

Recombinant Human Antithrombin: New Therapeutic Options

Michael J. Paidas, MD

Hereditary Antithrombin Deficiency

Antithrombin (AT) is a naturally occurring anticoagulant synthesized in the liver (1,3). It is a serine protease inhibitor (serpin) and principal inhibitor of coagulation (2). AT inhibits coagulation by irreversibly binding the thrombogenic proteins thrombin (factor IIa), factor Xa, and to a lesser extent factors IXa, XIa and XIIa (4). It forms a stable 1:1 complex between the active site of the serine protease and the reactive site of AT (2). The bond in AT reactive site is cleaved by the protease during complex formation, resulting in a conformational change that traps the protease (5). Heparin and heparans accelerate the formation of AT-protease complex (4,5).

There are 2 types of hereditary antithrombin deficiencies (HD AT). In type One, there is a quantitative defect in antithrombin and inadequate levels of AT produced. There is an approximate 50% reduction in AT activity and antigen levels (heterozygous). It represents up to 80% of symptomatic cases, and may be associated with greater risk for thrombosis than type II (4). In type Two HD AT, there is defective AT along with decreased AT activity (1,4). Antithrombin antigen levels are not necessarily reduced. Type Two HD AT is more common than type One. There are three subtypes:

Subtype a: Defect in reactive site, high risk for thrombosis

Subtype b: Defect in heparin-binding site, low risk for thrombosis

Subtype c: Defect in both sites, high risk for thrombosis (pleiotropic)

In addition to HD AT, there are acquired forms of antithrombin deficiency, and generally consist of conditions that are associated with decreased AT synthesis, increased excretion, accelerated consumption, drug induced, extracorporeal circulation, and other disorders (3).

HD AT patients are at significantly increased risk for venous thromboembolism and HD AT confers the highest thrombotic risk regarding existing thrombophilic conditions (1). For HD AT, the thrombosis risk increases significantly around 20 years. At least 50% of HD AT patients will have suffered an episode of VTE by 50 years. During transient, high thrombotic risk situations (surgery, trauma, or peripartum period), the risk of VTE and morbidity and mortality may be increased by as much as a factor of 10 to 50.2 (7). Regarding pregnancy, personal and family history are key to ascribing thrombotic risk in pregnancy (8). For example, if there is no personal or family history of VTE in a pregnant patient with HD AT, her risk for VTE is 7%, whereas if there is a personal and family history of VTE, her thrombotic risk associated with pregnancy ranges from 11-40%. The perioperative and peripartum periods are particularly risky for HD AT patients, secondary to generally lower or absent levels of anticoagulation due to the hemorrhagic risk, as well as the presence of multiple prothrombotic risk factors such as immobility, tissue trauma, and

coagulation changes associated with pregnancy. Hence, there is a rationale for providing temporary antithrombin replacement in HD AT patients during high risk periods such as surgery or pregnancy. There are 2 categories of antithrombin replacement: a plasma derived product (Thrombate®), which was FDA approved in 1991, and antithrombin recombinant, Atryn®, which was FDA approved in 2009.

Recombinant antithrombin, Atryn ®

Atryn® is a recombinant product produced in transgenic goats. There is a multi-step purification process which achieves >10Log viral reduction (including zoonotic & prion models). It has an identical amino acid sequence as human AT, and it has similar biological activity. It is glycosylated at same sites, but it has different side chains [Asn155]. Atryn ® has increased heparin affinity (4-fold), and a shorter half life (11h) (9, 10). Atryn® is a sterile, lyophilized powder that is prepared for reconstitution. Each single-dose vial of Atryn® contains approximately 1750 IU. Each vial of Atryn® is tested for potency stated on the product label using a reference standard calibrated against the World Health Organization international standard for antithrombin concentrate. It is stored refrigerated at 2°C-8°C (36°F-46°F). It should be used within 8 hours-12 hours once reconstituted when stored at room temperature. It does not contain preservatives; the unused product must be discarded. The pharmacokinetic profile consists of: clearance (mg/hr/kg) is 9.6; half life 11.6 hr. Of note, there are significant differences in the pharmacokinetic profile of Atryn® in surgical and pregnant patients. Specifically, the volume of distribution and clearance in pregnant patients are higher than in nonpregnant patients. The volume of distribution (L) is 14.30, and 7.70, and clearance (L/h) is 1.38 and 0.67 for pregnant and non-pregnant patients respectively. Compared to plasma-derived antithrombin, Atryn® has a shorter half-life and faster clearance (approximately 9 and 7 times, respectively).

Clinical experience with recombinant antithrombin, Atryn ®

There have been two phase three clinical trials using Atryn ®, and the results are summarized below (surgical patients, n= 11; pregnant patients, n=21*) (12,13). Baseline characteristics of the HD AT patients consist of the following, for the surgical and pregnant patients respectively: Mean age in years (range) was 49 (35-74) and 30 (21-40); female, n=5 and n=20; baseline AT activity (%) 53 and 45. The median (range) treatment duration for both groups was 3.9 (2.4-18.9). * One pregnant patient was not eligible for efficacy analysis.

Regarding efficacy, results were stratified into 2 time periods: a) during Atryn® treatment of up to 7 days later; and b) > 7 days after treatment cessation. During Atryn® treatment of up to 7 days later, there was 1 DVT (asymptomatic, post total hip replacement) and no events for the surgical patients and pregnant patients respectively. For the > 7 days after treatment cessation, there were no cases of VTE in the surgical patients; for the pregnant patients, there was one DVT 10 days after Atryn® treatment (during a period of reduced anticoagulation);

one pulmonary embolism 14 days post Atryn® treatment and 1 asymptomatic DVT 7 days post Atryn®, felt to be old clot (13,14).

For the two phase III studies, 85% of AT activity levels were within range, 80-120%; 4% were <80% and 11% were >120%. A total of 47 patients (PK study and 2 phase III studies) were evaluable regarding safety, adverse events consisted of anemia, headache, hypotension, infusion site reaction. There were no fetal or neonatal adverse events related to Atryn®, a Class C medication. There were 2 hemorrhagic severe adverse events, consisting of one case of wound hemorrhage, one case of abdominal bleeding and one case of knee hemarthrosis on day 1 post- total knee replacement. (14) There was no evidence of immunogenicity seen in 222 pts/subjects tested (GTC Biotherapeutics).

Atryn® has been given on a compassionate use basis. In a retrospective case review, 5 hereditary AT-deficient patients treated on 6 occasions. None of these patients reported a thromboembolic event. There was no clinical evidence of thrombosis or bleeding. A follow up ultrasound in 4 of 6 events showed no acute thrombosis (15).

Contraindications to Atryn® administration consist of known hypersensitivity to goat and goat milk proteins. Anaphylaxis and severe hypersensitivity reactions are possible. If symptoms occur, treatment should be discontinued immediately and emergency treatment should be administered. It is important to recognize that the anticoagulant effect of drugs that use AT to exert anticoagulation may be altered when Atryn is added or withdrawn. To avoid excessive or insufficient anticoagulation, perform coagulation tests at close intervals, especially in the first hours following the start or withdrawal of Atryn® and monitor patients for bleeding or thrombosis.

Thrombate® is the plasma derived (pd) antithrombin replacement which has been FDA approved since 1991. The pd-AT half life is approximately 24h. The dose of pd derived AT= [120-baseline AT level in %/1.5] x kg. Potential scenarios for antithrombin replacement consist of: symptomatic HD AT patients in high risk settings; heparin resistance; acquired AT deficiency states. preeclampsia.

References

1. Patnaik MM, et al. *Haemophilia*. 2008;14:1229-1239.
2. Kottke-Marchant K, et al. *Arch Pathol Lab Med*. 2002;126(11):1326-1336.
3. Bucur SZ, et al. *Transfusion*. 1998;38:481-498.
4. Maclean PS, et al. *Drugs*. 2007;67(10):1429-1440.
5. van Boven H et al. *Semin Hematol* 1997;34(3):188-204.
6. Mammen EF. *Semin Thromb Hemost*. 1998;24(1):19-25.
7. Walker ID, et al. *Br J Haematol* 2001; 114: 512-28
8. Zoltz RB, et al, *Best Pract Res Clin Haematol* 2003;16:243-59
9. Atryn US Package Insert. Lundbeck Inc. 2009.
10. Edmunds T, et al., *Blood* 1998; 91: 4561-4571.
11. Paidas M, et al. *ISTH* 2009 Poster PP-TH-414

12. Tiede A, et al. *Thromb Haemost* 2008; 99: 616-622.
13. Tait RC, et al. *Blood* 2008; 112: 986a.
14. Tait C, et al. *ISTH* 2009 – Poster PP-WE-405.
15. Konkle BA, et al. *Transfusion*. 2003;43(3):390-394.