# REGIONAL PURCHASING ADVISORY GROUP - HAEMOPHILIA

## Summary of Progress : September 1992.

Jill Meara : September 1992.

1. Dr J Meara is the co-ordinator of regional purchasing advice on haemophilia services.

2. A group of purchasers has not been convened, but initial discussions with local and national clinicians, together with an appraisal of recent relevant literature, has led to a suggested way forward. This is summarised in the paragraphs below. More detail is available in the accompanying paper.

3. The major current issue for haemophilia services throughout the country is the introduction of a new product for treatment of haemophilia VIII. It is manufactured in a different way to current products, is much more costly and is called "high purity" by its manufacturers.

4. The benefits of this new product could be less damage to the immune system of recipients. There is not yet adequate data to (a) support this hypothesis or (b) reveal other potential side effects of the new product as compared to current treatment.

5. Current evidence would not support early introduction of the new products in exchange for the existing ones for haemophilia VIII. This decision needs to be kept under review as more studies are published.

6. If the manufacturers withdraw supplies of the current product, then users will be forced to switch to the new product.

7. The next potential change in clinical practice will be an increasing use of prophylactic factor VIII.

8. The issues of prophylactic factor VIII also need to be discussed before there is widespread patient pressure to change existing treatment protocols.

# HAEMOPHILIA AND ITS TREATMENT IN THE OXFORD REGION.

## What is Haemophilia.

Haemophilia comprises a group of disorders characterised by low levels of the factors in the blood which are responsible for blood clotting. The most common disorders lead to decreased levels of Factor VIII in the blood. Factor VIII appears to be comprised of two main sub-units, Factor VIII which is controlled by the X chromosome, and von Willebrand factor which is autosomally inherited. Christmas disease, which is less common, is due to a deficiency of Factor IX.

## Prevalence of Haemophilia.

There are about 5500 patients with Haemophilia VIII (previously called Haemophilia A) and 1000 patients with Christmas disease also knwon as haemophilia B) in the UK. Most are familial cases but up to 40% may be the result of new mutations. The prevalence of haemophilia is rising.

## Clinical Haemophilia.

Haemophilia is not a homogeneous condition. The severity can be guaged by the proportion of normal factor level that is present in the affected individual. Symptoms can range from a slightly excess risk of bleeding after surgery, to regular spontaneous bleeding, often into large joints which can cause great pain and orthopaedic complications.

## Treatment.

Classically treatment has been by intravenous infusion of the missing blood factor as soon as possible after an episode of bleeding has begun. Prophylactic treatment with blood products is used to cover surgery and occasionally other at-risk activities.

Treatment of bleeds is often given at home by the patient who has a stock of the relevant factor.

Orthopaedic and other complications also require attention.

There is a tremendous variation between patients in the amount of factor treatment they require, depending on disease severity, lifestyle and amount of previous joint damage. High usage individuals can each use hundreds of thousands of units per year.

Sufficient supplies of haemophilia factor have only been available to all patients since the end 1970's.

## HIV/Hepatitis C and Haemophilia.

Unfortunately during the 1970's and early 1980s blood clotting factor supplies were contaminated by HIV virus and/or Hepatitis C virus. This contamination no longer occurs because products are heat treated or treated with solvent detergents. About 1200 haemophilia patients in the UK were infected with HIV. They would appear to follow a similar clinical course to patients infected with HIV from other routes.

Commercial Supplies of Haemophilia Factors.

Factor VIII and other clotting factor concentrates are manufactured by independent drug companies, and also by BPL at Elstree, which is linked with the DoH and the National Blood Transfusion Service.

Over the years the "purity" of clotting factor concentrates has improved by changes in the manufacturing process. At low levels of "purity" improvements in purity can greatly reduce the prevalence of side effects (allergy, etc). It is much more difficult to sort out the role of "purity" in decreasing side effects from the more modern products. The main concern with current intermediate purity products, is that they may cause depressed cell-mediated immunity leading to increased risk of infections. The risk of viral infection from contaminated blood products has been eliminated in all products currently on the market.

Currently there appears to be some confusion regarding the definition of purity in blood products. This has been well described in the recent review of the subject by the Regional Haemophilia Centre Directors. The biochemistry is complex but it appears that all commercial products have contaminants of some type. Intermediate purity products differ from high purity ones in the type of contaminants rather than the level of a particular known contaminant. This is important as using the terms "high purity" and "intermediate purity" does not express this difference well. In summary, intermediate purity products contain significant amounts of fibrinogen and albumin. High purity products are contaminated with mouse proteins and detergents although these are present in extremely small amounts.

A simplified list of the types of product currently available is shown below. The comparative costings are dependent on bulk purchase contracts and other commercial considerations. High purity factor VIII is roughly twice the price of the conventional product. If the manufacturers withdraw the intermediate purity product then there would be no alternative but to use the available (high purity) products for treatment of haemophilia.

The amount of factor needed to treat Christmas and von Willebrands disease is not so great. The high purity product for von Willebrands disease is not currently on sale in the UK. The intermediate product that is used is the same one used for haemophilia.

Clotting factor concentrates available in the UK.

| Factor. | Disease. | Purity. | Cost per International Unit. |
|---|---|---|---|
| * VIII | Haemophilia | Intermediate | 16 - 32p |
| VIII | " | High | 34 - 48p |
| IX | Christmas | Intermediate | 25 - 45p |
| IX | " | High | 30 - 40p |
| * VIII plus VW factor | von Willebrands | Intermediate | 16 - 24p (Same product can be used as for haemophilia, intermediate purity). |
| VIII plus VW factor | | High | 30 - 40p (not currently available in the UK.) |

Relative prevalence of the diseases in UK : Haemophilia 5500
Christmas 1000
Van Willebrands needing treatment 10's.

* These are one and the same product.

Evidence for the superiority of the high purity product compared with traditional products in the treatment of Factor VIII deficiency.

All of the controlled trials comparing high and intermediate purity products have been published in the last three years. These have been well reviewed by the UK Haemophilia Centre directors (1). The results of the studies are not consistent (5 supporting a hypothesis of less effect on cell medicated immunity in high purity products, 2 rejecting that hypothesis (7,8). Note that some of the work has been published as abstracts and not peer reviewed papers). Their interpretation is also complicated :

- none of the currently published controlled trials have follow-up for longer than 3 years.

- no evidence on real infection risk as opposed to biochemical markers of immunity is presented in any of the published papers.

- the number of cases included in the randomised trials is modest. The paper referred at (6) is an end point study for part of the meta-analysis in paper (3). A summary of the numbers of cases and follow-up times in the published randomised trials is attached.

- there is no history of immune problems in treated haemophiliacs before the advent of HIV infection.

- most studies have been done in patients with HIV who may not have normal immnunity anyway.

- no evidence on the long term effects of contaminants in high purity products that are not present in intermediate purity products.

- Most of the studies which showed a relationship between factor purity and immnunity, have themselves recommended further work be undertaken before changes in clinical practice are recommended.

- There is some evidence that patients treated with factor VIII products which have been purified by monocloncal antibody techniques which include the commonly available high purity products may be at greater risk of developing inhibitors (antibodies) to factor VIII, which hinders and increases the costs of future treatment.

Taken together the published work does not provide a clear case for a shift from the current products to new products, without further evaluation.

Some studies suggest that the newer products may be justified for sub-groups of patients with particular immunological needs (HIV infected patients, young children). It is clear that controlled trials need to be done in these sub-groups of patients, but current evidence would not support a definite benefit from changing to the new products for any patient sub-group.

In summary, current evidence suggests that caution should be exercised before a wholesale shift to the newer blood products is made for haemophilia VIII. Proper scientific evaluation of risks and benefits is essential, including real clinical risks and not just biochemical measures. The relative benefits in different sub-groups of patients also needs to be assessed. This summary does not agree with

the recommendations in the recent document from the UK Regional Haemophilia Centre Directors. They proposed a transfer to high purity products for haemophilia VIII in HIV+ve patients. In HIV negative patients they recommend a transition to the high purity products, linked with adequate scientific assessment and post-marketing surveillance.

The difference between these recommendations is not merely a reflection of different views of the pace of change. The present paper would suggest scientific evaluation prior to widespread introduction of new products. The UK Directors approach concentrates on evaluating a national change whilst it happens.

These two approaches are clearly not incompatible, dependent on an agreed pace of change, backed up by adequate reflection and evaluation.

Clearly a change in supplies available on the market may force a decision.

The evidence seems more straightforward for the other common inherited diseases of blood clotting factors. There is good evidence to support a shift to high purity factor IX for Christmas disease (1000 sufferers only in UK). Von Willebrands factor is not currently produced as a pure product, but the numbers of patients involved is very small. Current treatment is with intermediate purity factor VIII which also contains von Willebrands factor.

Use of Prophylactic blood factors in clotting disorders.

Prophylactic treatment with blood factors has been used for many years to cover surgery and related risks. In addition in Oxford it is practice to offer prophylaxis on a short term basis (say a month) to cover periods of increased risk of bleeds or when a bleed would be particularly inconvenient (e.g. new job, exams, camping holiday abroad).

A national working party has been set up to consider more widespread use of prophylactic treatment. It is likely that considerable evidence would be needed to establish its usefulness and safety as well as the relative costs and benefits of treatment at different ages and for different severity of disease.

If widespread prophylactic treatment were adopted, consumption of clotting factors would rise, but the impact upon overall treatment costs need to be assessed. In the long term it may be that prophylaxis will prove to be cheaper as bleeding and its crippling consequences will be prevented.

The need for national policies on haemophilia care.

England has 14 regional haemophilia centres with a total of 123 hospitals where haemophilia treatment takes place. The experience in Oxford, one of the larger regional centres, suggests there is a lot of cross district and cross regional flow of patients to their hospital of treatment.

It is important for clinicians in these units to be able to apply consistent policies for treatment of patients who live in different districts/regions. Given the scale of cross-boundary flow for treatment, a national policy would be the most appropriate.

References.


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4. Fukutake K, Ikematsu S, Fujimaki M, et al. Multicentree study on the influence of long term continuous uyse of ultra purified factor VIII preparations on the immunological status of HIV infected and non-infected haremophilia A patients. XIIth Congress of the International Society of Thrombosis and Haemostasis 30th June - 6th July 1991. Abstract 1075.

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7. Mannucci PM, Gringeri A, de Biasi R, et al. Immune status of HIV-positive hamophiliacs: a randomised, prospective comparison of treatment with a high-purity or an intermediatew purity factor VIII concentrate.
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8. Evans JA, Pasi KJ, Williams MD, Bill FGH. Consistently normal CD4+, CD8+ levels in haemophilic boys only treated with a virally safe factor VIII concentrate (BPL 8Y). Br.J Haeeematol 1991; 79: 457.

Summary of the controlled trials.

Controlled trials supporting a hypothesis of improved and cell-medicated immunity (as measured by CD4 counts) in patients treated with high purity products compared with intermediate purity products.

| First Author. | Design. | HIV status of participants. | Numbers receiving HP/IP product at end of follow-up. | Follow-up time. |
|---|---|---|---|---|
| Brettler (2) | non-random controlled. | All HIV + | 7 : 7 | 2 years. |
| Seremetis (3) | abstract of meta-analysis of two studies. | All HIV + | 36 : 17 | 1 year |
| Fukutake (4) | abstract multicentre trial. no controls used. | Half HIV + | 54 : | 18 months |
| Goldsmith (5) | non-random controlled. | All HIV + | 13 : 8 | 3 years |
| de Biasi (6) | randomised controlled. | All HIV + | 10 : 10 | 20 months |

Controlled trials rejecting the hypothesis.

| | | | | |
|---|---|---|---|---|
| Mannucci (7) | randomised controlled. | All HIV + | 16 : 17 | 2 years |

Controlled trial rejecting a hypothesis of reduced CF4 and CD8 counts in haemophiliac boys newly treated with intermediate purity factor VIII compared with non-haemophiliac boys.

| | | | | |
|---|---|---|---|---|
| Evans (8) | controls obtained from normal children attending a growth clinic. | None HIV | 15 : 42 | 32 months |