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ARMOUR PHARMACEUTICAL COMPANY LIMITED

TO: Plasma Team

FROM: Mr. R. B. Christie

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SUBJECT: "EVALUATION OF HUMAN VIRAL DISEASE TRANSMISSION THROUGH PLASMA PRODUCTS"

Heldebrant, C.M., Friedman, A.E. and Fedor, E.J.
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This paper describes a clinical study to assess the efficacy of Alpha's "wet" Heat Treatment process on Factor VIII and Factor IX products. Unfortunately, the one monthly follow up interval for liver enzymes does not follow accepted guidelines for studies of this sort and there is a real risk that transient elevations of NANB Hepatitis may have been missed.

Notwithstanding, 3 haemophilia A patients and one Von Willebrand's patient showed ALT elevation. Four patients out of 23, in a study where other elevations could have been missed, confirms earlier reports (Dr. Kernoff, et al) that the Alpha wet heat treatment is less than 100% effective in removing the causative organisms of Non A Non B Hepatitis. No patient sero-converted to HIV antibody positive, but the subset was a small group and there is evidence that one year may not be long enough for follow up.

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EVALUATION OF HUMAN VIRAL DISEASE TRANSMISSION THROUGH PLASMA PRODUCTS

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ABSTRACT

Alpha's Wet Heat-Treatment process is being applied to both Factor VIII (AHF) and Factor IX Complex (PTC). Twelve hemophilia A, five hemophilia B, and one von Willebrands patient have been followed for at least 6 months for evidence of non-A, non-B hepatitis. No ALT elevations were seen in the hemophilia B patients. There have been four cases of ALT elevation, three in hemophilia A patients and one in the von Willebrand's patient. A subset of these patients have been followed for over one year for anti-HTLV-III status. No patient, either hemophilia A, hemophilia B, or von Willebrand's seroconverted to anti-HTLV-III positive status.

Intravenous gamma globulin was studied in 11 normal patients given a single infusion and in 23 immune deficient patients with multiple infusions and evaluations of liver enzymes over a two year period. No elevated ALT or AST values were seen in either group.

INTRODUCTION

The transmission of viral disease through blood and blood products is a well known risk of replacement therapy. The effectiveness of our heat treatment methods for blood products to reduce the risk of viral disease transmission has been previously studied with marker viruses and in chimpanzee studies (1, 2). However the ultimate proof of the safety of any blood product, heat treated or not, must come from human studies.

MATERIALS AND METHODS

All lots of Profilate Heat-Treated™ Wet Method, HT Profilate™ Dry Method; and Profilnine Heat-Treated™ Wet Method were regular production lots. All lots of Venoglobulin® were clinical lots produced in production departments.

Human Studies

The human studies were approved by the Institutional Review Board of the participating institutions.

Factor VIII and Factor IX

A total of twenty-three patients (17, Hemophilia A; 1, von Willebrand's Disease; 5, Hemophilia B) were entered into a multicenter trial by five investigators to evaluate the safety of Profilate Heat-Treated™ and Profilnine Heat-Treated™ in preventing transmission of hepatitis B and non-A, non-

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B. Five patients were excluded due to > 55 U/l of AST and a > 50 U/l of ALT in the baseline blood samples and one due to follow-up of less than six months. A total of 18 patients were studied.

These males ranged in age from 0.2 to 29.5 years. All hemophilia B patients were virgin patients. Seven patients, who were exposed to neither AHF concentrate nor cryoprecipitate, were classified as «virgins»; 1 received an AHF concentrate within the last six months and 4 hemophilia A and one von Willebrand's patient were treated with single donor cryoprecipitate prior to the first injection of either Profilate Heat-Treated™ of Profilnine Heat-Treated™.

Fifteen different lots of Profilate Heat-Treated™, 2 different lots of HT-Profilate™ and four different lots of Profilnine Heat-Treated™ were used in this study. Profilate Heat-Treated™ was infused on 119 different occasions for a total of 109,550 units; HT-Profilate™ was inadvertently infused 11 times for a total of 6,440 units and Profilnine Heat-Treated™ was infused 73 times for a total of 42,880 units.

Intravenous Immune Globulin

Intravenous Immune Globulin, Venoglobulin®, was studied in 11 normal and 32 immune deficient patients over a two year period. The 11 normal patients were given a single infusion of Venoglobulin®, while the 32 immunodeficient patients received Venoglogulin at least monthly for a minimum of nine months. 32 patients were entered into the immunodeficiency study. 9 patients had abnormal ALT levels at the start of the study and were excluded from this analysis. All patients, in either study, were tested at least once a month for evaluation of liver enzymes. Immunodeficient patients received three or more different lots of Venoglobulin® during the course of the study.

RESULTS

Factor VIII and Factor IX

None of the 18 patients seroconverted to anti-HTLV-III positive status.

The potential transmission of non-A, non-B Hepatitis was evaluated by serial determination of liver enzymes. Table I lists ALT, AST and GGT values determined at selected intervals. None of the five Hemophilia B patients given 73 separate infusions of Profilnine Heat-Treated™ showed an ALT elevation. The single von Willebrand's disease patient (C001) and two of the 12 Hemophilia A patients (C005 and G006) showed an episode of ALT elevation greater than 2.5, the upper normal limit after 4 of 130 separate infusions (3%). One patient had two episodes of transaminitis, the other patients had only one. AST levels reflected the ALT increases. Three of the patients showed a transaminitis within 2 to 3 weeks after the infusion of concentrate. The von Willebrand's patient showed a transaminitis 7 weeks after his last infusion and 50 weeks into the study, presumably due to a different cause.

Two of the three patients who showed an ALT rise were treated with one lot of Factor VIII concentrate, however, other infusions of that lot to other patients did not produce an enzyme rise. Two patients showed an ALT rise after the first infusion, one of those patients had a second episode of transaminitis after a later infusion. The von Willebrand's patient received 7 previous infusions of the same lot without transaminitis. The von Willebrand's patient had been treated with single donor cryoprecipitate before entry into the study. The two hemophilia A patients were virgin patients. None of the patients with transaminitis received HT Profilate™. There were no other common factors among the four transaminitis episodes.

Table I. Hepatic enzyme determinations

Patient I.D.	Enzyme	Baseline	First infusion	2 weeks	6 weeks	3 months	6 months
A001	ALT*	32	—	20	69	68	31
	AST*	19	—	19	34	28	26
	GGT*	—	—	—	—	—	—
C001	ALT	52	56	16	27	42	12
	AST	59	56	34	43	36	38
	GGT	3	7	6	4	7	4
C002	ALT	12	13	11	10	6	9 (5) #
	AST	32	29	30	32	33	33
	GGT	7	4	3	4	10	11
C003	ALT	12	11	9	6	13	4 (4)
	AST	27	9	27	18	25	29
	GGT	5	10	31	2	6	1
C004	ALT	16	17	33	17	14	17
	AST	58	63	68	36	28	51
	GGT	6	8	7	11	7	6
C005	ALT	18	38	527	19	11	238
	AST	47	46	479	35	35	152
	GGT	13	5	10	5	3	3
C01	ALT	3	21	18	23	38	10
	AST	14	43	39	60	46	34
	GGT	10	14	12	7	8	3
C02	ALT	20	33	32	45	29	19
	AST	37	45	18	49	31	40
	GGT	8	21	4	5	8	5
C03	ALT	24	12	29	30 (8)	32	35
	AST	41	29	41	32	29	47
	GGT	14	48	10	17	1	10
C04	ALT	28	21	62	82	77	92 (6.5)
	AST	31	42	28	83	90	85
	GGT	7	11	7	10	21	16
D002	ALT	26	—	18	13	16	6
	AST	54	—	43	42	41	37
	GGT	9	—	19	14	0	7
D005	ALT	30	11	21	13	17	26
	AST	27	26	49	39	30	43
	GGT	9	—	2	8	6	1
G001	ALT	14	—	16	17	22	28
	AST	35	—	29	46	41	45
	GGT	—	—	—	—	—	5
G02	ALT	23	—	22	14	30	15
	AST	36	—	41	40	39	37
	GGT	1	—	—	—	—	0
G004	ALT	—	—	21	38	51	31
	AST	—	—	36	57	74	66
	GGT	—	—	—	—	7	24
G006	ALT	33	14	119	980	31	—
	AST	34	30	107	720	47	—
	GGT	15	—	—	120	29	—
H002	ALT	—	45	21	36	30	23
	AST	—	20	11	5	25	10
	GGT	—	—	14	7	12	6
H003	ALT	33	36	45	33	—	31
	AST	18	16	16	8	—	17
	GGT	8	9	25	8	—	7

* Normal values: ALT-<50 U/l, AST-5-55 U/l, GGT-<65 U/l; # Number of months or weeks at which the sample was taken.

Intravenous Immune Globulin

The 11 normal patients given a single infusion of Venoglobulin^R showed no episodes of ALT elevation. The 23 immunodeficient patients with normal enzyme levels at entry into the study showed no episodes of ALT elevation.

DISCUSSION

The results of these human studies on viral disease transmission show clearly that Profilnine Heat-Treated^{TM} and Venoglobulin^R are free of transmission of non-A, non-B Hepatitis and AIDS. Profilate Heat-Treated^{TM} has caused a mild transaminitis within 2 to 3 weeks after concentrate infusion, but without jaundice. These results of human studies show the improved safety of heat treated coagulation products and of properly fractionated intravenous immune globulin.

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