Antithrombin III Utilization in a Large Teaching Hospital
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**Key words:** antithrombin, Thrombate III, ATryn, veno-occlusive disease

**INTRODUCTION**

Antithrombin (AT), a naturally occurring anticoagulant, is a vitamin K–independent glycoprotein that functions as an irreversible inhibitor of thrombin and factor Xa in the coagulation cascade.1 Hereditary, congenital, or acquired AT deficiency is associated with inadequate endogenous anticoagulation that predisposes patients to an increased risk of thrombosis in times of clinical physiological stress (e.g., surgery, trauma, or pregnancy).1,2

**HEREDITARY ANTIITHROMBIN DEFICIENCY**

Hereditary AT deficiency affects approximately 1 in 500 persons to 1 in 5,000 among the general population, whereas the incidence increases significantly to 1 in 20 to 1 in 200 among patients with venous thromboembolism (VTE).3–6 Among individuals with a first episode of VTE, the prevalence of hereditary AT deficiency ranges from 0.5% to 1.7. In patients with type-1 or type-2 AT deficiency, AT levels are generally reduced to less than 50% of normal. Heterozygous type-1 deficiency is characterized by a reduction of approximately 50% in AT activity and concentration. The homozygous state is incompatible with life.

Type-2 AT deficiency is the result of a molecular defect within the protein, characterized by loss of functional activity, although AT immunological activity is maintained. To maintain a sufficient level of AT activity that effectively inhibits blood coagulation proteases, at least 70% of a normal functional level is required.

**AVAILABLE ANTIITHROMBIN PRODUCTS**

Two marketed formulations of AT concentrate are available in the U.S. Thrombate III (Grifols/Talecris), a lyophilized preparation of AT pooled from human serum, contains no preservatives. It is administered intravenously over a period of 10 to 20 minutes. ATryn (Ovation), a recombinant human AT developed from transgenic goat milk, is administered as a recombinant human plasma-derived AT concentrate. After reconstitution, administration must occur within 3 hours for plasma-derived AT concentrate and within 8 to 12 hours for the recombinant product. So far, no trials comparing the two formulations have been conducted.

**FDA-APPROVED AND OFF-LABEL INDICATIONS**

The safety and effectiveness of AT concentrate were confirmed in patients with AT deficiency and acute VTE.9,10 Recommendations for its use include severe thrombosis, the development of recurrent thrombosis despite therapeutic anticoagulation, or difficulty achieving acceptable anticoagulation.11 Thrombate III is approved by the FDA for the treatment of patients with hereditary AT deficiency in connection with surgical or obstetrical procedures or with thromboembolism. ATryn is indicated for the prevention of perioperative and peripartum thromboembolic events in hereditary AT-deficient patients.12 For these specific indications, the goal is to maintain functional AT levels between 80% and 120%.

Additional off-label clinical uses of AT concentrate have included the treatment or prevention of veno-occlusive disease,13,14 AT concentrate has also been used in patients undergoing extracorporeal membrane oxygenation (ECMO),15,16 in critically ill patients undergoing continuous renal replacement therapy,15,17 and in heparin-resistant patients who require cardiopulmonary bypass.18 Unlike the goal in patients with AT deficiency, the optimal antithrombin level is not clearly defined for these off-label indications. Because anticoagulation is imperative for inhibiting thrombus formation on the artificial surfaces of the ECMO circuit, adequate inhibition of AT is required with heparin. Patients supported on ECMO commonly experience AT deficiency, and studies have shown the use of AT concentrate to be beneficial.

Veno-occlusive disease is a complication of chemotherapy in the setting of hematopoietic stem-cell transplantation. Injury to sinusoidal endothelial cells and hepatocytes after chemotherapy promotes the disruption of the endothelium lining the sinusoids and the pores connected to the hepatic venular lumen. This causes a reduction of AT, precipitating a procoagulant state. Depending on each institution’s utilization, AT concentrates can be an area for which close monitoring is required. AT conc-
Antithrombin III Utilization

centrates are expensive, and they come with significant warn-
ings, a risk of bleeding, and a potential for unapproved uses.

**A STUDY OF ANTITHROMBIN USES**

**Purpose**

Jackson Memorial Hospital is a 1,500-bed tertiary-care, academic medical center in Miami-Dade County that serves medical, surgical, oncological, critical-care, transplant, and trauma patients throughout southern Florida. We explored the use of AT concentrates at the hospital to determine the most appropriate formulation for the formulary.

Our primary objective was to conduct a retrospective evaluation using medical and pharmacy databases to assess the use of AT concentrates and the appropriateness of the indication. The secondary objective was to determine which AT product would be most cost-effective for inclusion on the formulary.

**Methods**

We conducted a single-center, retrospective chart review to identify patients for whom the pharmacy dispensed at least one dose of AT concentrate from January 2009 to April 2013. The pharmacy system generated a report of AT product doses dispensed. At least one dose that was administered to patients met the criteria for inclusion in the evaluation.

We collected patient information through a review of electronic medical records (EMRs). Data collection included demographic characteristics (i.e., age, sex, and weight), indications for therapy with AT concentrate, the number of units used, and AT levels reported as percentages. After identifying off-label indications for the use of AT concentrate, we reviewed the literature to evaluate the product’s appropriateness in terms of the indication, dosage, and duration. All institutional review board procedures were followed.

We performed an analysis to quantify the cost of plasma-derived AT (Thrombate III), the AT formulary product at our hospital. We ascertained the hospital’s acquisition cost, in dollars per vial, and translated this into dollars per unit. The results were compared with the equivalent dollars per unit of recombinant human AT (ATryn), based on hospital acquisition cost in dollars per vial.

**Results**

Examining the EMRs, we identified 10 patients from January 2009 to April 2013 who received Thrombate III (Table 1). Of the 10 patients identified, six were children (ages 6 months to 16 years of age). In three of the four adults, the AT product was used to prevent or treat VTE in those with documented AT deficiency. In the remaining adult, the indication was related to cardiac surgery, and the patient was presumed to be AT-deficient. Five of the six pediatric patients were given AT concentrate to prevent veno-occlusive disease after bone marrow transplantation. In the remaining pediatric patient, the AT product was administered as part of a separate research study. The dosage per patient ranged from 285 to 3,500 units per dose (7–63 units/kg). The average duration of treatment was 2.7 days (range, 1–6 days).

The total cost of plasma-derived AT (Thrombate III) was $138,801.69. The highest spending occurred in 2012, with three patients receiving 12 doses of plasma-derived AT concentrate, for a total cost of $67,554.93. Comparing the costs of Thrombate III and ATryn, we observed that ATryn would cost $0.74 less per unit.

To determine whether a difference in cost between the two formulations would translate into cost savings, the three patients for whom AT concentrate was approved by the FDA (i.e., for antithrombin deficiency) received theoretical therapy for 2 days, based on the dosage specified in the prescribing information (Table 2). These three patients were selected because they received the medication based on FDA-approved indications, and this choice would facilitate extrapolation of dosing between formulations.

Our calculations showed an increased cost of approximately $23,800 with ATryn in these three patients for 2 days of treatment. We further estimated that for every 1 unit of Thrombate

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**Table 1 Baseline Characteristics of Study Patients With Antithrombin Deficiency at Jackson Memorial Hospital**

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Indication</th>
<th>Dose Range (Units)</th>
<th>Units/kg</th>
<th>Baseline AT Level</th>
<th>Post-administration AT Level Achieved*</th>
<th>Duration (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 years</td>
<td>F</td>
<td>Research</td>
<td>500</td>
<td>42</td>
<td>NA</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>60 years</td>
<td>M</td>
<td>Cardiac surgery</td>
<td>570</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>13 years</td>
<td>M</td>
<td>Veno-occlusive disease</td>
<td>2,196</td>
<td>44</td>
<td>NA</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>16 years</td>
<td>M</td>
<td>Veno-occlusive disease</td>
<td>2,196–3,843</td>
<td>30–50</td>
<td>35</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>6 months</td>
<td>M</td>
<td>Veno-occlusive disease</td>
<td>285</td>
<td>63</td>
<td>28</td>
<td>Yes</td>
<td>4</td>
</tr>
<tr>
<td>9 months</td>
<td>M</td>
<td>Veno-occlusive disease</td>
<td>350–535</td>
<td>30–50</td>
<td>70</td>
<td>Yes</td>
<td>5</td>
</tr>
<tr>
<td>41 years</td>
<td>M</td>
<td>AT III deficiency: thrombosis</td>
<td>3,500</td>
<td>50</td>
<td>30</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>42 years</td>
<td>M</td>
<td>AT III deficiency: perioperative</td>
<td>2,000–3,000</td>
<td>30–40</td>
<td>39</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>16 months</td>
<td>M</td>
<td>Veno-occlusive disease</td>
<td>584</td>
<td>50</td>
<td>1</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>20 years</td>
<td>F</td>
<td>AT III deficiency: acquired from nephritic syndrome</td>
<td>1,752</td>
<td>30</td>
<td>59</td>
<td>Yes</td>
<td>2</td>
</tr>
</tbody>
</table>

*AT = antithrombin; F = female; M = male; NA = not available.

*Achieved = antithrombin level greater than 80%.
Recombinant Antithrombin (ATryn) in Patients With Antithrombin Deficiency at Jackson Memorial Hospital

<table>
<thead>
<tr>
<th></th>
<th>Thrombate III (Theoretical)</th>
<th>ATryn (Theoretical)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loading Dose (Units) (Day 1)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>4,500</td>
<td>2,130</td>
</tr>
<tr>
<td>Patient 2</td>
<td>2,483</td>
<td>1,016</td>
</tr>
<tr>
<td>Patient 3</td>
<td>4,223</td>
<td>1,936</td>
</tr>
<tr>
<td><strong>Maintenance Dose (Units) (Day 2)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>2,700</td>
<td>11,520 (480 U/hour)</td>
</tr>
<tr>
<td>Patient 2</td>
<td>1,489</td>
<td>5,496 (229 U/hour)</td>
</tr>
<tr>
<td>Patient 3</td>
<td>2,534</td>
<td>10,488 (437 U/hour)</td>
</tr>
<tr>
<td><strong>Total Units for a 2-Day Course of Treatment (Units)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>7,200</td>
<td>13,650</td>
</tr>
<tr>
<td>Patient 2</td>
<td>3,972</td>
<td>6,512</td>
</tr>
<tr>
<td>Patient 3</td>
<td>6,757</td>
<td>12,424</td>
</tr>
<tr>
<td><strong>Cost of a 2-Day Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>$23,544.00</td>
<td>$34,534.50</td>
</tr>
<tr>
<td>Patient 2</td>
<td>$12,988.44</td>
<td>$16,475.36</td>
</tr>
<tr>
<td>Patient 3</td>
<td>$22,095.39</td>
<td>$31,432.72</td>
</tr>
<tr>
<td><strong>Cost Difference</strong></td>
<td>$58,627.83</td>
<td>$82,442.58</td>
</tr>
</tbody>
</table>

*loading dose (units) = [(120–baseline antithrombin III level) x weight (kg)] ÷ 1.4.

The maintenance dose (units) is equal to 60% of the loading dose administered every 24 hours.

*loading dose (units) = [(100–baseline antithrombin level) x weight (kg)] ÷ 2.3.

Maintenance dose (units/hour) = [(100–baseline antithrombin level) x weight (kg)] ÷ 10.2.

III used in these three patients, 1.6 to 1.8 units of ATryn would be needed over a 2-day period. The estimated difference in use and cost did not account for additional AT levels that might be required every 2 to 6 hours in order to adjust the ATryn dose according to the laboratory results.

**Discussion**

Although Thrombate III is indicated for patients with hereditary AT deficiency in relation to operative procedures or VTE, its use at our hospital encompassed both FDA-approved and off-label indications. Half of the time, Thrombate III was used to treat or prevent veno-occlusive disease in pediatric patients.

After a review of the literature regarding the management of veno-occlusive disease in pediatric patients, most of the published information mentioned plasma-derived AT concentrate; however, we also noted limited trials with alternatives, such as ursodiol (e.g., Urso, Axcan), heparin, and recombinant human AT. Although Thrombate III is not approved for pediatric patients, the literature is adequate to support its use in this population.

The published literature on the topic of plasma-derived AT concentrate for veno-occlusive disease is substantial. Morris et al. reported significant clinical improvements in organ dysfunction in 10 patients who received this product, as well as a significant reduction in the probability of death attributable to veno-occlusive disease, compared with a historical control group.

By contrast, no studies of recombinant human AT (i.e., ATryn) for the management of veno-occlusive disease have been published. Therefore, no data on dosage, duration, or outcomes with ATryn are available for these off-label uses. If ATryn were included on the formulary as our institution’s AT formulation of choice, a dosage recommendation for non-approved indications would be difficult to devise, considering the lack of clinical trials and interchangeability between formulations.

To determine which product would be most cost-effective at our institution, we calculated the cost per unit and estimated the number of units to be used per patient with AT deficiency. When weight-based dosing was considered, loading doses were higher with Thrombate III, but maintenance doses were higher with ATryn, thereby yielding more total units of ATryn needed over a course of treatment.

ATryn offers a reimbursement program for unused units, potentially decreasing the product’s cost per unit; however, 1.8 times more units would need to be used per treatment course compared with Thrombate III. A dedicated line for continuous infusion of ATryn is also required, because no studies comparing compatibility with other products have been published. This may present a significant barrier in patients with limited access to the medication.

After Thrombate III administration, peak, 12-hour, and trough levels should be monitored. Our results indicated that AT levels were obtained at baseline and on the following day. All patients with available AT levels attained the AT goal of greater than 80%. Monitoring recommendations for ATryn state that a 2-hour post-administration level should be determined. If the goal value is achieved, subsequent monitoring should take place 6 hours after initiation, followed by daily and twice-daily

| **Table 3** Thrombate III Dosage and Duration of Therapy at Jackson Memorial Hospital |
|-----------------------------|-----------------------------|-----------------------------|
| Indication                  | Thrombate III Dose (Units/kg) | Duration (Days) |
| Antithrombin deficiency     | Loading dose (units) = [(120–baseline AT III level) x weight (kg)] ÷ 1.4 |
|                            | Maintenance dose (units) = 60% of the loading dose administered every 24 hours |
| Veno-occlusive disease      | 30–100                       |

measurements. If the goal value is not achieved, the dose should be adjusted, and another level should be determined every 2 hours until the goal is reached. Measurements should then be taken once or twice daily.

Dependent on the initial AT level, ATryn may need to be monitored more frequently, and this could contribute to increased laboratory costs. After reviewing our hospital’s use of AT concentrate, the P&T committee recommended that the current formulary agent, Thrombate III, be continued because it was used appropriately for AT-deficient patients, had more published support for use in off-label indications, and was considered to be the most cost-effective option.

As noted in the published literature, the dosage and duration of treatment with the AT product was judged to be appropriate. In trials, the duration of AT concentrate therapy ranged from 2 to 16 days and the dosage ranged from 30 to 100 units/kg per dose. To ensure the continuous use of Thrombate III, we devised a table (Table 3) to delineate the appropriate dose and duration for the most common indications used at our hospital.

Limitations of the Study

Although the prevalence of AT deficiency is low, a small population of AT-deficient patients was identified over a 4-year period. We found it challenging to review Thrombate III and ATryn because the doses for these formulations are not interchangeable. To evaluate the cost difference between the products, we based our calculations on FDA-approved indications, despite a large number of off-label uses. In addition, the dosage for pediatric patients was extrapolated from the literature.

Prescribing the appropriate AT dosage and keeping in mind the off-label indications can be a complex task for physicians and pharmacists. A major strength of our review was the focus on the use of AT, a topic inadequately discussed in the literature.

Conclusion

Although we used a plasma-derived AT product (Thrombate III) primarily for unapproved indications in patients with AT deficiency, the literature generally supported this use, whereas data were lacking for recombinant human AT (ATryn). Finding that the dosage and duration of therapy were appropriate with plasma-derived AT, we judged this AT product to be more cost-effective than ATryn for these patients.

REFERENCES


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