Cutter

MILES

Ref: SJ27-84

TO. M. Sternberg

DATE. December 12, 1984

FROM Richard S. Schwartz

SUBJECT Analysis of Proposal from National Heart/Lung Blood Institute for Study of Safety of Heat-Treated Factor VIII Concentrates in the Treatment of Hemophiliacs

COPIES TO R. Rousell
S. Ojala

The proposal being put forward by Dr. Barbosa of the NHLBI is a proposal to conduct a five year prospective study of heat-treated Factor VIII preparation in virgin hemophiliac patients with mild hemophilia who have previous received only the unpooled products or none at all. Patients would be followed prospectively for five years with one group receiving heated AHF and the control group receiving non-heat treated product or cryoprecipitate.

I would make the following comments regarding the study design:

a. Although there are currently some institutions that continue to use non-heat-treated AHF preparations, as more information becomes available regarding the benefits of heat-treatment on AHF, it is very possible that it may at some time in the future become unethical to continue treatment with non-heat-treated AHF. I would therefore question the design of the study utilizing non-heat-treated AHF. The only practical alternative might be to utilize a control group on cryoprecipitate only which has recently been shown to result in a lower conversion of HTLV3 sero-conversion in hemophiliac patients compared to those receiving Factor VIII concentrate. I know that the protocol design problem has been under major discussion at the National Hemophilia Foundation and the NHLBI and we would want to participate in these discussions to satisfy ourselves that the study design in fact is practical.

b. The proposed five year duration of the study is long. I would think that it would not take five years to determine if there were going to be failures of hepatitis safety. Presumably the long period of study is being requested to determine the risk of AIDS.

c. As all patients in the proposed study are to be vaccinated with hepatitis B vaccine, we would not be able to determine the safety from hepatitis B in the study as being proposed.

d. The study as proposed will be extraordinarily expensive. Although not stated, it may well be that the manufacturers participating in this investigation will be expected to provide large amounts of funding towards this investigation.

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e. Last week Steve Ojala and I met with Dr. David Aronson at the Office of Biologics at which time we discussed several aspects of clinical studies including this one. He informed us that two manufacturers, Highland and Alpha, are already known to have established their own clinical investigation on safety of heat-treated AHF independent of the National Heart Lung Blood Institute and will therefore tie up many of the virgin hemophiliac patients in the United States. It therefore now appears that there may in fact not be enough virgin patients in the United States to conduct the NHLBI study and Dr. Aronson indicated that there is some consideration that part of the investigation may be conducted overseas in Europe. Although he did not indicate this, it is my feeling that as Hyland and Alpha already have studies ongoing, there would appear to be no reason for them to participate in the NHLBI study as being proposed. Should they not participate, of course more virgin patients would be available for study with Cutter product which might enable the investigation to be completed at an earlier date. Alternatively, however it may be that the two manufacturers Hyland and Alpha have tied up essentially all the virgin patients in the United States which may make it impossible for us to do an investigation in the United States.

f. The NHLBI investigation is not scheduled to commence until at least September 1985. This is perhaps unfortunate as the Highland and Alpha study will likely be nearing completion by this time and they will hve results for their preparations long before the collaborative study will commence. As an aside, I have been informed by Dr. Marion Koerper of the University of California, San Francisco that she is aware at the least one patient who has been receiving Hyland heat-treated AHF who has sero converted to HTLV3 positive status while receiving only heat-treated AHF and without other factors.

g. At our discussions with Dr. Aronson last week, I mentioned to him that should we choose to participate in this study, we would want to inlcude two preparations, a dry heat and a wet heat-treated AHF. This would have several implications however including requirement for increased funding from Cutter Laboratories, doubling the number of patients that would be required for study, and as the wet heat-treated AHF would not be a licensed product yet, we would be required to supply all wet heat treated wet product for the duration of the study until it was licensed as well to monitor all clinical supplies released for this purpose.

I hope these considerations will be helpful to you in your analysis of this proposal and discussions with the National Hemophilia Foundation and National Heart Lung Blood Institute.

RSS/sj GRO-C

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DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

National Institutes of Health
National Heart, Lung,
and Blood Institute
Bethesda, Maryland 20205

December 6, 1984

Dr. Steven Ojala
Cutter Laboratories
4th and Parker Streets
Berkeley, California 94701

Dear Steve:

Here is the initiative we discussed over the phone. Dr. Aledort of the Hemophilia Foundation is the moving force behind it.

Please examine this document and call me as soon as possible. I have to make a decision on whether to keep this initiative in the system or drop it before Christmas.

Perhaps a more focused study looking at NANB and HTLV-III would be feasible. As I said to you, a NHLBI-Cutter study is a distinct possibility.

Sincerely yours,

GRO-C

Luiz H. Barbosa, D.V.M.
Blood Resources Branch
Federal Building, Room 5C10

Enclosure

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GRO-C

October 12, 1984
DIVISION OF BLOOD DISEASES AND RESOURCES

PROPOSED INITIATIVE FOR FY'S 84/85

TYPE OF MECHANISM

Request for Proposal; FY 1985

TITLE

Safety of Heat-treated Factor VIII Concentrates in the Treatment of Hemophiliacs

OBJECTIVES

1. To conduct a double-blind, randomized, prospective study comparing incidence of serum ALT elevations relative to NANB hepatitis in hemophiliacs given heat-treated or untreated preparations of factor VIII concentrate.

2. To compare the frequency of induction of factor VIII inhibitors, immune complexes and transfusion-transmitted viruses in patients given heat-treated and untreated factor VIII preparations.

3. To compare the frequency and extent of changes in lymphocyte populations in patients given heat-treated and untreated factor VIII preparations and to correlate these findings with the appearance of AIDS-like symptoms.

This effort is envisioned as a multicenter, cooperative, clinical study to evaluate the long-term effects of several heat-treated or untreated factor VIII preparations on patients with hemophilia.

NEED AND JUSTIFICATION

In 1975, a workshop was sponsored by the Bureau of Biologics (BoB), the National Hemophilia Foundation, and the National Institutes of Health (NIH), to examine the complications of hemophilia therapy since the introduction of concentrated therapeutic preparations. The problems of liver function abnormalities, transaminitis, chronic active hepatitis, and inhibitors were discussed at the workshop.

Since 1975, there has been a marked increase in utilization of concentrated factor VIII preparations in this country. An NIH-sponsored inhibitor study evaluated over 1,500 patients between 1975-79 and found that the average annual amount of factor VIII, or antihemophilic factor (AHF), utilized per patient was approximately 40,000 units. In a recent study the average use of AHF in patients with severe hemophilia has risen from 62,000 units to approximately 85,000 units per patient per year in 1983. Since 1975, there have been many studies on the complications of AHF treatment. Some of the findings include:

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1) The incidence of inhibitors to AHF has increased to approximately 15 percent in patients treated with AHF. This increase may be due, in part, to more sensitive assays of inhibitors, but it may also be due to a more intense use of product. This issue has not been resolved.

2) Patients on AHF therapy have been shown to develop immune complexes. The meaning of this finding is unclear.

3) Persistent transeminitis occurs in approximately 52 percent of hemophilia patients on AHF therapy and hepatitis B antigenemia occurs in 5 to 7 percent of patients with the disease.

4) An international study of 155 patients showed that 25 percent of patients receiving AHF therapy had either cirrhosis or chronic active hepatitis on the basis of liver biopsies.

5) In 1982, the first case of hemophiliac with acquired immunodeficiency syndrome (AIDS) was diagnosed. As of October 1984, 42 cases have been reported.

During the past year, the American and European fractionation industries have produced heat-treated AHF products. There are now four manufacturers in the United States licensed to produce heat-treated AHF. The heat-treatment procedure has been shown to reduce virus infectivity in chimpanzees. Currently, the one heat-treated product licensed for use in the U.S., Hemophil, is manufactured by Hyland Laboratories and was first marketed in early 1983. This product has been claimed to be safe for use in hemophiliacs based upon the findings that chimpanzees infused with this preparation have not developed non-A,non-B hepatitis and that the infectivity of hepatitis B marker virus is reduced by this process. In early human clinical trials in Europe, however, approximately 50 to 60 percent of virgin hemophiliacs (previously untreated) receiving this product developed non-A,non-B hepatitis. Nevertheless, the incidence of non-A,non-B hepatitis may be lower with the heat-treated product than with currently used untreated preparations. There is reasonable evidence that hepatitis B is not transmitted by these treated products.

At present, heat-treated preparations manufactured by Alpha Therapeutics, Armour and Cutter are licensed. It is thus an ideal time for an investigation of the safety and effectiveness of these products. This information has both fiscal and blood resource implications. Heat-treated products lose some factor VIII activity during processing and thus require more starting material to yield an equivalent amount of factor VIII. In addition, these products cost more than untreated products. The national health care costs could thus increase significantly above the current average cost of $9,000 per patient per year.

There is concern that the use of untreated AHF in large quantities may be associated with an increased frequency in the appearance of factor VIII inhibitors. Heat-treated products, with their larger amount of denatured protein, could cause an even higher rate of inhibitor

formation. In addition, studies of T-cell subpopulations among hemophiliacs since the emergence of AIDS have suggested that untreated concentrate, and cryoprecipitate, results in changes attributable, at least in part, to allogeneic stimulation. In fact a case of AIDS has now been reported in a patient solely treated with cryoprecipitate. If so, then heat-treated products may be associated with even more profound immunosuppression. Finally, the incidence of adverse reactions to concentrate has not been determined. The work of Gallo and Montaignier suggest a key role for retroviruses in producing AIDS. The appearance in the plasma of antibodies to HTLV-III and LAV concomitantly with the onset of AIDS in the nomosexual as well as hemophilia population add credence to this hypothesis. These retroviruses produce T cell changes indentical to those found in AIDS. Retroviruses are very heat labile and the new products may well be able to erradicate the presence of retrovirus contamination of concentrates. The findings that liver disease has an increasing mortality for hemophiliacs, and that 85 percent of hemophilia patients have antibody to HTLV makes a prospective study of virgin hemophilia patients critical if we are to determine if altering blood products can impact on these serious complications of transfusion therapy.

It is envisioned that this project would be a five-year, multicenter, cooperative, clinical study, involving prospective evaluations of patients. Ideally, this study must have virgin patients as a key to patients with mild hemophilia who have previously received only unpooled product but develop a temporary need for therapy that can best be met by administration of concentrate. It is believed that only in the pediatric age group are sufficient numbers of such patients likely to be found. Patients would be randomized to receive either cryoprecipitate, or heat-treated preparations. Viral infectivity studies with the heat-treated product have been performed in chimpanzees but few studies have been performed in humans. If viral infectivity is reduced by heat-treatment, then the relationship of this treatment to a possible reduction in the transmission of AIDS can also be addressed. All patients entered into the study should receive hepatitis B vaccine so that this disease will not be confused with the transmission of other viral illnesses such as non-A,non-B hepatitis, EBV (mononucleosis) or CMV. All members of the immediate family unit should be tested for the presence of these viruses prior to and during the study to insure that transmission of disease is not from family members. Patients should be tested at two month intervals for a period of at least 3 years, for evidence of non-A,non-B hepatitis in addition to CMV, EBV, immune complexes and inhibitors. Laboratory data for HTLV-III antibodies should be sought. Clinical and laboratory data consistent with AIDS such as lymphopenia, thrombocytopenia, and depressed T-cell ratios should also be collected. In addition, samples should be frozen on a periodic basis for future use to insure that, if a marker for AIDS is identified, it could be evaluated as a possible diagnostic test for the disease.

In summary, several aspects of hemophilia treatment with heat-treated preparations need to be addressed:

1) The possible development of non-A,non-B hepatitis as measured by the incidence of transaminitis;

2) The possibility that heat-treated preparations contain altered proteins that stimulate the development of factor VIII inhibitors;

3) The relationship of these new products to the increased incidence of immune complexes in recipients;

4) The development of evidence of HTLV-III transmission, signs or symptoms of AIDS, and;

5) The determination of the incidence of CMV and EBV in patients receiving heat-treated preparations to verify if transmission of these viruses are significantly reduced.

It is anticipated that this study would be a cooperative effort and include the FDA and the pharmaceutical industry. The pharmaceutical industry is willing to contribute a portion of the funds for this study. No other agencies are currently studying this issue.

RELATION TO EXISTING PROGRAMS

This initiative is related to the safety of blood therapy long-range objective of the Blood Resources Program. Presently, the Blood Resources Program is supporting research on the development of methods to detect transfusion-transmitted viruses and on the development of methods to assure the safety of blood derivatives prepared from donor pools.

PROJECTED COSTS

(Dollars in Thousands)

	Pre-85 Total	85	86	87	88	89	90
This initiative	0	0	800	848	899	953	1010
Total	0	0	800	848	899	953	1010

ADMINISTRATIVE INFORMATION AND MANAGEMENT PLAN

1. Project Origin and Approval Status

   The idea for this initiative originated in the Blood Resources Working Group of the Blood Diseases and Resources Advisory Committee.

2. Method of Review

   The primary technical review of applications will be by a special ad hoc study section managed by the Division of Extramural Affairs, NHLBI. A secondary, programmatic, review will be by the DBDR. It is anticipated that only one study will be funded.

3. Management Plan

Branch: Blood Resources

Project Officer: Luiz H. Barbosa, D.V.M.
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Bethesda, Maryland 20205
GRO-C 496-1537

Submission of the concept to Council	September 1984
Issuance of RFP	December 1984
Letters of Intent	January 1985
Receipt date of applications	May 1985
Technical review	June 1985
Programmatic review	July 1985
Award date	September 1985

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