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UK REGIONAL HAEMOPHILIA CENTRE DIRECTORS' COMMITTEE

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

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1. BACKGROUND

Recognition of HIV infection/AIDS as a hazard of blood product therapy for haemophilia has led to a heightened awareness of the general issue of safety. This is particularly as regards transfusion-transmitted viral infections but also, more recently, as regards other possible problems consequent upon impurities present in clotting factor concentrates. 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 document is to present a consensus view of UK Regional Haemophilia 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 third edition represents an update of the original recommendations which were issued on 16th May 1988, and updated on 22nd May 1989. The situation with regard to scientific data, product availability and licensing has changed in some important respects over the last year.

2. DATA ON WHICH RECOMMENDATIONS ARE BASED AND LEGAL ISSUES

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and therapeutic efficacies of different products are based on evidence which is often incomplete, and in many cases unpublished.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 with little 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 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. The legal basis of use of products made by the NHS

is uncertain. None is currently licensed, but they are covered by 'Crown immunity'. Where this leaves the prescribing physician is unclear. Probably, peer group support in the event of problems will be a physician's best defence.

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. 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.

Despite these caveats, there can be little doubt that most clotting factor concentrates now available for the treatment of haemophilia A or B have a very small or negligible risk of transmission of HIV-1 or hepatitis viruses. An issue of increasing importance is whether product purity has implications for safety. This is particularly in respect of alterations in immune function which may be detected either in vitro or in vivo. The clinical implications of the results of in vitro data are usually difficult to determine. In/ex vivo data is much more scanty, and interpretation complicated by numerous background variables.

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

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. 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 for 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 (usually 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, as well as viral inactivation steps which may precede or follow them, may contribute significantly to freedom from viral contamination. Low yield may be a problem, and some products have albumin added as a stabiliser in their final formulation, thus reducing their specific activity. Such added albumin is presumed, but not proven, to be inert. The new technologies used in the preparation of these products may carry hazards which are currently unrecognized.

Whether high purity products have a greater margin of safety as regards risk of viral transmission is unknown. Assuming 'sterility', the main conceptual advantage of such products lies in their potential to avoid the protein and antigenic loading which is an inevitable consequence of treatment with concentrates of lesser purity. Possibly, such loading may contribute to immune dysfunction, especially in already immunocompromised 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, which may be particularly beneficial in anti-HIV positive patients. While it seems reasonable to suppose that patients with haemophilia require only factor VIII or IX, rather than the other proteins which 'contaminate' therapeutic concentrates, this claim in our view remains unsubstantiated from a scientific standpoint. However, 'proof' would be difficult or impossible to obtain, and would require studies of many years duration.

Additional but peripheral claimed advantages of these products are a possible lesser propensity to cause transfusion reactions and, because of 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 document.

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.

Where a price is shown, this is approximate and given for reasons of comparability. Prices may vary according to local circumstances, discounting, volume purchasing and other factors.

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
- price: 23 p/u

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 but still significant risk of NANBH transmission
- price: 25 p/u

4.2.2 Haemate 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
- limited availability
- price: 37 p/u

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
- not yet available
- price: not quoted

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. Second VP study showed no such transmission.
- price: 30 p/u

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 'Crown immunity' basis
- VP studies: minimal risk of NANBH transmission
- anecdotal evidence: no reports of positive events
- price: 25 p/u

4.2.6 NHS 9A (factor IX) (Elstree)

- 'dry' heated (72 hr, 80°C)
- CTX anticipated for VP study; otherwise used on 'Crown immunity' basis
- 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
- price: 20 p/u

4.2.7 NHS Z8 (factor VIII) (Edinburgh)

- 'dry' heated (72 hr, 80°C)
- unlicensed: used on a 'Crown immunity' basis
- 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
- price: not quoted

4.2.8 NHS DEFIX (factor IX) (Edinburgh)

- 'dry' heated (72 hr, 80°C)
- unlicensed: used on a 'Crown immunity' basis
- 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.
- price: not quoted

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 products
- anecdotal evidence: no reports of positive events
- price: 25 p/u

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

4.3.1 Monoclate P (Armour)

- monoclonal purified
- pasteurised by heating in solution (10 hr, 60°C) before monoclonal purification
- full product licence
- 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
- price: 45 p/u

4.3.2 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
- price: 40 p/u

4.3.3 Octa VI (Octapharma)

- chromatography purified
- solvent/detergent treated (TNBP/Tween)
- CTX for safety/efficacy study in multi-transfused patients; otherwise used on a '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
- price: 27 p/u

5. RECOMMENDATIONS FOR TREATMENT

5.1 General recommendations

5.1.1 We regard it as self-evident that all patients should be treated with the safest possible therapeutic products.

5.1.2 HIV and the hepatitis viruses cause serious and often fatal disease, and although it remains uncertain whether re-exposure in an already infected patient causes additional hazard, every effort should be made to prevent both initial infection and re-exposure. Therefore, only concentrates having minimal risks of HIV and hepatitis transmission should be used to treat patients.

5.1.3 Provided there is no compromise on safety, only fully licensed products or NHS products used on a 'Crown immunity' basis should be used for routine treatment. When used in formalised clinical trials, products should carry CTX approval. We strongly discourage the 'named patient' use of unlicenced concentrates unless there are compelling reasons not to use the recommended preparations listed in 5.2 below.

The legal situation regarding NHS concentrates is anomalous, and we regard it as a matter of the greatest importance that these products are subjected to normal licensing procedures with the least possible delay.

5.1.4 As noted in 3.3 above, third generation high purity concentrates are advocated by their proponents both because of their presumed lack of viral contamination, and because of possible beneficial effects on the immune system. While we do not consider current scientific evidence sufficiently strong to justify general adoption of such products for routine therapy, we recognize the difficulties of obtaining such evidence and the merits of the 'common sense' argument.

In our view, the case for using high purity products is strongest in (a) anti-HIV seropositive patients with evidence of advancing disease; (b) anti-HIV seropositive patients who need high dosage courses of therapy to cover, for example, major surgery; and (c) patients who have transfusion reactions with

other products. Additionally,some members of the Committee favour high purity products, for reasons of possible superior safety, in (d) previously unexposed or only lightly treated anti-HIV seronegative patients, especially children.

5.1.5 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 both clinical and legal reasons, Directors are strongly advised to resist attempts to force purchase of non-recommended preparations on grounds of lesser cost.

5.2 Specific recommendations

5.2.1 For the treatment of patients with haemophilia A:

- NHS 8Y (Z8 in Scotland and Northern Ireland)
- Monoclate P
- Haemate P (limited availability)

It should be noted that in view of the availability of licenced alternatives of probable superior safety, two currently licenced products (Koate HT and Profilate HT) are no longer recommended.

5.2.2 Where a high purity product is considered indicated for the treatment of patents with haemophilia A:

- Monoclate P

5.2.3 While evidence of safety may be acceptable, we recommend 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.

5.2.4 For the treatment of patients with haemophilia B:

- NHS 9A (DEFIX in Scotland and Northern Ireland)

5.2.5 Wherever possible and appropriate, previously untreated patients should be formally registered for inclusion in a VP study.

5.2.6 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.

Although there is currently no clear evidence indicating that DDAVP carries a significant risk of thrombosis, caution is advised in elderly patients, those with coronary or cerebral occlusive arterial disease, and pregnant women, in whom the balance of risks may favour blood product therapy. Concomitant use of antifibrinolytic agents in such patients should be avoided.

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 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 or Haemate P; where the haemostatic efficacy of concentrate is in doubt, cryoprecipitate should be considered.

5.2.7 Hepatitis B vaccination should be offered to all patients likely to receive blood product therapy who have no serological evidence of past exposure to the virus, and Directors have an obligation to attempt to identify such patients before blood product therapy may be needed.

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