Jean
— Final Copy 22.5.88

UK HAEMOPHILIA REFERENCE CENTRE DIRECTORS

RECOMMENDATIONS ON CHOICE OF THERAPEUTIC PRODUCTS FOR THE TREATMENT OF NON-INHIBITOR PATIENTS WITH HAEMOPHILIA A, HAEMOPHILIA B OR VON WILLEBRAND'S DISEASE

1. BACKGROUND

Recognition of HIV infection/AIDS as a hazard of blood product therapy for haemophilia has caused a heightened awareness of the general problem of transfusion-transmitted disease, particularly as regards non-A, non-B hepatitis (NANBH). Whilst it is clear that risk can never be completely eliminated, major advances have been made in risk reduction, and physicians are faced with the problem of choosing between therapeutic products of possibly differing risks.

The purpose of this paper is to present a consensus view of the UK Haemophilia Reference Centre Directors on the relative merits of therapeutic products which are either currently available in the UK, or likely to become so in the near future. We intend to update our recommendations as the rapidly changing situation evolves.

The Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) in the USA have recently published their own recommendations. The situation in the UK differs from that in the USA, both in the availability of different therapeutic products, and in the legal framework which governs their use. Also, our opinions on the interpretation of available data differ in some respects from MASAC.

2. DATA ON WHICH RECOMMENDATIONS ARE BASED

It must be emphasized that our opinions about the risks and therapeutic efficacies of different products are based on evidence which is often incomplete, and in many cases unpublished. Despite these problems, physicians necessarily have to make therapeutic decisions in the best interests of their patients, within the resources they have available. It has always been the case in the UK that such decisions have often had to be made without guidance from the regulatory authorities. Whilst this situation is to be deprecated, it is important for physicians to be aware of the legal framework in which they prescribe therapeutic products, particularly as regards the 'named patient' use of currently unlicensed preparations. Whilst it may be that such preparations have advantages over fully licensed products, data supporting such conclusions is often scanty. At the very least, therefore, a physician using a product on a 'named patient' basis should be confident of peer group support if his/her decision to use that product is questioned. It is also important to remember that all manufacturers, including those within the NHS, have an

interest in interpreting data concerning their own products in the most optimistic light, and vice versa.

The strongest evidence on the magnitude of risk of viral transmission from any particular product is derived from 'virgin patient' (VP) studies, of which there have been relatively few. It is generally considered that at least 60 patients with uneventful follow-up are needed to satisfactorily prove safety at the 95% level of confidence. To our knowledge, no studies yet carried out have fulfilled this criterion. While anecdotal reports can provide reasonable evidence of viral transmission (and hence the probability of product contamination), the lack of such reports is very poor evidence of product safety - what isn't looked for will often not be found. Extrapolation from apparently similar manufacturing processes is of doubtful validity, since subtle and sometimes unperceived differences may markedly influence viral inactivation/removal. We remain unhappy about the prognostic value of in-vitro and animal data, since both these sources have been proved to be fallible in the past.

3. GENERAL COMMENTS ON METHODS OF VIRAL INACTIVATION/ REMOVAL AND PROCESSING

All factor VIII and IX concentrates currently available in the UK are derived from HBsAg and anti-HIV screened source plasma. Additionally, commercial products are generally obtained from donors screened for elevated alanine aminotransferase (ALT), a possible surrogate marker of NANBH risk. The 'cut-off' limits for ALT screening, and its effectiveness on NANBH risk-reduction, are poorly defined.

Heat-treatment as a method of viral inactivation was initially developed as a means of reducing hepatitis risk. Since the introduction of methods of viral inactivation/ removal, it has become generally accepted that HIV is more easily inactivated than HBV or NANBH. Other agents, such as human parvovirus (HPV), may be less susceptible to inactivation than hepatitis viruses. Although such agents are not necessarily pathogenic in the context of haemophilia care, serological evidence of transmission may be useful as a marker of process efficacy.

It is important to appreciate that the method of fractionation, and not just the nature of any viral inactivation step, may contribute substantially or predominantly to final product safety. In the case of NHS concentrates, final safety may also be dependent on the lesser likelihood of contamination of the source donor plasma.

We have arbitrarily assigned groupings to products available to haemophilia care:

3.1 1st generation products are conventionally fractionated and usually heated in the lyophilized state ('dry' heated), according to various protocols. Clear evidence of NANBH

transmission by some of these products, and anecdotal evidence of HIV transmission (always disputed by manufacturers), has led to all these products except one (Koate HT, Cutter) being withdrawn from the market.

3.2 2nd generation products were developed in response to the perceived inadequacies of 1st generation processes, and have generally been found to have lesser risks of hepatitis transmission. A disadvantage of several methods is low yield, which results in needs for larger quantities of source plasma and higher production costs.

3.3 3rd generation products are prepared by monoclonal immunoabsorption, which results in extremely pure final products of high specific activity. It is claimed that fractionation processes, rather than any viral inactivation steps which may precede or follow them, are predominantly responsible for freedom from viral contamination. Assuming such 'sterility', the main conceptual advantage of these products lies in their potential to avoid the protein and antigenic loading which is an inevitable consequence of treatment with 1st and 2nd generation concentrates. Possibly, such loading may contribute to immune dysfunction, especially in HIV-infected patients, and it is claimed that therapy with monoclonal-fractionated concentrates may have a favourable influence on immune function. In our view, this claim is at present unsubstantiated.

4. PRODUCTS AVAILABLE OR SOON TO BE AVAILABLE

In the following list, comment is made on evidence or lack of evidence from virgin patient (VP) studies on hepatitis transmission compared with the near certain risk of NANBH transmission associated with unheated concentrates.

All the products listed below are considered to have a negligible risk of HIV transmission.

4.1 1st generation products

Koate HT (Cutter)
- 'dry' heated (72 hr, 68°C)
- full product licence
- VP studies: insufficient data, anecdotal evidence of HBV transmission

4.2 2nd generation products

4.2.1. Profilate HT (Alpha)
- slurry heated in immiscible solvent (n-heptane; 20 hr, 60°C)
- full product licence
- VP studies: reduced risk of NANBH transmission

4.2.2. Hemate P (Behringwerke - may be marketed by Armour)
- pasteurised by heating in solution (10 hr, 60°C)

- full product licence
- VP studies: minimal risk of NANBH transmission

4.2.3. Koate HS (Cutter)
- pasteurised by heating in solution (10 hr, 60°C)
- unlicensed: used on 'named patient' basis only
- VP studies: insufficient data

4.2.4. Kryobulin TIM3 (Immuno)
- heated under controlled water vapour pressure (10 hr, 60°C)
- unlicensed: used on 'named patient' basis only
- VP studies: minimal risk of NANBH transmission, possible risk of transmission of HBV

4.2.5. NHS 8Y (factor VIII) (Elstree)
- 'dry' heated (72 hr, 80°C)
- Clinical trial exemption certificate (CTX) for VP study; otherwise used on a 'named patient' basis
- VP studies: 'soft' data suggest minimal risk of NANBH transmission

4.2.6. NHS 9A (factor IX) (Elstree)
- 'dry' heated (72 hr, 80°C)
- unlicensed: used on 'named patient' basis only
- VP studies: 'soft' data suggest minimal risk of NANBH transmission

4.2.7. NHS Z8 (factor VIII) (Edinburgh)
- 'dry' heated (72 hr, 80°C)
- unlicensed: used on 'named patient' basis only
- VP studies: insufficient data

4.2.8. NHS DEF IX (factor IX) (Edinburgh)
- 'dry' heated (72 hr, 80°C)
- unlicensed: used on 'named patient' basis only
- VP studies: insufficient data

4.2.9. Octa VI (Octapharma)
- solvent/detergent treated (TNBP/Tween)
- unlicensed: used on 'named patient' basis only
- VP studies: 'soft' data suggest minimal risk of NANBH transmission

4.3 <u>3rd generation products</u>

4.3.1. Monoclate (Armour)
- monoclonal purified
- 'dry' heated (30 hr, 60°C)
- unlicensed: used on 'named patient' basis only
- VP studies: minimal risk of NANBH transmission

4.3.2. Hemofil M (Baxter)
- monoclonal purified
- solvent/detergent treated before fractionation
- unlicensed: used on 'named patient' basis only
- VP studies: insufficient data

5. RECOMMENDATIONS FOR TREATMENT

5.1 General recommendations

We regard it as self-evident that all patients should be treated with the safest possible therapeutic products. HIV and the hepatitis viruses cause serious and often fatal disease, and every effort should be made both to prevent initial infection and re-exposure. In attempting to meet this ideal, however, there remain several problems:

5.1.1. Although it seems clear that different therapeutic products are associated with differing risks of contamination, it is not possible to quantitate these risks accurately. The data on which judgements should be based is to a large extent unavailable.

5.1.2. Not all the products listed are currently easily obtainable.

5.1.3. If there are supply problems patients at highest risk (e.g., those previously unexposed or only lightly exposed to blood products) should take priority in the use of products perceived to carry the least risk of viral transmission. It should be appreciated that it is not known whether re-exposure to HIV or hepatitis viruses in an already infected patient causes any additional hazard.

5.1.4. As noted in 3.3 above, the use of monoclonal-purified factor VIII is advocated by its proponents not so much because of its presumed lack of viral contamination, but because of its possible immune modulating effect in anti-HIV seropositive patients. While there will undoubtedly be a movement towards the use of more highly purified products, we do not consider current evidence sufficiently strong to justify adoption of such products as routine therapy, outside the context of formalised clinical trials.

5.1.5. Other factors being equal, we favour fully licensed products, or products having CTC or CTX approval, rather than those which have to be used on a 'named patient' basis. We recognise the anomalous situation of NHS concentrates in this respect, which we hope will be rectified in the near future.

5.1.6. Financial considerations inevitably influence availability of therapeutic products, and it is the responsibility of Haemophilia Centre Directors to make appropriate efforts to obtain adequate funding for therapeutic products. We hope our recommendations will be of help in this respect.

5.2 Specific recommendations

5.2.1. For patients in England and Wales with haemophilia A who have received little or no previous exposure to blood products, and who need treatment with concentrate:

1st choice: NHS 8Y, patient to be included in current VP study if appropriate
2nd choice: Hemate P
3rd choice: Profilate HT.

5.2.2. For multitransfused patients with haemophilia A:

Any of the products listed in 5.2.1. above, plus Koate HT.

5.2.3. For patients in Scotland and Northern Ireland with haemophilia A, NHS 8Y is not available and we recommend either Z8 or the commercial products mentioned above in 5.2.1.

5.2.4. All other commercial factor VIII concentrates listed in Section 4 above are currently unlicensed, and in our view should only be used outside formalised clinical trials if the need is considered compelling by the prescribing physician, who must accept and understand the constraints of using on a 'named patient' basis.

5.2.5. For patients with haemophilia B: NHS 9A (Elstree) or in Scotland DEFIX (Edinburgh) should be used.

5.2.6. For mildly or moderately affected patients with haemophilia A and von Willebrand's Disease, desmopressin (DDAVP) should always be considered before use of blood products.

5.2.7. We consider random donor cryoprecipitate to have an only very limited application in the treatment of congenital coagulation disorders, mainly because of its non-HIV-related risks in particular NANBH and transfusion reactions. For the few patients with vWD who cannot be managed with DDAVP, it is recommended that NHS factor VIII concentrate or Hemate P be used. Cryoprecipitate should only be considered if the haemostatic efficacy of concentrate therapy is in doubt.

5.2.8. Hepatitis B vaccination should be given to all patients likely to receive blood product therapy who have no serological evidence of past exposure.

Prof. A.L. Bloom
Dr. I.W. Delamore
Dr. P. Hamilton
Dr. P. Jones
Dr. P.B.A. Kernoff
Dr. C.A. Lee
Dr. G.D.O. Lowe
Dr. C.A. Ludlam
Dr. E.E. Mayne
Dr. G.A. McDonald
Prof. F.E. Preston
Dr. C.R. Rizza
Dr. G. Savidge
Dr. R.T. Wensley

16th May, 1988