Antithrombin III (Human) (AT III) was administered to 18 patients with documented hereditary AT III deficiency. In eight patients with no ongoing clinical symptoms of thrombosis, the percent increase per unit AT III infused per kilogram of body weight ranged from 1.66% to 2.74%, and the half-life from 43.3 to 77.0 hours. No significant difference was noted between patients receiving and those not receiving coumarin therapy. In clinically ill patients, the in vivo recovery was significantly lower and ranged from 0.64% to 1.90% increase per unit AT III infused/kg. Efficacy of AT III was evaluated in 13 patients for the prevention or treatment of thrombosis. AT III was efficacious as assessed by the absence of thrombotic complications after surgery and/or parturition, and the nonextension and nonrecurrence of thrombosis in patients exhibiting an acute thrombotic episode. No side effects were noted. Follow-up studies indicated no hepatitis B seroconversion and no alanine aminotransferase elevations in patients who were not transfused with other blood products.

HEREDITARY antithrombin III (AT III) deficiency is a rare autosomal-dominant disorder characterized by recurrent deep vein thrombosis and pulmonary embolism. In patients with a history of deep vein thrombosis or pulmonary embolism of unknown etiology, the prevalence of AT III deficiency is 2% to 3%. Heterozygous patients have AT III activity levels between 25% and 60% of normal; the antigen levels vary with the type of the disease. More than half of the affected individuals, between 10 and 35 years old, experience at least one thrombotic episode. AT III concentrate, with or without the concurrent administration of heparin, has been used successfully in Europe in patients with hereditary AT III deficiency for the prevention or treatment of thrombosis.

In 1982, the American Red Cross (ARC) convened an Advisory Board to determine the criteria that would demonstrate the efficacy of AT III. It concluded: (1) The study should be conducted in patients with documented hereditary AT III deficiency. (2) AT III in vivo recovery and half-life (phase I study) should be evaluated in patients with no ongoing clinical symptoms of thrombosis. (3) Efficacy of AT III (phase II study) would be established by (a) prevention of thrombosis in high-risk situations, such as trauma, surgery, or parturition, or (b) nonextension of an existing thrombus for 1 week, and prevention of a new thrombotic event during the treatment period. (4) Because of the rarity and severity of the disease, the study should be uncontrolled.

MATERIALS AND METHODS

Patients

Twenty-eight patients entered the study after institutional review board approvals, and were assigned sequential identification numbers. All patients were advised of procedures and attendant risks in accordance with institutional guidelines and gave written informed consent. Eighteen of these patients (13 kindreds), aged 5 to 85 years, with hereditary AT III deficiency, are the subject of this report. Five patients were enrolled in phase I study, 10 in phase II, and three participated in both.

Patients' characteristics are provided in Table 1. Eleven patients were female; six had no clinical history of thrombosis. Age of onset for the first thrombotic episode ranged between 14 and 46 years. Thirteen patients had a concomitant and parallel decrease in AT III functional and antigen levels, with activity levels ranging from 29% to 65%, and antigen levels from 20% to 60%. Two patients (two kindreds) had low activity levels but normal antigen levels. One patient had an AT III activity level significantly higher than the antigen level. Antigen levels were not provided for two patients.

Phase I Study (Pharmacokinetic Study)

In vivo recovery and half-life were evaluated after the intravenous (IV) administration of a single dose of AT III calculated to raise the AT III activity level to 120% of normal, assuming a 60% recovery. AT III determinations were performed on citrated blood samples collected before infusion and within 30 minutes, and at 1, 2, 4, 12, 24, 32, 48, 72, and 96 hours postinfusion. In vivo recovery (expressed as percent increase/unit administered/kg body weight) was calculated by subtracting the base level from the postinfusion level and

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## Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient ID No.</th>
<th>Sex/ Age</th>
<th>AT III Level (Act/Ag %)</th>
<th>First Thrombotic Episode: Age/Type</th>
<th>Other Thrombotic Episode</th>
<th>Family History of Thrombosis or Known AT III Deficiency</th>
<th>Study Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M/33</td>
<td>43/36*</td>
<td>21/DVT</td>
<td>Multiple DVT, mesenteric vein thrombosis with resection of small bowel</td>
<td>Father: patient no. 9 Son: AT III deficient Cousin: AT III deficient, thrombosis</td>
<td>I + II</td>
<td></td>
</tr>
<tr>
<td>3 F/22</td>
<td>38/20†</td>
<td>N/A</td>
<td>None</td>
<td>Mother and sister: AT III deficient and PE during pregnancy</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>4 M/29</td>
<td>22/25‡</td>
<td>29/DVT + PE on heparin</td>
<td>None</td>
<td>Father: DVT and 5 PE, died age 38 with massive PE Sister: AT III deficient</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>6 F/24</td>
<td>52/50*</td>
<td>N/A</td>
<td>None</td>
<td>Mother: patient no. 7</td>
<td>I (twice)</td>
<td></td>
</tr>
<tr>
<td>7 F/49</td>
<td>44/39*</td>
<td>39/Thrombophlebitis</td>
<td>10–15 episodes. Thrombophlebitis associated with oral contraceptives, DVT, PE</td>
<td>Daughter: patient no. 6 Son: died age 19 at first thrombotic episode Family: 18 known affected members</td>
<td>I (twice)</td>
<td></td>
</tr>
<tr>
<td>9 M/68</td>
<td>57/51*</td>
<td>46/DVT + PE</td>
<td>Multiple DVT, PE (2), vena cava ligation</td>
<td>Son: patient no. 1</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>10 F/18</td>
<td>54/92‡</td>
<td>15/DVT associated with oral contraceptives</td>
<td>DVT during pregnancy on low-dose heparin</td>
<td>Father and Brother: AT III deficient/ NL Ag</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>14 M/22</td>
<td>(65/60*§)</td>
<td>22/DVT + PE</td>
<td>None</td>
<td>Mother: AT III deficient, 2 episodes of DVT Aunt: thrombophlebitis Other relatives: thrombophlebitis and PE</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>15 F/30</td>
<td>70/26‡</td>
<td>21/DVT</td>
<td>DVT, DVT during pregnancy</td>
<td>Mother: thrombosis</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>16 M/62</td>
<td>60/106*§</td>
<td>14/DVT associated with surgery</td>
<td>DVT (at least 3 episodes) + PE</td>
<td>Father: patient no. 17 One son died age 32 with PE Two other sons AT III deficient</td>
<td>I + II</td>
<td></td>
</tr>
<tr>
<td>17 M/86</td>
<td>62/ND†</td>
<td>N/A</td>
<td>None</td>
<td>Son: patient no. 16</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>19 F/06</td>
<td>61/50†</td>
<td>N/A</td>
<td>None</td>
<td>Sister: patient no. 21 Father, 3 uncles and 2 cousins: AT III deficient Grandmother: died age 30 with MI Great uncle: AT III deficient, PE Great aunt: AT III deficient, DVT Great grandmother: DVT, died age 56 with MI</td>
<td>II (twice)</td>
<td></td>
</tr>
<tr>
<td>21 F/05</td>
<td>62/56‡</td>
<td>N/A</td>
<td>None</td>
<td>Sister: patient no. 19</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>22 M/17</td>
<td>45/45‡</td>
<td>15/DVT</td>
<td>DVT (2 episodes)</td>
<td>Mother: AT III deficient postpartum DVT Sister: AT III deficient</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>25 F/28</td>
<td>60/50*§</td>
<td>24/DVT + PE associated with oral contraceptives</td>
<td>None</td>
<td>Sister: patient no. 26 Father and uncle: DVT</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>26 F/24</td>
<td>52/46*§</td>
<td>N/A</td>
<td>None</td>
<td>Sister: patient no. 25</td>
<td>I + II</td>
<td></td>
</tr>
<tr>
<td>27 F/33</td>
<td>49/ND*</td>
<td>33/DVT during pregnancy</td>
<td>Postpartum vena cava and pelvic thrombosis</td>
<td>One brother: died age 31 with vena cava thrombosis Another brother: multiple thrombosis</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>28 F/35</td>
<td>58/51*§</td>
<td>24/DVT associated with oral contraceptives</td>
<td>DVT (3 episodes)</td>
<td>One brother: at least 3 DVT One sister: DVT during pregnancy</td>
<td>I</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: N/A, nonapplicable; Act/Ag, activity antigen; DVT, deep vein thrombosis; PE, pulmonary embolism; NL, normal.

*Preinfusion level determined at ARC.
†Preinfusion level determined by investigator.
‡Level at diagnosis provided by investigator.
§Level determined while on coumarin therapy.
ANTITHROMBIN III (HUMAN) IN AT III DEFICIENCY

dividing this result by the units administered/kg body weight. Half-life was calculated using a two compartment model. Curve fitting was done using RS/1 software on a VAX 8350 minicomputer (Digital Equipment Corp, Concord, MA).

AT III activity assays' and antigen (Laurell rocket technique) were performed at the ARC. The standard used was calibrated against the First International Reference Preparation.

Phase II Study (Efficacy Study)

Patients were treated with an initial dose of AT III calculated to raise the AT III level to 120% of normal, and with repeat doses to maintain a minimum level of 80% for at least 5 days. Heparin administration was used according to each investigator's judgement.

AT III determinations were performed by the investigators according to methods in place in the various laboratories.

Safety of AT III (Human)

After administration of the product, patients were monitored for side effects. Follow-up studies for hepatitis were performed on serum samples collected before infusion, and at 2, 4, 6, and 9 months postinfusion. Testing for antibody to human immunodeficiency virus type 1 (anti-HIV-1) was performed on a limited number of samples. All samples collected were tested by the ARC for HBsAg, anti-HBs, and anti-HBc. Alanine aminotransferase (ALT) and anti-HIV-1 tests were performed at the investigator's institution.

AT III (Human)

AT III was prepared for the ARC according to the method of Wickerhauser and Williams by the Michigan Department of Public Health (MDPH), Lansing, and by Baxter Healthcare Corporation, Hyland Division, Glendale, CA. The method of manufacture included heating the product for 10 hours at 60°C in a solution containing 0.5 mol/L sodium citrate. Ten AT III lots manufactured by MDPH and two by Hyland were used. AT III specific activity of the final container product ranged from 4.3 to 7.6 IU/mg of protein.

Statistics

Student's t test was used to compare mean values of unpaired samples drawn from normal populations with equal variances. All P values are two-tailed unless otherwise specified. The acceptable type 1 error rate was taken to be .05.

RESULTS

AT III In Vivo Recovery and Half-Life (Phase I Study)

AT III in vivo recovery and half-life were determined on 10 occasions in eight patients (five kindreds) using three lots. Two patients were studied twice, first with and then without the concurrent administration of coumarin. Four patients were under chronic coumarin therapy and two had no medication. The dose administered ranged from 27.7 to 117.8 IU/kg.

The percent activity increase/unit AT III infused/kg body weight, determined 15 to 30 minutes after administration of the product, ranged from 1.56% to 2.74% (mean, 2.05 ± 0.36). AT III antigen increase ranged from 1.66% to 2.59% (mean, 2.09 ± 0.34%).

AT III half-life (T 1/2), calculated for eight patients, from the second component of the curve beginning at 24 hours postinfusion, ranged from 43.3 to 77.0 hours (mean, 61.3 ± 12.5 hours) and the antigen half-life from 43.3 to 76.1 hours (mean, 53.3 ± 10.3 hours). Disappearance curves observed for one patient are illustrated in Fig 1.

There were no significant differences (data not shown) in AT III recovery and half-life whether patients were receiving coumarin therapy or not, nor was there a significant difference between products (MDPH vs Hyland).

AT III Clinical Efficacy (Phase II Study)

In vivo recovery. Results of AT III assays, performed on samples obtained within 30 minutes after the first administration of AT III, were provided by the investigators for 11 patients. With the exception of the bone marrow donor, the percent AT III activity increase/unit infused/kg body weight ranged from 0.64% to 1.90% (mean, 1.28% ± 0.36%) and

![Fig. 1. Disappearance curves of AT III activity (- - - - - - - - - -), and AT III antigen (---). AT III (Human) at 58.8 IU activity/kg (73.2 IU antigen/kg) was administered to patient no. 6. Blood samples drawn at regular intervals were tested for AT III activity and antigen. The results less the patient's AT III base level (0.52 activity IU/mL; 0.50 antigen IU/mL), were entered on a semilogarithmic plot. Data were fitted to a two-compartment model. Half-life calculated from the slope of the regression line (- - - - - - - -) for the beta component was 68.7 hours for AT III activity and 48.7 hours for AT III antigen.](image-url)
Table 2. Clinical Use of AT I11 in Surgical Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Procedure</th>
<th>% AT I11 Recovery per IU/kg Infused†</th>
<th>Range AT I11 During Treatment</th>
<th>No. Days AT I11 Infused/No. Days Treatment Course</th>
<th>Total IU AT I11 Infused</th>
<th>Heparin (no. days)</th>
<th>Other Blood Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ureteral lithotomy</td>
<td>0.64</td>
<td>68-120</td>
<td>13/13</td>
<td>23,298</td>
<td>7</td>
<td>FFP (500 mL)</td>
</tr>
<tr>
<td>4</td>
<td>Ileum resection</td>
<td>1.51</td>
<td>40-134</td>
<td>7/11</td>
<td>27,168</td>
<td>15</td>
<td>PRC (2 U)</td>
</tr>
<tr>
<td>16</td>
<td>Colectomy</td>
<td>1.02</td>
<td>37-71</td>
<td>2/3</td>
<td>5,780</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>17</td>
<td>Transurethral prostatectomy</td>
<td>1.41</td>
<td>72-132</td>
<td>3/4</td>
<td>8,265</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>19</td>
<td>Resection retroperitoneal neuroblastoma</td>
<td>1.17</td>
<td>64-173</td>
<td>10/14</td>
<td>6,528</td>
<td>3</td>
<td>NO</td>
</tr>
<tr>
<td>21</td>
<td>Bone marrow transplant</td>
<td>ND</td>
<td>82-126</td>
<td>5/8</td>
<td>3,809</td>
<td>NO</td>
<td>PRC (8 U)</td>
</tr>
</tbody>
</table>

Abbreviations: PRC, packed red cell; ND, not determined; FFP, fresh frozen plasma.
*AT I11 activity levels in percent of normal.
†Within 30 minutes after first infusion with AT I11.

was significantly lower than that observed in the phase I study (2.05 ± 0.36) (P < .0001) (one-tailed P value).

Surgical procedures. AT I11 was administered prophylactically, with or without heparin, to six patients (Table 2) who received 3 to 11 infusions for 3 to 14 days, in doses ranging from 13 to 52 IU/kg. With one exception (no. 16), AT I11 activity levels were increased to between 95% and 164% before surgery. Maximum levels maintained during the treatment course ranged between 71% and 173%. Minimum levels observed before the infusion of a dose of AT I11 ranged from 37% to 82%. None of the patients developed clinical symptoms of thrombosis. Patient no. 19 received a bone marrow transplant with no replacement therapy 2.5 months after resection of a retroperitoneal neuroblastoma. One week after transplant, while thrombocytopenic (platelets <10,000/mm³), clots developed in her Hickman catheter (Davol Corp, Cranston, RI). Because of repetitive clotting in the catheter (two episodes cleared with urokinase), treatment with AT I11 was started 10 days posttransplant. All clotting ceased within 48 hours of treatment and no subsequent episode occurred. No heparin was administered.

Pregnancy and parturition. Past obstetrical history and management of the current pregnancy for the five patients entering the study are summarized in Table 3. AT I11 was administered prophylactically, with or without heparin, to four patients (Table 4) during labor and/or for 5 to 6 days after delivery. Each patient received 5 to 6 infusions; the first dose ranged from 30.4 to 93.0 IU/kg. Maximum levels maintained during the treatment course ranged between 137% and 208%. Minimum levels observed before infusion of a dose of AT I11 ranged from 52% to 102%. Each patient had a normal vaginal delivery resulting in a viable infant. None of these patients developed clinical symptoms of thrombosis in the postpartum period.

The fifth patient was not treated prophylactically and developed vena cava and pelvic vein thrombosis at 4.5 weeks postpartum. AT I11 (33 IU/kg/d) was administered with heparin for 7 days. Maximum AT I11 levels maintained during the treatment course ranged between 135% and 175%. Minimum levels observed before infusion of a dose of AT I11 ranged from 84% to 116%. Symptoms resolved and the patient was discharged.

Deep vein thrombosis and pulmonary embolism. Patient no. 14, with the angiogram diagnosis of pulmonary embolism, developed extensive venous obstruction while treated with heparin. Despite an increased heparin dose and the concomitant administration of coumarin, a repeat Doppler test suggested extension of the leg vein thrombosis with possible vena cava involvement. AT I11 was administered for 2 consecutive days (27 IU/kg/d) with heparin, and AT I11 levels were maintained close to 100%. The patient improved and was discharged.

Severe acute systemic lupus erythematosus. A 17-year-old boy (no. 22) treated with coumarin was admitted to the

Table 3. Pregnancy and Thrombosis

<table>
<thead>
<tr>
<th>Patient ID (no./age)</th>
<th>Gravida</th>
<th>Para</th>
<th>DVT During Previous Pregnancy</th>
<th>Heparin Beginning at</th>
<th>DVT</th>
<th>Labor/Delivery</th>
<th>AT III</th>
<th>Postpartum</th>
<th>AT III</th>
<th>Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/22</td>
<td>I</td>
<td>N/A</td>
<td>No</td>
<td>Yes, 3 weeks, 15,000 b.i.d.</td>
<td>No</td>
<td>No/No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>10/18</td>
<td>III</td>
<td>0</td>
<td>Yes on heparin</td>
<td>Yes, 10 weeks, post-DVT, 30,000 t.i.d.</td>
<td>No</td>
<td>Yes/Yes</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15/30</td>
<td>IV</td>
<td>1</td>
<td>Yes</td>
<td>Yes, at pregnancy, 6,000 daily</td>
<td>No</td>
<td>Yes/Yes</td>
<td>Yes</td>
<td>Yes (tubal ligation)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>26/26</td>
<td>II</td>
<td>1</td>
<td>No</td>
<td>Yes, at pregnancy, 14 weeks, post-DVT, 16,000 t.i.d.</td>
<td>No</td>
<td>Yes/Yes</td>
<td>Yes</td>
<td>No/No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>27/33</td>
<td>II</td>
<td>0</td>
<td>No</td>
<td>Yes, at 14 weeks, post-DVT, 16,000 t.i.d.</td>
<td>No</td>
<td>Yes, post-DVT</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: N/A, nonapplicable; DVT, deep vein thrombosis; b.i.d., twice per day; t.i.d., three times per day.
hospital for rectal bleeding, facial rash, and a pulmonary infiltrate. Evidence of acute severe lupus erythematosus with lupus pneumonitis was documented. He was treated with high-dose corticosteroids and AT III. Thereafter, he developed acute respiratory failure, pneumothorax, pneumocystis pneumonia, autoimmune thrombocytopenia, and hemolytic anemia. He was treated aggressively with immunosuppressive therapy, plasmapheresis, IV immune globulin, multiple blood components, and antibiotics. Ultimately, all symptoms resolved and the patient was discharged. A total of 144,700 IU AT III (50 infusions) was administered during a 52-day hospitalization. AT III levels were maintained between 100% and 180%. No thrombotic complications were noted during or after hospitalization.

**Side Effects and Adverse Reactions**

AT III was well-tolerated by all patients; no adverse reactions were noted. One patient complained (12 hours postpartum) of light headedness that resolved rapidly, and the infusion was not interrupted.

**Hepatitis B markers.** Of 18 patients who received AT III, four were treated on two separate occasions and six were transfused with other blood components. No hepatitis B seroconversion was noted for 15 patients followed for a period of 6 months or more, nor for one patient (no. 17) followed for a period of 3 months. Two patients showed evidence of hepatitis B markers. Patient no. 19 became positive for anti-HBs at 9 months after the second treatment with AT III (11 months after first treatment). Patient no. 22 became transiently anti-HBs and anti-HBe positive.

**ALT follow-up testing.** Test results were provided by the investigators for 10 patients. ALT or serum glutamic-oxaloacetic transaminase (SGOT) elevations were noted for two patients (no. 1 and 19). With the exception of two patients tested at 2-week intervals, all other patients were tested every 2 months.

**Anti-HIV-1 follow-up testing.** Results in four patients were negative at 9 weeks, 6 months, and 8 months postinfusion.

**DISCUSSION**

The phase I and phase II studies were designed to evaluate the safety, recovery, half-life, and clinical efficacy of AT III in patients with documented hereditary AT III deficiency.

Among 18 patients studied, six had no history of thrombosis; the clinical history of the remaining 12 patients was remarkable for a high incidence of pulmonary embolism (six), multiple thrombosis associated with the use of oral contraceptives (four), pregnancy (two), delivery (one), or surgery (one). Thirteen patients (10 kindreds) were type I, one type II, and one patient with activity levels consistently higher than the antigen remains unclassified. Twelve of 13 kindreds had a positive family history of thrombosis. There was no family history of thrombosis for the type II patient.

In patients with no ongoing clinical symptoms of thrombosis, administration of one AT III IU/kg body weight resulted in an increase of AT III activity ranging from 1.56 to 2.74% and a half-life of 61.3 ± 2.5 hours (range 43.3 to 77 hours). These results are consistent with those previously published. The mean antigen half-life of 53.3 hours was shorter than that of the biologic activity.

There was no significant difference in AT III recovery and half-life whether patients were on coumarin treatment or not, confirming previous observations, nor was there a significant difference between products.

In contrast, AT III in vivo recovery was significantly lower ($P < .0001$) in patients who were ill (phase II study). Differences obtained between the two groups of patients may be due to the fact that all AT III assays for the phase I study were performed in the ARC laboratory, whereas for the phase II study, assays were performed by other laboratories that did not use the same reference as a standard or the same assay method. Differences obtained for these two groups of patients need further investigation.

Administration of AT III to patients with hereditary AT III deficiency has been reported to be successful for the prevention of thrombosis after surgery and for the control of recurrent thrombosis refractory to heparin therapy. There were no thrombotic complications after surgery in any of the six patients treated. Of three of these patients also undergoing surgery without replacement therapy, two developed thrombosis (one fatal, no. 17), whereas one had no thrombotic complications. AT III-deficient patients undergoing surgery without replacement therapy have a high incidence of thrombosis. To our knowledge, there is no reported case of thrombotic complication after surgery in patients under replacement therapy. Control of thrombotic events also occurred subsequent to the administration of AT III.
III in all three patients treated for acute and recurrent thrombosis.

Thromboembolic complications occur in 68% of AT III-deficient pregnant women. Prophylactic management of these patients is difficult. While coumarin drugs cross the placenta and have a teratogenic effect, heparin has the potential of further reducing the level of AT III. Successful prophylaxis with low-dose heparin has been reported in some instances, but not in others. In our series, low-dose heparin did not prevent thrombosis during one pregnancy, but was efficacious at 15,000 units twice per day during another pregnancy (no. 10).

During the current pregnancy, heparin was administered prophylactically to two patients and to two other patients after a thrombotic episode.

To prevent thrombotic complications during labor, delivery, or termination of pregnancy, replacement therapy using either plasma or AT III appeared to be successful. In our series of five patients, the only one who developed thrombosis in the postpartum period had not been treated prophylactically with AT III.

One minor side effect (light-headedness) was noted after administration of 14 lots of AT III to 18 patients who received a total of 128 infusions (344,280 IU) for 24 treatment courses.

Heat treatment used in the manufacturing process has been shown to inactivate intentionally added viruses in this product. Patient follow-up studies indicate that the only two patients in whom antibodies to hepatitis B virus were detected were among those who received multiple transfusions with other blood components. For one of these patients (no. 22), the sequence of events (appearance of antibodies at 2 weeks and disappearance at 10 weeks postinfusion) is in favor of passive transmission by the multiple transfusions. For patient no. 19, it is difficult to assess whether the late seroconversion at 9 months was related to the transfusion of the many other blood products administered or to another cause. The two lots of AT III infused to this patient did not induce seroconversion in three other patients. ALT or SGOT elevations were noted for two patients; both had a disease involving the liver: cirrhosis of the liver (no. 1) and neuroblastoma with liver involvement (no. 19). There were no ALT elevations in the remaining 10 patients tested. However, it should be noted that only two patients were followed at short time intervals (every 2 weeks), while the others were followed at 2-month intervals. At the time the study was initiated (1982), AIDS was just emerging and testing for anti-HIV-1 was not begun until 1985. Therefore, follow-up studies were limited to four patients, none of whom indicated seroconversion to HIV.

In summary, AT III manufactured for the ARC has a normal in vivo recovery and half-life. Use of this product for the prevention and treatment of thrombosis in patients with hereditary AT III deficiency fulfilled the criteria establishing safety and efficacy.

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