PART IV STUDIES IN HUMANS

1. HUMAN PHARMACOLOGICAL STUDIES

See also Part III 1.1.

The influence of activated prothrombin complex concentrates such as FEIBA IMMUNO™ on coagulation and fibrinolysis, particularly with regard to the formation of fibrinopeptide A and platelets has been investigated by:

- S. Vigano et al.
  Increased FPA after Prothrombin Complex Concentrate
  Thrombosis and Hemostasis, vol.44, 2, Oct. 31, 1980 (Encl. 15)

- W. Schramm
  Fibrinopeptide A: Detection during therapy with FEIBA
  Presentation at the 2nd Workshop on F VIII Inhibitors
  March 19, 1979, Vienna. (Encl. 16)

- Vermylen et al.
  Evidence that Activated Prothrombin Complex Concentrate Enhance Platelet Coagulant Activity
  BMJ, 38, 235 (1980) (Encl. 17)

2. CLINICAL TRIALS

2.1. Summary of all clinical trials

Clinical investigations with FEIBA IMMUNO™ may be roughly divided into the following groups:

I Initial trials in Europe and Japan in Hemophilia-A patients with F VIII Inhibitor.

II Continuous combination therapy with FEIBA IMMUNO™ and F VIII concentrate in Hemophilia-A patients with F VIII Inhibitor

III Clinical application of FEIBA IMMUNO™ in non-hemophiliac patients with acquired inhibitors

IV Clinical application of FEIBA IMMUNO™ in Hemophilia-B patients with F IX inhibitor

V US multi-clinic open non-controlled study

VI Randomized double-blind trial

The total number of patients treated with FEIBA IMMUNO™ amounts to approximately 262 cases. About 160 cases in group I, 23 cases in group II, 10 patients in group III, 5 patients in group IV, 49 patients in V, and 15 patients in group VI. The number of bleeding episodes treated amounts to approx. 400 in group I, 11 in group III, about 6 in group IV, 165 in group V and 150 in group VI. As to group II the number of bleeding episodes cannot be indicated since the combined treatment of FEIBA plus FACTOR VIII concentrate was given as continuous therapy.

I. Initial trials

During this initial phase starting in1974 clinical experience with FEIBA IMMUNO™ was first gained in Austria, and later in various other European countries including the FRG, Italy, France, Spain, Switzerland, Great Britain, the German Democratic Republic, Denmark, Poland, Hungary, Sweden, as well as Japan. For the most part the reports consist of retrospective case histories on the treatment of bleeding episodes in Hemophilia-A patients with inhibitor to F VIII. The preparation had also been

used for minor surgery, primarily dental extractions, as well as for three cases of major surgery - one gastrectomy and two orthopaedic operations. In a Swiss trial the effectiveness of FEIBA IMMUNO™ in controlling bleeding episodes was assessed by the time required to control the episode after FEIBA treatment compared to the time required for recovery by the same patient without treatment. The dosage range for a single individual application was between 5 and 400 units/kg bodyweight, but for the majority of single applications the dosage was between 50 and 100 units/kg bodyweight, administered intravenously. Some bleeding episodes were controlled by a single infusion, but where necessary the dose was repeated 2 or 3 times a day for a few days.

II Continuous combination therapy: FEIBA IMMUNO™ + F VIII

Prof. Egli at the Haemophilia Center in Bonn (FRG) gave FEIBA IMMUNO™ in combination with F VIII concentrate in an attempt to reduce or eliminate the F VIII inhibitor in 14 hemophiliacs with inhibitor to F VIII. The study was subdivided into 3 phases. In phase I the patients were given 50 units of FEIBA/kg bodyweight and 75 units of F VIII concentrate/kg bodyweight twice a day. In phase II they received 50 units FEIBA and 75 units F VIII concentrate once a day. In the third phase the patients were given only F VIII concentrate.

Each of the patients was treated for several months with the three different regimens.

This form of therapy has also been used by some other investigators among them Prof. Schimpf (Heidelberg, FRG), Dr. Scharrer (Frankfurt, FRG), and Prof. Lechner (Vienna, Austria).

III Clinical application in non-haemophiliacs with acquired inhibitor

Several reports on the successful treatment with FEIBA IMMUNO™ of bleeding episodes in non-haemophilic patients with acquired inhibitors have been received.

8 cases of spontaneous bleeding due to an acquired inhibitor against F VIII were reported on.
In 3 patients with acquired F XI inhibitor bleeding was controlled with FEIBA IMMUNO™. Rolovic (Belgrad, Yugoslavia) reported on a patient - a 45 year old woman - with a severe haemorrhage after

hysterectomy, which after unsuccessful treatment attempts could finally be controlled with FEIBA.The two other cases relate to a coronary bypass operation, and a cardiopulmonary bypass intervention in a patient with prolonged Kaolin-Cephalin Clotting Time.

IV Clinical application in Hemophilia-B patients with F IX inhibitor

Recently a few cases with F IX inhibitor in Hemophilia-B were reported where bleeding was controlled with infusions of FEIBA IMMUNO in a dose of 50 - 100 units/kg bodyweight.

V US multi-clinic open non-controlled study

In July 1979 a multiclinic study with FEIBA IMMUNO™ was started in the US. This study was designed to test the safety and efficacy of FEIBA IMMUNO™ in the treatment of joint bleedings, mucous membrane, musculo--cutaneous hemorrhage, as well as emergency bleeding episodes such as central nervous system hemorrhage and surgical bleeding. Patients with inhibitor titers greater than 5 Bethesda Units were recruited among 9 cooperating US hemophilia-centers. Bleeding episodes were treated with different lots of FEIBA at intervals of 12 hours, except for mucous membrane bleedings, which were treated at 6 hour intervals for up to 48 hours, over a period of 16 months.165 bleeding episodes were treated in 49 patients. 102 episodes were joint bleeds, 20 mucous membrane bleedings, 33 muscle/soft tissue bleedings, and 10 emergency cases.

For the majority of bleeding episodes a uniform dosage of 50 units FEIBA/kg bodyweight was used and only in a few patients (mostly emergencies) the dose was increased to 100 units/kg bodyweight).

Bleeding was controlled in 151 episodes (91.5 %); in 58 episodes this was achieved with one infusion (35.2 %), and in 93 cases with two or more infusions (56.3 %). Bleeding was not controlled in 14 episodes (8.5 %).

VI Randomized double-blind trial

During 1979 and in the beginning of 1980 Sixma and his team carried out a randomized double-blind clinical trial comparing the effect of activated prothrombin complex concentrate (FEIBA IMMUNO™) and non-activated prothrombin complex concentrate

(PROTHROMPLEX IMMUNO) in patients with Hemophilia-A and antibody to Factor VIII. In this study 15 patients were treated for a total of 150 bleeding episodes. The bleeding episodes evaluated were for the most part joint and musculo-skeletal bleeding, and a few cases of mucocutaneous bleeding. The dosage of FEIBA used was 88 units/kg bodyweight. Subjective evaluation after 24 hours by patients themselves without using stratified pairs resulted in 41.0 % effective and 24.6 % partially effective (together 65.5 %) for FEIBA against 25.0 % effective and 21.4 % partially effective (together 46.4 %) for the placebo.
Statistical evaluation of the results according to the Wilcoxon-Mann Whitney two-tailed test resulted in a value of $p = 0.0542$ (patient evaluation); comparison of stratified pairs 24 hours after administration by the investigator gave a p value of 0.0084 in favour of FEIBA; comparison of joint mobility after 6 hours ($p = 0.04$) and after 24 hours ($p = 0.006$) also showed significant and highly significant results, respectively. Sixma concluded however, that the better effectiveness of FEIBA was not necessarily due to its activated nature, because it also contained more F IX units than the control preparation.

Side effects

The following side effects have been recorded:

- 11 cases of disseminated intravascular coagulation (DIC) were reported. In 3 of these cases, in addition to the laboratory values indicative of DIC, there were also clinical symptoms such as pallor, sweating and hypotension.

- 2 cases of thromboembolic complications possibly linked with FEIBA have been reported. One is a case of transient amaurosis fugax described by Rasche, and the other is a case of severe pulmonary embolism and infarction, which however was not fatal, in a patient treated with FEIBA after gastrectomy.

- 22 cases of allergic reactions were reported,which for the most part can be classified as minor adverse reactions (dizziness, headache, nausea, urticarial rashes), apart from one severe reaction of pulmonary congestion, dilatation of the heart and decompensation.

- In 9 cases the transmission of hepatitis as a result of FEIBA treatment could not be excluded. In some of these cases it is impossible to ascertain with absolute certainty whether the transmission of viral hepatitis was caused by FEIBA or another blood product given simultaneously.

These 44 side effects are related to a total number of treatment episodes of about 740 cases which results in an incidence of 5.9 %.

Summing up it may be said that in the opinion of the majority of investigators, who have used FEIBA IMMUNO™, the material is effective and safe in the treatment of bleeding in patients with coagulation factor inhibitor.

2.2. Summary relating to use of drug in each of the proposed clinical indications

See item 2.1. of this part and enclosures 38 - 55 and 57.

2.3. Summaries of each individual clinical trial

See item 2.1. of this part and

For group I' Initial trials in Europe and Japan' see enclosures 18,19,20,21,22,23

26,29,30,31,33,34,35,36

37,39,42,43,46

47,48,49,50,51,52

The number of side effects reported is included in the paragraph 'side effects' in the overall summary according to item 2.1.

This means that related to a total of approx. 400 treatment episodes the following side effects were reported:

11 cases of DIC

2 cases of thromboembolic complications

7 cases of allergic reactions

6 cases of hepatitis

For group II see enclosures 24,32,41,44

No side effects were reported

For group III see enclosures 25,38,40,50,54

No side effects were reported

For group IV see enclosures 27,27a,27b,28, 57

No side effects were reported

For group V 'US multi-clinic open non controlled'study' see summary included in item 2.1. as well as enclosures 27, 27 a and 27 b.

With regard to adverse reactions, no serious side effects were observed, and only 15 cases of minor allergic reactions such as dizziness, headache, nausea, and mild hives were reported.

In group VI 'Randomized double-blind trial' no side effects were recorded apart from 3 cases of hepatitis, which,however, may also have been caused by the placebo.

A summary on the clinical efficacy is included in item 2.1.

3. ADVERSE REACTIONS

See item 2.1. of this part (Side effects) and enclosure 56