SURVEILLANCE OF PREVIOUSLY UNTREATED PATIENTS FOR POSSIBLE VIRUS TRANSMISSION BY BPL FACTOR VIII AND FACTOR IX CONCENTRATES, 8Y AND 9A: INTERIM REPORT

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(Summarised 30.9.86 by Dr. J.K. Smith, BPL/PFL).

Introduction

In the spring of 1985, all HCDs were circulated with a protocol for detection of NANBH, HB and HIV transmission in susceptible patients receiving BPL factor VIII (8Y) and factor IX (9A) concentrates, both severely heated with the intention of inactivating viruses. All centres were invited to collect data on eligible patients and results so far are summarised here.

Patient selection

Although the original protocol did not distinguish between unpooled products, e.g. cryoprecipitate, and large-pool concentrates, and accepted patients who had had very little previous treatment with concentrates, the present analysis is restricted to patients who had had no large-pool concentrate before 8Y or 9A, but may have had variable amounts of cryoprecipitate etc. Table 1 gives a summary of the patients' previous treatment.

Frequency of testing

Fortnightly ALT or AST was requested, up to 12 weeks, then monthly to 26 weeks and quarterly to one year. The present analysis for NANBH covers only those patients who have been followed for at least 16 weeks and who have had at least four samples for ALT/AST during that period. The group analysed here had a mean of seven ALT/AST tests during the first 16 weeks.

Where a patient had been satisfactorily followed by ALT/AST after the first infusion, infusion of a second batch of the same concentrate has been accepted as a second "case", and successive "cases" distinguished by a, b, c, etc. in the diagram, Figure 1, showing the precise timing of the ALT or AST tests.

Products tested

Bearing in mind that, in clinical trials of other coagulation factor concentrates, only certain batches have been implicated in the transmission of NANBH, it has been important in this study to expose patients to many batches. In the group analysed here, 11 batches of 8Y and seven batches of 9A were used, containing approximately 120,000 donations of plasma. The plasma was entirely derived from NBTS unremunerated donors, not screened for HIV antibody or elevated LFT. Batches for trial were allocated at random from standard production stocks available at the time.

Both concentrates were heated in the freeze-dried state at 80° for 72h as the final stage in processing, and results of clinical trial for virus transmission will be presented jointly for both products.

Results

1. NANBH transmission

None of the patients in the group analysed had any ALT or AST above 2.5 times the upper limit of the normal range - taken as the definition of a significantly elevated level. The highest ALT seen in patient 8Y/5 was accompanied by a normal AST and followed less than one week later by a mid-range level. Relatively high ASTs in patients 8Y/10 and 8Y/12 and 9A/7 were comparable to pre-exposure levels.

One patient, excluded from the present analysis because of infrequent testing, showed AST levels: normal at 9.5 weeks, significantly elevated at 11 weeks, normal three days later, and normal at 20.5 weeks. The

single elevation was not attributed to NANBH infection because it was unconfirmed at the repeat sampling. Two other patients in the study group received the same batch of 8Y without showing any ALT/AST elevation.

No other patient in categories other than those analysed here has shown a significant ALT/AST elevation.

2. HIV transmission

No case of HIV seroconversion has been reported in over 100 patients, in this study group and in others on whom we have formal data on regular follow-up, and there has been no report of seroconversion in the many hundreds of patients who are now receiving these products regularly.

(No seroconversion has been attributed to the interim product HLH/8CRVH issued in early 1985, and heated only at 70° for 24h.)

3. HB transmission

Few patients have yet completed the 12 month programme of testing for LFTs and HB markers; no evidence of HB infection has been seen.

What next?

These data, showing no clinical or laboratory events attributable to transmission of the three main blood-borne viruses, may further encourage HCDs to use 8Y and 9A in previously untreated patients.

The present data are inconclusive in that some gaps in follow-up allow a small chance of having missed a very transient ALT/AST elevation. Data are currently being more rigorously assessed by a statistician, but one simple treatment (the "Rule of Three") suggests that, within 95% confidence limits, 21 negative cases are still compatible with an infectivity rate of 0-14%. This is plainly better than the underlying rate of >90% for unheated concentrates, but at least 60 successive negative cases will be required to reduce this probability to 0-5%. It is proposed that this pilot study be followed by a formal prospective clinical trial with a stricter protocol to establish with at least this degree of confidence whether severe dry heating has eliminated transmission of blood-borne viruses.

Table 1. Data on patients in study group.

Patient code	Batches used	Age	Previous exposure	ALT iu/ml		AST iu/ml	
				Pre-exposure	Highest	Pre-exposure	Highest
8Y/1	8Y 2201	37	None	-	-	18	17
8Y/3	8Y 2201	35	None	-	-	18	24
8Y/4	8Y 2201	27	None	-	-	14	32
8Y/5	8Y 2203, 3263, 3286	5	Cryoppt.	20	107	-	56
8Y/6	8Y 3296	32	Cryoppt. in 1977	-	-	16	39
8Y/7	8Y 3308	30		-	-	12	27
8Y/10	8Y 3280, 3319, 3329	16	~35 cryoppt. in 1980	24	30	66	56
8Y/11	8Y 3286, 3296, 3280	44	Cryoppt. in 1976	5	9	20	20
8Y/12	8Y 3323	11	None	-	-	39	48
8Y/13	8Y 3263	18	~80 cryoppt. in 1982	35	30	-	-
9A/1	9A 2204, 3286, 3302, 3327, 3321	0.2	<10 FFP + blood	-	-	23	52
9A/3	9A 2203	76	FFP in 1981	-	-	15	15
9A/4	9A 3273	17	None	20	24	-	-
9A/5	9A 3293	21	None	-	-	20	31
9A/6	9A 3299	13	None	-	18	-	-
9A/7	9A 3290	5	None	32	102	55	65

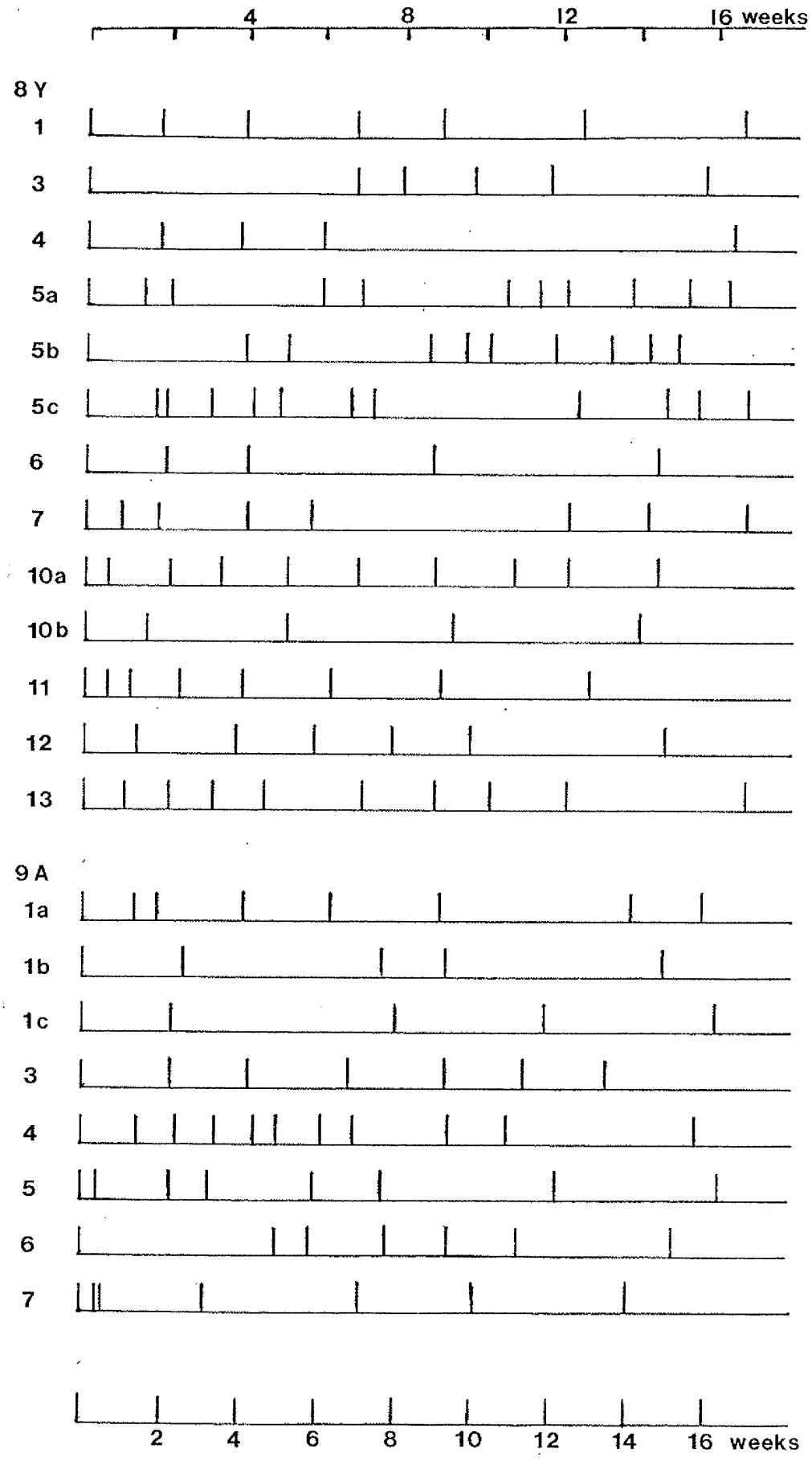

Fig 1. Timing of ALT/AST testing in 21 cases.