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RORER HEALTH CARE LIMITED

TO: Plasma Team

FROM: Mr. R. B. Christie

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SUBJECT: HAEMOPHILIA DIRECTORS' MEETING - SYMPOSIUM ON RECENT ADVANCES IN THE HAEMOPHILIAC

Royal College of Physicians, Edinburgh - October 11, 1986

The Symposium meeting followed the Directors' Business Meeting held on Thursday, 10 October, at which a statement (copy attached) regarding our withdrawal of Factorate products was presented. In the circumstances, we expected some difficult questions and comments and provided an opportunity for answers to written questions at a lunch time session in the middle of the Symposium on 11 October.

The scientific papers were very interesting and, particularly those presented in the afternoon, contained references that were very helpful in the current situation and especially to our Monoclate and the concept of the advantages of product purity.

The morning session commenced with a paper from Dr. Giles on cloned Factor VIII. He mentioned the Armour product withdrawal in his introduction and proposed that Factor VIII produced by genetic engineering was potentially free of such problems.

After an outline of the problems and techniques involved in production of a cloned Factor VIII, Dr. Giles described in-vivo tests in haemophiliac dogs of a purified product produced by genetic engineering. Essentially, the product gave very similar results to plasma derived Factor VIII both in terms of half-life and recovery

and arresting cuticle bleeding. Binding to Von Willebrand factor on a Sepharose 4B column was normal. One very significant development reported was the possibility of tailoring the molecule of Factor VIII and so raising the possibility of improving its physical and biological properties. Maybe this is also a method of circumventing patent coverage on standard Factor VIII products. An example involving the deletion of 200 amino acids from the Factor VIII molecule was described. This product was virtually identical to natural Factor VIII in terms of half life, binding to Von Willebrand Factor and arresting cuticle bleeding in dogs.

It should be noted that all in-vivo work described was in dogs. No clinical studies have been performed yet. Dr. Giles was not able to forecast any time scale of availability of cloned Factor VIII. Possibly the first clinical studies could start next year.

Dr. Dominique Meyer gave a very elegant paper on the very complex pathogenesis of Von Willebrands disease. Although this is not at present directly related to any of our current products, the possibility of producing pure Von Willebrand Factor in our Monoclate process exists, and as you know there is some U.K. interest in this.

Drs. Peale and Clayton described the scientifically complex, but very ingenious methods of screening for Haemophilia B and Haemophilia A using gene probes.

The final paper before lunch was given by Professor Eric Preston who reviewed the laboratory methodology associated with platelet aggregation tests and their significance to the way in which platelets adhere to each other and the blood vessel wall.

During the lunch break, an Armour team of Mr. L. Lucas, Mr. C. Bishop and myself replied to 13 questions, presented in advance in writing from the previous day's Directors' Meeting. The questions and answers given are attached. Follow up comments and requests for clarification were generally helpful. Overall, the impression was one of sympathy with our predicament and an indication that our situation may not be unique. We await publication of data hinted at with interest!

Dr. Levine's presentation after lunch was entitled "Immune Function and HTLV-III". He summarised the results in publications by Dr. Frank Hill, Dr. Ludlam, Dr. Ragni et al, who all demonstrated immunological changes in multiply treated haemophiliacs which could not be accounted for by exposure to HTLV-III.

Dr. Levine concluded that haemophilia alone makes you significantly abnormal, heavy treatment with Factor VIII and, of course, HIV positivity enhances this situation. This is manifested by globulin changes, multiply independent variable T4/T8 ratios and lack of response to antigens in scratch testing. In a group of 83 haemophiliacs, just over half did not respond to allergens. None of the controls in this test were anergic.

Some links with EBV could be shown, particularly with T4 changes. 15% of haemophiliacs have liver disease and a significant number have chronic active hepatitis.

Dr Levine then looked for explanations for the findings that he had summarised.

1. One vial of Factor VIII contains pooled donations from between 2,300 and 32,000 donors!
2. The average haemophiliac in U.S. is treated with Factor VIII 40 - 60 times a year for the past 10 years.
3. This represents a parenteral exposure to an array of allo-antigens (and infectious agents) of a magnitude that is unparalleled in medicine or biology.

Between 1981 and 1984, 94% of U.S. haemophiliacs have become sero-positive for HIV. On the other hand, it should be remembered that the average life expectancy of haemophiliacs has increased from 11.5 years in 1972 to 20 - 23 years in 1986, and is now around normal for the population as a whole. This situation is largely due to adequate replacement therapy.

Reports of AIDS in haemophiliacs has plateaued in 1985. It has been confirmed that this is not due to under-reporting. AIDS risk for haemophiliacs when properly assessed is 1% (not 10% as some figures purport to show).

Dr. Levine then continued on known methods of producing a Factor VIII that might be free of risk to the immune system. Cloned Factor VIII was a possibility but is known to be produced from hamster cells in tissue culture. No one knows how total separation of hamster protein can be achieved or what the effect of this allo-antigen will be when administered to haemophiliacs.

Dr. Fairlie has shown that HIV antibody can disappear and the virus can re-appear on challenge with allo-antigen. No one can predict these effects or their significance.

He then described in summary his work on Monoclate. 7 patients had been treated for 7 - 9 months. No abnormal antibodies were seen from mouse antibody challenge and he concluded that mouse antibody is not a strong immunogen by i.v. injection. The half life of the Monoclate is normal at 15 hours. Haemophiliacs using the product have reported a preference for Monoclate over standard Factor VIII. A single infusion has controlled haemarthrosis. A very preliminary assessment has shown that impaired T cell ratios are returning towards normal, probably because they are not bombarded with an array of foreign proteins.

Finally, Dr. Levine considered hepatitis - in spite of Hepatitis B screening and 90% effectivity of the test, the risk of Hepatitis B remains. It is not known what the effect of ALT screening will be on Hepatitis B and Non A Non B.

Staphylococcal haemarthrosis is becoming more common in haemophiliacs so possibly B cell function is also affected.

Dr. Cuthbert then presented results of the Edinburgh cohort study. A cohort of 34 patients who were sero-negative for HIV Ab were exposed to a known infected lot of Scottish Factor VIII. 16 of these sero-converted within 40 weeks.

Sero-conversion was related to:

(a) Number of bottles of the known infected batch received.
(b) Annual Factor VIII consumption.
(c) Reduced T4/T8 ratio before exposure.

During a 2 year follow up, 3 further patients became HIV antibody positive, i.e. LATE sero-converters. The remaining 15 patients remain sero-negative.

It was concluded that sero-conversion can occur at least 36 weeks after exposure and is not dose related.

The sero-positive group were significantly greater users of Factor VIII. The three late converters were on the low side of usage.

Both the sero-positive group and the late converters had lower T4 counts before sero-conversion and a T4/T8 ratio tending downwards, compared to the sero-negative group.

Viral isolation has been attempted using probes and active virus has been confirmed in 3. 3 awaiting confirmation. 1 sero-negative patient is virus-free.

Clinical state of the sero-positive patients is as follows:

1 - Glandular Fever-like symptoms.
4 - Lymphadenopathy.
2 - Splenomegaly
3 - Thrombocytopenia
1 - ARC
0 - AIDS

Dr. Lee then gave Dr. Peter Kernoff's paper on 'Safety of Factor VIII Concentrates'. She began by saying that Factor VIII usage has increased by 15% per year since the 1970s. Haemophiliacs had been led to expect a practically normal life - then the bubble burst with the advent of AIDS. This focuses the problem on the elimination of viral transmission.

General approaches to prevention are -
(a) Alternatives to blood products.
(b) Donor selection/screening.
(c) Special seriological screens.
(d) Surrogate serological/biochemical screens.
(e) Recipient vaccination.

(f) Product sterilisation.
(g) ? Pool size.

Hepatitis B should be preventable. Individual screening for anti-HIV is now mandatory. Non A Non B hepatitis is a dominant cause of morbidity and may in the future be a much higher mortality risk than AIDS.

Surrogate screening using ALT levels in donors is being used in USA and Germany to some extent and may follow in U.K. Hepatitis risk is reduced using the following product treatment methods -

(i) Heat.
(ii) Physical state.
(iii) Organic solvents/detergents/other agents.
(iv) Fractionation methods - purity.

Dry heat alone is not very effective, but in conjunction with organic solvents it may be more effective due to the effect of the solvent on the envelope of the virus. Influence of fractionation methods is illustrated by Factor IX. A lower incidence of HIV Ab positive results follow Factor IX treatment.

Processes that inactivate virus aggressively also destroy clotting factors. Stabilisors also stabilise virus to the influence of the sterilisation process. Yields are an important consideration because they govern how much plasma is required initially.

A balance is therefore needed and the ideal process has not yet been found. A great variety of heating processes exist, both dry and wet. All of these have been shown to be effective in laboratory tests. However, cases of sero-conversion have been reported and further cases were discussed yesterday.

A case of sero-conversion 8 months after administration of dry heat treated commercial concentrate has been observed but this patient also had non-heat treated NHS, one batch of which was incriminated in HIV sero-conversion elsewhere.

Other cases have received non-heated material or have other risk factors.

It is certain that all concentrates transmit Non A Non B hepatitis. There is no test for the causative agents. It is not possible to screen donors or test the efficacy of a sterilisation process in the laboratory. Chimpanzee tests looked promising but have, by long experience, proved unreliable. The difference between humans and primates is not clear. The only way to confirm safety is to carry out tests in virgin patients. Such studies are difficult to mount and difficult to complete. They are, however, essential. Because of the shortage of such patients, they need to be multicentre.

Problems of trial design can be categorised as follows:-

- Large number of patients have already received concentrate. They must be excluded.
- There must be minimal or no exposure to blood products.
- LFT's must be normal pre-treatment; no evidence of liver disease.
- Frequent ALT/AST checks follow treatment, i.e. 2-weekly.
- Hepatitis B vaccination.
- End-points must be carefully defined.
- Allowance for batch to batch variability is essential.
- Statistical analysis to confirm validity of conclusions.
- Ethical considerations.

ALT of 2.25 times normal is accepted as the upper limit of normal rise. More than one batch must be tested. None of current trials are perfect in design.

The NHS Factor 8Y at 1st October, 1986 had 13 patients treated with 14 batches. None have contracted hepatitis. There are weaknesses in this trial and there is a growing feeling that <u>proof</u> of safety can only come from a second study with a tighter protocol.

Trials about to start with virgin patients are:

NHS 8Y (2nd study)
Profilate (2nd study - ALT screned)
Monoclate (Armour)

Commencing Soon are - Kryoglobulin - vapour heated
Cutter & DNA Factor VIII
Travenol - monoclonal purified

The purpose of the second Profilate study is to check the advantageous effect of ALT screening. So far, 8 patients are clear. Profilate is the only study not needing named patients.

Monoclate is of extremely high purity. It is a 3rd generation product and could be the product of the future. The method of fractionation is the main factor in this product to assure freedom from virus.

It is desirable and possible to run all these studies at the same time. Statistically, 60 clean patients after treatment are needed. However, we will have to be satisfied with fewer than this. At present, all are equally safe in the eyes of the physician but if one patient develops hepatitis, the situation will be changed.

I have described several papers in great detail because of the importance of their content. You should particularly note the confirmation of the potential benefit to the patient of reducing the burden of repeated allo-antigen challenge, i.e. further confirmation of the potential advantage of Monoclate, the potential problems with genetically engineered products that are not perceived with Monoclate and that Monoclate is seen as the 'product of the future'. The "ideal trial design" cited by Dr. Kernoff matches our Monoclate protocol exactly!

Finally, we may not be the only heat treatment process that is associated with sero-conversion to HIV positive, but due to mixture of sources of supply and other risk factors, together with a variable period to sero-conversion, results are very difficult to interpret with confidence.

GRO-C

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