OXFORDSHIRE HEALTH AUTHORITY

OXFORD HAEMOPHILIA CENTRE

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Dear Colleague

Re: Recomendations on choice of therapeutic products for the treatment of non-inhibitor patients with Haemophilia A, haemophilia B or von Willebrand's disease.

I enclose an updated version of the above document.

If you have any comments please do not hesitate to contact me.

Yours sincerely

GRO-C

C.R. Rizza
Chairman
UK Haemophilia Centre
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Enc.

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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

SECOND EDITION: 22ND MAY 1989

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. This second edition represents an update of the original recommendations which were issued on 16th May 1988. The situation with regard to scientific data, product availability and licensing has changed in some important respects since that time.

The Medical and Scientific Advisory Council (MASAC) of the National Haemophilia Foundation (NHF) in the USA have 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and therapeutic efficacies of different products are based on evidence which is often incomplete, and in many cases unpublished.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.

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Whilst it may be that such preparations have advantages over fully licensed products, data supporting such conclusions is sometimes 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.

The strongest evidence on the magnitude of risk, or lack of risk, of viral transmission from any particular product is derived from 'virgin patient' studies (VP studies; previously unexposed patient, PUP studies), of which there have been relatively few. The International Committee on Thrombosis and Haemostasis (ICTH) has made stringent recommendations on VP study design and performance. Very few studies have met these recommendations. To demonstrate at a 95% level of confidence that the true risk of a viral transmission incident is less than 5%, it is generally agreed that at least 60 patients with uneventful follow-up are needed. No VP study has yet met this criterion. For pragmatic reasons, ICTH recommends at least 20 patients. At this number, the true risk can be up to 15%. For this reason, anecdotal reports of viral transmission from larger scale clinical practice and 'post-launch surveillance' must also be taken into account when assessing the probable risk of product contamination. However, 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 can of doubtful validity, since subtle and sometimes unperceived differences may markedly influence viral inactivation/removal. However, the paucity of evidence from VP studies, and the often reasonable scientific evidence from in-vitro experiments, necessitates a degree of extrapolation, both as regards similar but not identical manufacturing processes, and pathogenic agents other than HIV-1 and the hepatitis viruses. It is recognised that data derived from both in-vitro and animal experiments has sometimes in the past proved to be fallible as regards prediction of effects in patients.

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-1 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, an its effectiveness on NANBH risk-reduction, are poorly defined. Some commercial source plasmas are, or will be, also screened using other tests systems including anti-HBc and anti-HTLV-1.

Heat-treatment as a method of viral inactivation was

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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. It is probable, however, that this factor is of much less importance than it was in the past.

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 or minimal 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 high purity products are prepared by monoclonal immunoabsorption and other newer techniques which result in purer final products of high specific activity. Fractionation processes, rather than any viral inactivation steps which may precede or follow them, may be predominantly responsible for freedom from viral contamination. Low yield may be a problem.

Assuming 'sterility', the main conceptual advantage of high purity products lies in their potential to avoid the protein and antigenic loading which is a consequence of treatment with concentrates of lesser purity. Possibly, such loading may contribute to immune dysfunction, especially in HIV-infected patients, and it is claimed that therapy with monoclonal-fractionated and other high purity concentrates may have a favourable influence on immune function. In our view, this claim is at present unsubstantiated. Additional but in our view peripheral claimed advantages of these products are a possible lesser propensity to cause transfusion reactions and, because of

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their smaller infusion volumes, improved convenience.

3.4 4th generation products are synthetically prepared by rDNA technology, and currently only available for use in formalised clinical trials. They will not be considered further in this paper.

4. PRODUCTS AVAILABLE OR SOON TO BE AVAILABLE

In the following list, comment is made on evidence or lack of evidence from virgin patients (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 product

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)

- pasteurised by heating in solution (10 hr, 60°C)
- full product licence
- VP studies: minimal risk of NANBH transmission
- anecdotal evidence of HBV and NANBH transmisison
- **NOT AVAILABLE AND UNLIKELY TO BECOME AVAILABLE IN THE UK**

4.2.3 Koate HS (Cutter)

- pasteurised by heating in solution (10hr, 60°C)
- unlicensed: used on 'named patient' basis only
- VP studies: insufficient product specific data: probable minimal risk of NANBH transmission inferred from VP studies of similarly processed product(s)
- anecdotal evidence: no reports of positive events

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4.2.4 Kryobulin TIM3 (Immuno)

- heated under controlled water vapour pressure (10hr, 60°C)
- unlicensed: used on 'named patient' basis only
- VP studies: minimal risk of NANBH transmission.
- anecdotal evidence from VP study of HBV transmission, disputed by manufacturer.

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 only
- VP studies: minimal risk of NANBH transmission
- anecdotal evidence: no reports of positive events

4.2.6 NHS 9A (factor IX) (Elstree)

- 'dry' heated (72 hr, 80°C)
- CTX anticipated for VP study; otherwise used on 'named patient' basis only
- VP studies: insufficient product specific data. Probable minimal risk of NANBH transmission inferred from VP studies of similarly processed product(s).
- anecdotal evidence: no reports of positive events

4.2.7 NHS Z8 (factor VIII) (Edinburgh)

- 'dry' heated (72 hr, 80°C)
- unlicensed: used on 'named patient' basis only
- VP studies: insufficient product specific data. Probable minimal risk of NANBH transmission inferred from VP studies of similarly processed product(s).
- anecdotal evidence: no reports of positive events

4.2.8 NHS DEFIX (factor IX) (Edinburgh)

- 'dry' heated (72 hr, 80°C)
- unlicensed: used on 'named patient' basis only
- VP studies: insufficient product sufficient data. Probable minimal risk of NANBH transmission inferred from VP studies of similarly processed product(s)
- anecdotal evidence: no reports of positive events.

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4.2.9 Profilate SD (Alpha)

- solvent/detergent treated (TNBP/Tween)
- CTX anticipated for recovery and VP studies; otherwise used on 'named patient' basis only
- VP studies: insufficient product specific data. Probable minimal risk of NANBH transmission inferred from VP studies of similarly processed product(s)
- anecdotal evidence: no reports of positive events

4.3 3rd generation high purity products

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
- anecdotal evidence: no reports of positive events

4.3.2 Monoclate P (Armour)

- monoclonal purified
- pasteurised by heating in solution (10 hr, 60°C)
- CTX for VP study; otherwise used on 'named patient' basis only
- VP studies: insufficient product specific data. Probable minimal risk of NANBH transmission inferred from VP studies of similarly processed product(s).
- anecdotal evidence: no reports of positive events

4.3.3 Hemofil M (Baxter)

- monoclonal purified
- solvent/detergent treated before fractionation
- CTX for safety/efficacy study in multi-transfused patients; otherwise used on 'named patient' basis only
- VP studies: minimal risk of NANBH transmission
- anecdotal evidence: no reports of positive events

4.3.4 Octa VI (Octapharma)

- resin purified
- solvent/detergent treated (TNBP/Tween)
- unlicensed: used on 'named patient' basis only
- VP studies: insufficient product specific data. Probable minimal risk of NANBH transmission inferred from VP studies of similarly processed product(s).
- anecdotal evidence: no reports of positive events

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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 to prevent both initial infection and re-exposure. In attempting to meet this ideal, however, there remain several problems:

5.1.1 Although it seems probable that different therapeutic products may be associated with differing risks of viral transmission, 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 above 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, hepatitis or other viruses in an already infected patient causes any additional hazard. However, reactivation of latent infection has been raised as a possibility.

5.1.4 As noted in 3.3 above, the use of monoclonal-purified and other high purity concentrates are advocated by their proponents both because of presumed lack of viral contamination and because of possible beneficial effects on the immune system. 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 general adoption of such products for routine therapy, on grounds of their purity alone.

5.1.5 Other factors being equal, we favour fully licensed products, or products having 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 the 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.

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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:

NHS 8Y or Monoclate P

IT SHOULD BE NOTED THAT NEITHER OF THESE TWO PRODUCTS IS LICENSED FOR GENERAL CLINICAL USE. ONLY PRODUCTS WHICH HAVE A CTX FOR VP STUDIES ARE RECOMMENDED FOR USE IN THIS TYPE OF PATIENT. WHEREVER POSSIBLE AND APPROPRIATE, PATIENTS SHOULD BE FORMALLY REGISTERED FOR INCLUSION IN A VP STUDY

5.2.2 For general use in multitransfused patients with haemophilia A we regard any of the products listed in section 4 above as being acceptable from the point of view of safety. While preliminary evidence suggests that 'super' dry heating, heating in solution, solvent-detergent treatment, vapour heating and monoclonal purification may all result in greater degrees of viral inactivation than conventional dry heating or heptane slurry heating, we do not feel that this evidence is currently sufficiently strong to recommend general adoption of unlicensed commercial products for routine treatment. It remains our view, therefore, that unlicensed commercial products 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 therapeutic products on a 'named patient' basis.

5.2.3 For patients in Scotland and Northern Ireland with haemophilia A, we recommend Z8 (Edinburgh).

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

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

5.2.6 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 those patients with vWD who cannot be managed with DDAVP, there is insufficient information concerning the comparative in-vivo efficacies of different concentrates and cryoprecipitate to make firm recommendations on choice of product. For reasons of safety, we would generally recommend NHS factor VIII concentrate; where the haemostatic efficacy of concentrate is in doubt, cryoprecipitate should be considered.

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

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