SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE
Headquarters Unit
Ellen's Glen Road
Edinburgh EH17 7QT
031-664 2317

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Indexed ✓

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8th July 1987

Mr Duncan Macniven
Scottish Home & Health Department
St Andrew's House
EDINBURGH

Dear Duncan

Clinical Trials: Compensation SHHD

Thank you for your letter of the 23rd June, 1987. I can concur that it is my understanding that there is now a need for 2 developments: the extension of the existing (non-therapeutic) arrangements for heat treated factor VIII to other products (Type I) and the creation of a new concept - the arrangement of systems for compensation for products undergoing trials when the product is being given for therapeutic purposes (Type II).

With reference to my letter of the 11th February and your response of the 23rd June I would respond as follows:-

PFC Products currently undergoing Clinical Trials

Products

(a) Special albumin solutions for burns
(b) Normal IVIG for active treatment of idiopathic thrombocytopenic purpura and other immune haematological disorders
(c) Anti-CMV IVIG for the active treatment of CMV infection in renal and bone marrow transplantation
(d) Anti-measles IVIG for prevent of measles in childhood leukaemia
(e) Normal IVIG for the active management of neonates infected with HIV.

Comments

1. All these trials are Type II - therapeutic.

2. The risks associated with the use of albumin solutions (burns study) are extremely low and not likely to be different from normal albumin solutions, because the trialled product is but a modest change in formulation from our regular product.

3. The major current concern with all IVIG preparations is the possibility of transmission of viruses. We have already studied

this problem in our product and believe that our current manufacturing process virtually eliminates the potential hazard (see enclosed). There have been a number of other complications reported to be associated with IVIG therapy (bleeding and thrombosis in ITP and immune depression in leukaemia) but these isolated reports have not been confirmed by others and must be extremely rare (incidence of no greater than 1/1,000,000).

Conclusions

At the present time we would conclude that the risks associated with the use of all the PFC products currently under clinical trial are extremely low.

Candidate PFC Products for Clinical Trials

Products

(a) Anti-thrombin III concentrate
(b) Factor VII concentrate
(c) Fibrin glue kit
(d) Activated factor IX concentrates
(e) Murine monoclonal antibody to hepatitis (B) surface antigen
(f) Murine monoclonal antibody to bacterial (coliform) endotoxins

Comments

1. Products (a) and (b) above will require compensation arrangements for both non-therapeutic and therapeutic purposes.

2. Products (c) - (f) inclusive will require compensation arrangements for therapeutic purposes only.

3. Products (a) - (d) inclusive will be heat treated (80°C/72 hours) as a final "sterilising" procedure. Products (e) and (f) will be processed in a manner similar to IVIG in an attempt to reduce/ ?eliminate virus transmission. It is therefore concluded that the virus transmission risk of all these products is likely to be extremely low (less than $1/10^6$).

4. Comments relating to individual products can be summarised as follows:-

   (i) **AT-III** - no risk (aside from virus transmission - see above) is envisaged. Prescribing doctors will have to be careful in the use of heparin in some types of patients.

(ii) **Factor VII concentrate** - no risk (aside from virus transmission - see above) is envisaged. Some batches may be thrombogenic but these will be screened out prior to product issue.

(iii) **Fibrin glue** - no risk (aside from virus transmssion - see above) is envisaged.

(iv) **Activated factor IX concentrates** - It is assumed that the heat treatment will eliminate virus transmission. There is a theoretical risk of thrombogenicity associated with this product. At the present time we cannot realistically assess the likely incidence of this. However, data from the only UK licensed similar product would suggest that it is extremely low (less than 1/100,000 administrations). New parallel SNBTS developments (animal testing) will be introduced to further reduce this potential problem.

(v) **Murine monoclonal antibodies** - It would seem to us that there are 3 potential areas of toxicity with regard to the use of these mouse derived products: contamination with rodent viruses; allergic reactions to mouse proteins and complications associated with immune complex formation involving a foreign protein. There is some evidence to suggest that the PFC processing procedures (pH4 pepsin treatment) will eliminate the mouse virus problem, that allergic reactions are not necessarily an insuperable problem and that concerns over imune complex formation may be exaggerated (see enclosed). Nonetheless all these concerns are to be taken seriously and these products will not be used, for the foreseeable future, in patients unless there is no alternative therapy. Current uses for murine monoclonal antibody preparation to endotoxin will be confined to patients with septicaemic shock and those to hepatitis (B) virus for patients with hypogammaglobulinaemia and persistent hepatitis (B) viraemia, to patients prior to liver transplantation who are HBsAg positive and to patients with rapidly deteriorating liver function as a result of hepatitis (B) virus infection.

Conclusions

1. All the products listed require consideration for arrangements for compensation during trials which are therapeutic in type (Type II). Products (a) and (b) may also require clearance for non-therapeutic (Type I) studies.

2. The risks associated with products (a) - (d) inclusive are judged to be extremely low.

3. The risks associated with products (e) and (f) are much more difficult to evaluate at the present time but are judged to be significantly higher than products (a) - (d).

I hope these comments will be sufficient to permit you and your colleagues to progress the matters in hand.

Kindest regards,

Yours sincerely

John D Cash

Encl.

Dictated by Professor Cash, signed in his absence

Dillman et al - J. Biol. Response Modifiers 5:73-82 (86) (B15)

Carthew - J. Gen. Virol 67: 963-974 (86) (B15)

S. Lees et al - Scottish Med J (submitted to) - (B5(1))