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EINGEGANGEN
3. Jan. 1984
POSTSTELLE

Dr. H. Eibl.

Dr. O.F. Schwarz

Dr. K. Anderle

Mrs. I. Diernhofer

3rd January 1984
NB/BMC

ELA T
09. JAN. 1984

I attach a suggested layout for my presentation to the Medicines Commission.

I shall be pleased if you will furnish the information at A, B and C.

I am not so sure the Sjamsoedin paper should be highlighted in view of the big surplus of Factor IX available in the U.K.

I am still awaiting comment on my proposed letter to Haemophilia Directors about the retrospective Factor VIII Feiba Trial.

I am still awaiting a statement from Dr. Elsinger concerning the testing method for Feiba.

It is necessary to treat this whole matter with great urgency as new legislation is under way which may stop us providing large quantities of Feiba on a doctor/named patient basis.

Yours sincerely,
for IMMUNO LTD.

GRO-C

Managing Director

Enc.

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1980 figures show that in U.K. there are 4,321 haemophilia A patients, (Rizza et al, BMJ Vol. 286 1983 p929-34).
Of these 1903 (44%) are described as severe and have frequent spontaneous bleeds into elbows, knees and ankles. 1236 (29%) are moderately severe and will have occasional spontaneous bleeds, but will have severe bleeding if injured or have to undergo surgery. 1182 (27%) are mild and will require control before undergoing major surgery.

In the normal way, these patients would respond to the infusion of cryoprecipitate or Factor VIII concentrate. Unfortunately, about 6% of them have developed an inhibitor to Factor VIII. These inhibitors are antibodies directed at the pro coagulant part of the Factor VIII complex and the patient becomes resistant to treatment with Factor VIII which has previously been successful in arresting haemorrhage. The titre of the antibody can be measured in Bethesda or New Oxford units and in the Bethesda scale a patient whose level remains below 20 units per ml is regarded as low titre and those above as high titre..

The treatment of haemophiliacs in U.K. is carried out under the supervision of a consultant [redacted] in a recognised Haemophilia Centre, defined by the DHSS as in Memorandum HC 764. There are 110 centres of which 10 are designated as Reference Centres which provide advisory and special clinical and laboratory services to the other Centres. The Reference Centres are invariably consulted when a haemophiliac has special problems - one of which is an occurrence of a Factor VIII inhibitor.

The different therapeutic options available for treating inhibitor patients have been summarised by Bloom 1981, Roberts 1981 and The Lancet Editorial April 2nd 1983, pages 742-3. Briefly, these are as follows:-

Factor VIII Concentrate Human

This is required in very large doses of 20,000 to 30,000 units to swamp the inhibitor. The therapeutic effect of these large doses can vary from patient to patient, and in many cases an anamnestic response would push inhibitor titres even higher. There is a tendency to under treat as to avoid elevating the patients titre. Treatment with Factor VIII is not given for minor bleeds so that its effect can be reserved for major bleeds or life threatening situations. This would mean even higher doses of Factor VIII and even these may be ineffective. (The Lancet Editorial 2.4.83 pp742-3). German workers have shown that massive doses of human Factor VIII given daily over a long period will eradicate the inhibitor. But the cost of this treatment is very, very high. On average, A.....per patient

Plasmapheresis

Patients with suitable veins may have some of their plasma changed for plasma protein fraction and/or other plasma substitutes to reduce the titre of the inhibitor antibody and, therefore, allowing Factor VIII concentrate to be effective, (Wensley 1980). The cost of this treatment is up to £1000 per patient plus the cost of Factor VIII used.

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Factor VIII Concentrate Animal

Porcine Factor VIII has been successfully used as it is not inhibited by the antibody to human Factor VIII. However, the porcine Factor VIII can in itself create immunological sensitivity thus making repeat applications ineffective. Also anaphylactic reactions occur.

More recent material fractionated on polyelectrolytes has proved to be an improvement, but again severe anaphylatic reactions have been reported. (Erskine and Davidson BMJ, Vol. 282 1981 pp2011-2). As with human Factor VIII, to prevent elevation of porcine inhibitors, treatment is withheld for minor bleeds.

Immunosuppressive Treatment

These regimes have been disappointing. They will help to reduce anamnestic response, but only occasionally eradicate the inhibitor. In view of their potentially acute toxicity and their long term adverse effects, they are not an attractive proposition as part of the management of repeat haemorrhage. (The Lancet Editorial 2.4.83, pp742-3).

Non Activated Prothrombin Complex Concentrate

This is routinely used for treating haemophilia B (Christmas Disease). It also appears to be effective in arresting haemorrhage in 50% of bleeds in haemophilia A patients with an inhibitor. However, Lusher (New England Journal of Medicine, 21st August 1980, Vol. 303 pp421-5) reports a placebo effect of 25% when albumin alone is used. There is, however, a risk of disseminated intravascular coagulation (DIC). This is a term used to describe a profound breakdown of haemostasis as a whole. The initial effect is the activation of the coagulation sequence.

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The activation causes consumption of coagulation factors and platelets with fibrin deposition in the micro circulation. Its severity can be measured by the platelet count which falls, the fibrinogen concentration which falls and the fibrin degradation products concentration which is raised.

FEIBA for which we seek a licence

This product has now been widely used in Europe for 8 years, during which time.....B.....units have been administered. It is licenced in C

. . in July 1982, it was licenced in USA by the FDA.

Efficacy

The Section 21.3 letter has asked us to implement the information previously supplied. This included the Hilgartner paper, (Blood, Vol. 61, No. 1, 1983) which pointed out that Feiba controlled 92% of bleeding episodes. 36% of these episodes were controlled in 12 hours by one infusion. A further 42% were controlled in 36 hours with one or more infusions and 14% in more than 36 hours.

The paper also shows that no person developed hepatitis, nor did DIC occur.

We also included the Sjamsoedin report (New England Journal of Medicine, 305, pp717-721, 24.9.81) describing a double blind trial indicating that non activated prothrombin complex was effective in 52% of haemorrhagic episodes, but when Feiba was used, efficacy rose to 64% after a single dose. In addition, joint mobility was significantly improved with Feiba treatment and comparison of treatment at the same site with Feiba and control, again showed a significant advantage for Feiba.

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It has been difficult to compare Feiba directly with Factor VIII as many patients receiving Factor VIII will have their inhibitor level rapidly increased. We have, therefore, secured and presented new data comparing Feiba with Factor VIII on a retrospective basis.

We have also submitted a copy of the "Efficacy of Prothrombin Complex Concentrate in Haemophiliacs with Antibodies to Factor VIII. A retrospective study of 114 haemorrhagic episodes (J. Martin-Villar et al)" This shows clear advantages of Feiba over Factor IX concentrate, both clinically and in laboratory results.

We have also submitted a paper by Bosser and Jourdan 1982, (The evaluation of the Clinical Efficacy of Feiba in Minor Bleeding Episodes). This also shows good clinical response to Feiba and is supported by in vitro laboratory tests.

Quality

Item 3.4 - We have now provided the necessary details from the manufacturer of needles provided in the packs, with especial reference to the ethylene oxide sterilisation procedures which have been used.

Item 3.5 - We have provided the necessary details concerning the lyophilised inhibitor plasma.

We have also provided actual packs of Feiba and the necessary reagents to Dr. D.P. Thomas, National Institute for Biological Standards and Control, Holly Hill, Hampstead, London NW3 6RB. Dr. Thomas has assured us in writing that he will have no difficulty in testing batches of Feiba.

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Item 3.7. - We have provided a new summary of the pack contents to include the minor changes concerning the origin of items of supplementary equipment.

To conclude, we are asking for a licence for a product which is safe, effective and of good quality.

It will be used in the treatment of a small number of patients to arrest their bleeding - sometimes in situations which are life threatening.

It will only be prescribed by Consultants who are experts in the sphere of haemophilia.