cent of the anti-HIV negative patients receiving interferon (12/29, p<0.005) lost HBeAg and 17% (5/29) lost hepatitis B surface antigen (HBsAg). The response rate among these anti-HIV negative patients receiving at least three months therapy was 46% and 19% respectively. Low pretreatment HBV-DNA and absence of anti-HIV were the only significant independent variables predicting response to therapy (p<0.03 and p<0.05 respectively). In six patients, neutralising antibodies to alpha interferon were detected during therapy, the majority being non-responders.

Both adenine arabinoside monophosphate (Ara-AMP) and the alpha interferons have been used successfully to treat chronic hepatitis B virus (HBV) infection. Lymphoblastoid interferon, used on a thrice weekly basis for three months, has been shown to have equal or possibly greater effectiveness than Ara-AMP. Furthermore, lymphoblastoid interferon, in contrast to Ara-AMP, may result in clearance of HBs as well as HBeAg. More recently, when recombinant interferon with alfa 2A was used in both high and low dosages, it was shown to produce transient inhibition of viral replication.

The aims of the present study were, first to evaluate the effectiveness of rIFN alfa A in eradicating HBV and second to see if lower doses than have previously been used would be effective.

Methods

Patients
Sixty adult male patients (58 Caucasian, two Chinese) who met the trial criteria were entered into the study (Table 1). All eligible patients gave informed consent and were randomised into four groups by opening numbered computer generated randomisation envelopes in sequential order; the control group received no treatment and the three treatment groups received rIFN alfa A at the doses of 2.5, 5.0, and 10 MU/m² thrice weekly for six months.

The patient characteristics are given in Table 2.
Table 1  Criteria for inclusion of patients in the trial

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged 18-65</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>HBsAg positive for &gt;6/12</td>
<td>Severe concomitant disease other than hepatitis</td>
</tr>
<tr>
<td>HBV-DNA positive</td>
<td>Continuing drug or alcohol abuse</td>
</tr>
<tr>
<td>Normal haematological indices</td>
<td>Immunosuppressive or</td>
</tr>
<tr>
<td>Normal renal function</td>
<td>antiviral therapy within the</td>
</tr>
<tr>
<td>Karnovsky performance &gt;80%</td>
<td>last 6 months</td>
</tr>
<tr>
<td>Ability to comply with the trial</td>
<td></td>
</tr>
<tr>
<td>Liver biopsy within the last 6 months</td>
<td></td>
</tr>
<tr>
<td>showing chronic hepatitis</td>
<td></td>
</tr>
</tbody>
</table>

TREATMENT

Recombinant interferon alfa 2A (Roferon-A) was supplied by Hoffman-La Roche and Co, Basel, Switzerland.

The treated patients received thrice weekly intramuscular injections for six months as outpatients. The majority were taught to selfadminister the injection at night, which they found more convenient.

All trial participants were seen weekly for one month, then every fortnight for five months. After treatment was stopped they were seen at three monthly intervals for 12 months. A clinical evaluation, history of interferon side effects, full blood count, urea and electrolytes, a blood sugar level, prothrombin index, liver function tests, as well as hepatitis serology and an HBV-DNA level were performed on each visit.

All patients were requested to have a liver biopsy at the end of the trial. Pre- and post-treatment biopsies were compared by an experienced histopathologist without knowledge of the serological status and relationship to therapy.

Table 2  Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>2.5</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>15</td>
<td>13</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>37</td>
<td>31</td>
<td>31</td>
<td>40</td>
</tr>
<tr>
<td>Baseline HBV-DNA pg/ml (SE)</td>
<td>4200 (2500)</td>
<td>4560 (1842)</td>
<td>4500 (2117)</td>
<td>3960 (1924)</td>
</tr>
<tr>
<td>Baseline AST IU/l (SE)</td>
<td>52 (5)</td>
<td>79 (13)</td>
<td>72 (13)</td>
<td>73 (15)</td>
</tr>
<tr>
<td>Liver histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAH*</td>
<td>7</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>CPH</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>CLH</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>MD</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Anti-HIV positive (n)</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Heterosexuals (n)</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

*CAH: chronic active hepatitis; CPH: chronic persistent hepatitis; CLH: chronic lobular hepatitis; MD: minimal disease.

Fig. 1  Loss of HBsAg over time comparing rIFN alfa A treated and control patients.

SEROLOGICAL METHODS

HBsAg was measured by a monoclonal antibody based immunoradiometric assay,7 HBsAg, anti-HBe, and anti-HBs (antibody to hepatitis B surface antigen) by radioimmunoassays (Abbott Laboratories, North Chicago, Ill), serum HBV-DNA by molecular hybridisation using 3P-labelled cloned HBV-DNA* and anti-HIV by ELISA (Wellcome Laboratories, Beckenham, UK). Serum was also tested regularly for the development of interferon antibodies (see below).

STATISTICAL ANALYSIS

The response rates comparing the three treatment groups and the control group, as well as the response rate in the anti-HIV positive and negative treated patients, were compared using the χ2 test with Yate’s correction. The predictive value of pretreatment variables was assessed by multivariate analysis.

INTERFERON ANTIBODIES

These were measured by a biological assay in which antibody containing serum inhibits the cytoprotective effects of alpha interferon when assayed with V3 monkey kidney cells (Wellcome Laboratories) challenged with Semliki Forest virus. The cells were grown in MEM supplemented with 5% fetal

Table 3  Response rates with different doses of rIFN alfa A

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>2.5</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n (%) of patients losing HBsAg</td>
<td>2 (15)</td>
<td>3 (21)</td>
<td>7 (39)</td>
<td></td>
</tr>
<tr>
<td>n (%) of patients losing HBsAg in the anti-HIV negative group</td>
<td>2 (29)</td>
<td>3 (33)</td>
<td>7 (54)</td>
<td></td>
</tr>
<tr>
<td>n (%) of patients losing HBsAg in the anti-HIV negative group</td>
<td>1 (14)</td>
<td>1 (11)</td>
<td>3 (23)</td>
<td></td>
</tr>
</tbody>
</table>
calf serum and antibiotics. Briefly six serial half dilutions containing 10⁴ to 10⁰ IU/ml of recombinant alpha interferon were mixed with equal volumes of 1/10 dilutions of the test or positive and negative control serum in maintenance medium (MEM with 0·2% fetal calf serum) and 150 µl added to duplicate microtitre wells containing V3 cell monolayers. After overnight incubation at 37°C the wells were challenged with virus and reincubated for a further 48 hours. A serum sample was regarded as being positive when cytoprotection occurred in a minimum of one whole well less than the negative controls and was confirmed in duplicate assays. The cut off was equal in magnitude to three standard deviations of 50 negative controls and gave the assay a maximum sensitivity in detecting neutralisation of 25 IU/ml alpha interferon.

Serum samples were taken at least 48 hours after the last dose of interferon, and measured monthly, during and after therapy.

Results

Response to rIFN alfa A treatment
Response (loss of HBeAg and HBV-DNA) occurred significantly more frequently in treated than control patients (12/45 v 0/15; p<0·05, Fig. 1). No responses were seen in 16 anti-HIV positive patients, whereas 12/29 (41%) of the anti-HIV negative treated patients lost HBeAg (p<0·01) and five (17%) HBsAg (Table 3, Fig. 2). The response rate amongst those anti-HIV negative patients who received more than three months' therapy was 12/26 (46%) for loss of HBeAg and five of 26 (19%) for loss of HBsAg.

The 10 MU/m² dose appears to be more effective than the 2·5 and 5 MU/m² doses but this does not reach statistical significance on multivariate analysis. On univariate analysis, the response rate on treatment with 2·5 or 5 MU/m² was not significantly greater than in controls. Treatment with 10 MU/m² was significantly better than no treatment (p<0·05).

There was no difference in pretreatment HBV-DNA levels comparing treatment and control patients, but after six months of therapy (or observation), the treated patients had significantly lower levels (p<0·01). HBV-DNA remained persistently higher in the treated anti-HIV positive patients during therapy when compared with the anti-HIV negative patients.

Effect of rIFN alfa A treatment on liver pathology
Thirty four patients agreed to post-trial liver biopsies and these included all five who had lost HBsAg.

Four of the patients losing HBsAg went from moderate or mild CAH to chronic persistent hepatitis (CPH) and one remained unchanged. Immunofluorescent staining for HBe, HBc, and HBs antigens revealed complete loss of these antigens from the liver. Of the seven responders who remained HBsAg positive, two agreed to post-treatment biopsy and in both cases the histology had improved (moderate to mild CAH and moderate CAH to CPH).

Features of responding patients
Ten of the 12 responders had CAH on pretreatment liver biopsy, two had CPH. The responders had higher pretreatment AST values [105 (21) v 63 (7) IU/l, normal levels <40 IU/l; p<0·03] and lower pretreatment HBV-DNA values [2880 (230) v 3620 (65) pg/ml; p<0·0002].

The only factors which were identified as independent variables predicting response, were low pretreatment HBV-DNA levels (p<0·03), and negative anti-HIV status (p<0·05).

The anti-HIV positive patients had significantly lower pretreatment AST values than the anti-HIV negative patients.

Fig. 2 Loss of HBsAg over time comparing rIFN alfa A treated and control patients.

Fig. 3 Typical response seen in a complete responder, with a period of subclinical rise in AST occurring at the time the HBV-DNA levels were rapidly falling, with later clearance of HBeAg and HBsAg, and development of anti-HBe and anti-HBs.
negative group, [45 (7) v 90 (10); p<0.006]. HBV-DNA levels were similar in the two groups.

Four of the seven heterosexuals responded.

Patterns of Response

In 26 of the 45 patients receiving interferon, there was an immediate fall in HBV-DNA during the first week of treatment. The HBV-DNA levels continued to fall until the fourth week of therapy. In 10 a further rapid drop then occurred between the eighth and twelfth weeks of therapy, with clearance of HBV-DNA and later HBeAg. One patient had a rapid fall in HBV-DNA after 24 weeks of therapy, with later clearance of HBeAg. Another patient became HBeAg negative after 24 weeks of therapy, but remained HBV-DNA positive for a further six months, when he became negative for both. In eight of the 12 responders increased AST levels were detected at the time HBV-DNA levels were rapidly falling. In all patients transaminase levels returned to normal after HBeAg was cleared. This was delayed for one month after the disappearance of HBV-DNA. Four complete responders cleared HbsAg at the same time as HBeAg. In one case HbsAg clearance was delayed for two months. A typical responder losing both HBeAg and HbsAg is shown in Figure 3. Eight responders have developed anti-HBe, and four of five losing HbsAg also developed anti-HBs.

Fifteen patients did not experience a rapid fall in HBV-DNA after the initial gradual fall. In these patients the HBV-DNA level continued to be sup-

pressed, maximally at the second month, then the level started to increase towards pretreatment values at the fifth and sixth months, despite continued interferon therapy (Fig. 4). One patient lost both HbsAg and HBeAg after four months therapy but became HbsAg positive again at the end of treatment. He remained, however, HBeAg negative.

Eighteen patients did not exhibit any changes in HBV-DNA while on rIFN alfa A. Ten of 18 of this group were also anti-HIV positive.

Anti-interferon Antibodies

These were detected during therapy in six anti-HIV negative patients, four being treated with 10 MU/m². Five of these patients were non-responders in whom antibodies were first detected at 1, 3, 4, 5, and 6 months respectively. One patient who responded by loss of HbsAg, HBeAg, and HBV-DNA at three months, developed anti-interferon antibodies at six months of therapy. In two non-responders, the HBV-DNA had initially fallen in response to therapy but rose again after the anti-interferon antibodies appeared (Fig. 5). For the remainder of non-responders the HBV-DNA remained at a constant high level which was unaffected by therapy or development of antibodies.

Side Effects of rIFN Alfa A

The side effects of therapy are listed in Table 4. More side effects were seen as the dose increased. The physical performance reduction from 100% to 80% (WHO classification) in the majority of those treated with 10 MU/m² meant that their ability to work was impaired resulting in much time off work.

A number of patients reported mood changes, irritability, and depression. This was worse towards the end of the treatment and was more marked at the higher doses. One anti-HIV positive patient
Eight patients required a dose reduction in the last two to three months of therapy. Three were on 5 MU/m² dose (two because of fatigue and one because of irritability and depression). Five were on the 10 MU/m² dose, four because of extreme fatigue (irritability and difficulty concentrating in two) and one because of a drug induced granulocytopenia (which reversed on reducing the dose).

Symptomatic and haematological side effects reversed within a week of stopping therapy, whilst decreased hair growth took up to six months to recover.

**Discussion**

Recombinant alpha interferon used thrice weekly for six months, has been found to be a safe and effective treatment for chronic HBV infection in these predominantly homosexual HBV carriers. Overall there was a 27% response rate (loss of HBeAg and HBV-DNA), which is significantly higher than that observed in our control group and higher than the 5–10% predicted annual seroconversion rate quoted in the literature for this group of patients. All treatment responders were anti-HIV negative giving a response rate of 41% in this group. For patients who tolerated a minimum of three months therapy the response rate was 29% overall and 44% in anti-HIV negative individuals respectively. In addition 41% of the responders lost HBsAg over the six month treatment period, which is much higher than the observed loss in our control group and that expected from the literature. Although responses were seen with 2·5 and 5·0 MU/m² dose regimens, the best results were obtained with 10 MU/m² thrice weekly for six months.

There are certain theoretical reasons why alpha interferon may be effective in chronic HBV carriers. A number of authors have shown *in vitro* and *in vivo* defects in alpha interferon production in chronic HBV carriers, and the administration of alpha interferon may correct these defects. We have shown both in this and a previous trial that alpha interferon is effective in homosexual HBV carriers, whereas Ara-AMP is not. This may relate to the immunostimulatory properties of interferon. Immunological abnormalities have been shown in homosexual men in the absence of anti-HIV.

The detection of anti-interferon antibodies in a small minority of the treated patients was not the less significant as the majority of these were non-responders. Other workers have shown that such antibodies can significantly reduce the response to treatment of patients with chronic myeloid leukaemia and hairy cell leukaemia. The appear-

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Patients (n)</th>
<th>2-5</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fevers, chills, rigors, myalgias</td>
<td>13</td>
<td>14</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>10</td>
<td>11</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Needing dose modification</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Depression, irritability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Acute psychosis</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&gt;5% loss in body weight</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Granulocytopenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Grade II</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Grade III</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Grade II</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Grade III</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Decreased hair growth</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*WHO classification of intolerance.

Developed an acute psychotic depression after being on 5 MU/m² of rIFN alfa A for 14 weeks. This resolved on withdrawal of interferon and appropriate therapy with antidepressants.

Eight patients had a >5% reduction in body weight while on therapy and four patients reported decreased hair growth. One patient developed long eyelashes.

**HAEMATOLOGY**

No patients developed a greater than 10% drop in their platelet count while on rIFN alfa A except one patient who was anti-HIV positive and was diagnosed as having HIV associated thrombocytopenia.

Granulocytopenia was noted in a number of patients, but this necessitated a dose reduction in only one patient on the 10 MU/m² dose. No patients developed complications as a result of their granulocytopenia.

**WITHDRAWALS**

Two patients withdrew from the trial within one week of commencement for personal reasons.

Six patients (all anti-HIV positive) felt unable to tolerate more than three months' therapy because of depression. This occurred equally on 2·5, 5, or 10 MU/m² doses. Therapy was discontinued in the HIV associated thrombocytopenic patient after three months. One patient withdrew after two months therapy when he acquired syphilis which was treated elsewhere.

Eight patients required a dose reduction in the last two to three months of therapy. Three were on 5 MU/m² dose (two because of fatigue and one because of irritability and depression). Five were on the 10 MU/m² dose, four because of extreme fatigue (irritability and difficulty concentrating in two) and one because of a drug induced granulocytopenia (which reversed on reducing the dose).

Symptomatic and haematological side effects reversed within a week of stopping therapy, whilst decreased hair growth took up to six months to recover.

**Discussion**

Recombinant alpha interferon used thrice weekly for six months, has been found to be a safe and effective treatment for chronic HBV infection in these predominantly homosexual HBV carriers. Overall there was a 27% response rate (loss of HBeAg and HBV-DNA), which is significantly higher than that observed in our control group and higher than the 5–10% predicted annual seroconversion rate quoted in the literature for this group of patients. All treatment responders were anti-HIV negative giving a response rate of 41% in this group. For patients who tolerated a minimum of three months therapy the response rate was 29% overall and 44% in anti-HIV negative individuals respectively. In addition 41% of the responders lost HBsAg over the six month treatment period, which is much higher than the observed loss in our control group and that expected from the literature. Although responses were seen with 2·5 and 5·0 MU/m² dose regimens, the best results were obtained with 10 MU/m² thrice weekly for six months.

There are certain theoretical reasons why alpha interferon may be effective in chronic HBV carriers. A number of authors have shown *in vitro* and *in vivo* defects in alpha interferon production in chronic HBV carriers, and the administration of alpha interferon may correct these defects. We have shown both in this and a previous trial that alpha interferon is effective in homosexual HBV carriers, whereas Ara-AMP is not. This may relate to the immunostimulatory properties of interferon. Immunological abnormalities have been shown in homosexual men in the absence of anti-HIV.

The detection of anti-interferon antibodies in a small minority of the treated patients was not the less significant as the majority of these were non-responders. Other workers have shown that such antibodies can significantly reduce the response to treatment of patients with chronic myeloid leukaemia and hairy cell leukaemia. The appear-
Roferon-A therapy for chronic HBV

ance of these antibodies became significant mainly after six months of therapy. These results suggest that the response may be prevented in a small number of patients during early therapy, especially as the HBV-DNA was seen to rise after antibody detection in two patients.

The lack of response in the anti-HIV positive patients is an important observation. Homosexual men in the United Kingdom comprise the bulk of the population with chronic HBV: 5% are HBsAg and 2% are HBeAg positive and in 1984 22% of homosexuals attending STD clinics in the UK were anti-HIV positive. Homosexual men positive for anti-HIV have more pronounced immunological abnormalities, which includes a diminished ability to appropriately produce and respond to alpha interferon. Additionally their B cells are unable to make specific antibodies to neoantigens. We have observed that as a group the anti-HIV positive patients have significantly lower levels of antibodies to hepatitis B core antigen (unpublished observations). Thirdly, they have a marked dysfunction in cell mediated immunity. Hepatitis B is an immunopathogenic virus against which a competent cell mediated response to HBcAg and HBeAg is required if the virus is to be eliminated. There have also been reports of HBV-DNA sequences in the lymphocytes of AIDS patients, regardless of HBV serology and it is possible that HBV replication in lymphocytes may impair their immune responsiveness. The lack of effect of rIFN alfa A in anti-HIV positive carriers is not confined to hepatitis B, however, as these patients also appear to be resistant to its effects when used intrasplenially for the treatment of anal warts.

We found that 41% of our responders lost HBsAg as well as HBeAg, and it is our preliminary observation that those treated early on in the course of their chronic HBV infection are more likely to completely eradicate the virus.

Ten of 12 of our responders had cleared HBV-DNA after three months of therapy. In a previous trial from this centre comparing the effectiveness of three and six months of lymphoblastoid interferon, the six months' therapy did not show any advantage over the three months' course, and our present results appear to confirm this.

Other investigators have found that high pretreatment AST values and chronic active hepatitis on liver biopsy to be important independent variables in predicting a favourable outcome of treatment. The only predictive factor we found was a low pretreatment HBV-DNA level and negative anti-HIV status. It is noteworthy that these patients have lower AST and higher HBV-DNA values than patients in previous trials from this centre, most likely reflecting the higher proportion of homosexuals and anti-HIV positive patients present in this study.

We conclude that recombinant alpha interferon is an effective and well tolerated form of therapy for the management of chronic HBV infection in some anti-HIV negative carriers. Chronic HBV carriers who are anti-HIV positive tolerate treatment less well and may need some additional immune modulation to increase their likelihood of response.

Dr J A McDonald was the recipient of a Commonwealth Fellowship scholarship and was supported by Hoffman-La Roche. Dr L Caruso received a grant from Hoffman-La Roche. We would like to thank Sister Mary Crossey for the nursing care of the patients recruited in the trial.

References
2 Lok ASF. Novick DM. Karayiannis P. Dunk A. Sherlock S. Thomas HC. A randomised study of the effects of adenine arabinoside 5'-monophosphate (short or long courses) and lymphoblastoid interferon on hepatitis B virus infection. Hepatology 1985; 5: 1132–8.
10 Weller IVD, Brown A, Morgan B. Spontaneous loss of HBeAg in male homosexual hepatitis B virus carriers and implications for therapy. 6th International STD conference 1985; abstract 78.


