M E M O

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10th March, 1986.

Interim report on surveillance for NANBH after first infusions of 8Y and 9A into deficient patients

This is an interim collation of data kindly provided by Dr. Rizza, Dr. Colvin, Dr. Kernoff, Dr. Hill, Dr. Daly, Dr. Bateman, Dr. Mitchell, Dr. Whitmore, Dr. Baugh, Dr. Sheppard and Dr. Shirley.

The concentrates being studied are:

8Y: a new high purity factor VIII concentrate heated in the dry state at 80° for 72 hrs.

9A: a factor IX concentrate closely resembling the old 9D, heated in the dry state at 80° for 72 hrs.

In this particular analysis we have not included a number of patients who have received very infrequent treatment with concentrates in the past, although some workers believe that this group may be almost as susceptible to infection as completely untreated patients.

The data presented here cover only three categories of patient:

Nine patients receiving 8Y as their first ever treatment with factor VIII.

Nine patients receiving 8Y after exposure only to cryoprecipitate or plasma.

Seven patients receiving 9A as their first ever treatment with large pool factor IX concentrate.

These three categories all show the same pattern of results so far, so we will talk about them as a single group.

Of 25 patients enrolled, 24 are past three months from infusion. We know of only one well documented case (Colombo's case 19) claimed to have had a longer incubation period than three months.

Of the 24 patients past three months, only three have had virtually faultless fortnightly LFT testing strictly according to our own and ISTH recommendations. Eight have missed only one or two samples and seven have had appreciably less surveillance, usually because of age and insufficient incentive to venepuncture. We also include in this interim report six cases where results have been given verbally but we have not yet received full documentation as of 10th March.

Seven batches of 8Y have been used in 18 patients, six in the 17 patients who have passed three months. Five out of seven batches were from approximately 6000 donors each. To get the earliest possible information, two PFL batches were pressed into this trial immediately after stage 1 tests of safety and efficacy. These smaller batches were

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from 700 and 1416 donors respectively.

Seven batches of 9A have been used in seven patients, all of whom have passed three months. Again, one of these batches was from 1119 donors, and the rest were from about 6000 donors each. There was no other conscious selection mechanism in choosing batches for clinical trial.

In these 24 patients, no index even suggestive of non-A non-B hepatitis has been seen.

No seroconversion to LAV/HTLV III has been seen in the patients who have been exposed for up to eight months. This is hardly surprising since there is only a very small chance that these batches were contaminated with HTLV III even before heating.

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Can we draw any tentative conclusions yet?

Although only three patients so far meet the strictest ISTH criteria for frequency of testing, data which are less than perfect cannot simply be dismissed. Even the fortnightly testing protocol recommended by ISTH would have missed one or two exceptional cases in the three best published studies, totalling 32 positive cases (Fletcher et al, Colombo et al, Kernoff et al). We have compared the timing of successful LFT tests in 18 of our patients with the precise timing of raised LFTs in each of 32 published cases. Apart from the two or three published cases which might have been missed even by an immaculate LFT protocol, only two more of the published cases would have been missed by any of our testing patterns; only three of our cases would have missed these two short-lived published events.

We think that these incomplete results can reasonably be interpreted as showing a significantly lower incidence of NANBH transmission than formerly found in unheated NHS concentrates, or Hemofil HT, or Armour heated Factorate. This is what one might expect from the known severity of heating. We do not think we can yet make any claims in relation to the low incidences of NANBH from concentrates heated in a dry solvent slurry like Alpha Profilate, or heated in protective solution like Behringwerke's HT.

The Profilate study shows that we need many more patients than we originally thought, possibly 50 on each product and including 20 batches of each product. The only excuse for an incomplete interim report is to encourage you to believe that our concentrates are among the safest for previously untreated patients. We are very conscious that the most obviously eligible patients are precisely those who are most difficult to bleed fortnightly for LFT surveillance. Published data suggest that there is room for movement on the criteria recommended by ISTH. For instance, four-weekly rather than fortnightly LFT surveillance would have risked missing only four of the 32 positives in the three published studies. Acknowledging all the other uncontrollable factors in detection of NANBH transmission, should we not really concede that we are looking for a qualified and statistical answer rather than a definitive one in each of these longitudinal studies?

We are conscious that some centres are not contributing eligible patients and would take any opportunity to learn what the obstacles may be. The protocol was drawn up under some pressure of events, and a second or overlapping series of cases might well be studied with different entry of follow-up criteria. Dr. Lane, Dr. Snape or Dr. Smith will be glad to receive any suggestions, and BPL will consider providing practical resources for any proposals which enjoy your concerted support.

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