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Hereditary and Acquired Antithrombin Deficiency

Epidemiology, Pathogenesis and Treatment Options

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Contents

Abstract

Antithrombin is a glycoprotein critical to the regulation of coagulation. Its primary action is the inhibition of the activated coagulation factors IIa (thrombin) and Xa. In addition there is growing evidence to suggest that antithrombin also plays a role in the inhibition of inflammation within the environment of the vascular endothelium. Reduced plasma antithrombin may result from congenital deficiency or arise secondarily from a range of disorders such as liver dysfunction,

premature infancy and sepsis, or as a result of interventions such as major surgery or cardiopulmonary bypass.

Congenital antithrombin deficiency is the most clinically important of the inherited thrombophilias resulting in thrombosis in the majority of those affected. The challenge in managing these patients is preventing potentially life-threatening thrombosis, while minimising the equally significant risk of haemorrhage associated with long-term anticoagulation. This is achieved in the first instance by identifying high-risk episodes such as surgery, immobility and pregnancy for which prophylactic anticoagulation can be used in the short term. Prophylaxis for such periods is best provided by the use of low molecular weight heparin (LMWH) with substitution by or addition of antithrombin concentrate in particularly high-risk circumstances. In the case of pregnancy, antithrombin concentrate is often used around the time of birth when LMWH may increase the risk of postpartum haemorrhage. As patients with congenital antithrombin deficiency get older so their thrombotic risk gradually increases and for many patients long-term anticoagulation becomes unavoidable because of recurrent episodes of venous thromboembolism.

There has been much interest in the role of antithrombin deficiency in the setting of sepsis and the critically ill patient where there is a clear correlation between severity of illness and degree of antithrombin reduction. It is not clear yet, however, to what extent the depletion of antithrombin affects the clinical condition of such patients. A number of trials have investigated the use of antithrombin as a treatment in the intensive care setting with the overall conclusion being that there is some benefit to its use but only if large supra-physiological doses are used. It has also become clear that the concurrent use of any form of heparin removes whatever benefit may be derived from antithrombin treatment in this setting. Until recently, antithrombin replacement was only available as a pooled plasma-derived product, which despite effective viral inactivation still carries an uncertain risk of transfusion transmitted infection. A recombinant antithrombin product now under investigation, and recently licensed in Europe, may provide a useful alternative treatment option.

In August 2006, the European Commission authorised a novel recombinant antithrombin product. This article summarises the epidemiology and pathology of antithrombin deficiency, and reviews the role that recombinant antithrombin may play in its management alongside more established therapeutic options. Literature to be reviewed was identified by MEDLINE and Embase searches updated to 30th March, 2007. Search keywords were: 'antithrombin', 'antithrombin III', 'ATIII' and 'AT-III' with 'deficiency', 'hereditary' and 'acquired'.

1. Background

Antithrombin is an 58 kDa glycoprotein belonging to a group of inhibitory factors known as serpins (serine protease inhibitors).[1] It plays a critical role in the regulation of coagulation, being the major inhibitor of thrombin (factor IIa), factor Xa and to a lesser extent factors IXa, XIa and XIIa (figure 1). It is estimated that antithrombin provides 80% of the natural anticoagulant effect against thrombin. A knockout mouse model has shown complete antithrombin deficiency to result in death *in utero* from thrombosis and haemorrhage.[2]

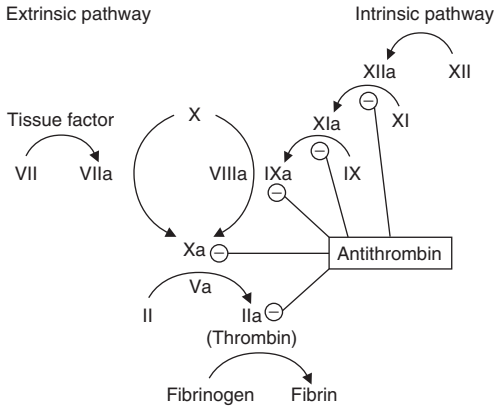

Fig. 1. The role of antithrombin in the coagulation cascade. Antithrombin is inhibitory to factors IIa (thrombin) and Xa, and to a lesser extent factors IXa, XIa and XIIa. − indicates the inhibitory actions of antithrombin.

The antithrombin gene includes 7 coding exons situated at 1q 23-25 covering 80 kilobases.[3] The resultant protein is produced in liver parenchymal cells; however, unlike the other natural anticoagulants, protein C and protein S, is not vitamin K dependent. In normal conditions, a plasma concentration of about 112–140 μg/mL is maintained with a half-life of 2–3 days,[4] this equates to approximately 100 IU/dL of antithrombin activity. Results of both antigenic and activity assays are expressed as a percentage of the normal level. For most assays the normal range of two standard deviations from the mean is around 80–120 IU/dL. Antithrombin function is dependent on two active sites, the reactive site, which performs its proteolytic function, and the heparin-binding site.

1.1 Anticoagulant Function of Antithrombin

The antithrombin protein performs its primary function: the inhibition of serine protease coagulation factors by the formation of 1 : 1 irreversible complexes.[1] Heparins including heparan sulphate glycoproteins (HSPGs) catalyse a change in shape in the antithrombin molecule, which increases the efficacy of this inhibitory interaction at least 100-fold. For most of its substrates, this conformational change is enough to fully enhance the activity of antithrombin; however, for full effect against thrombin, the thrombin molecule must also be bound by heparin and held in proximity to antithrombin. Thus, while pentasaccharide heparin is adequate to allow maximal inhibition of factor Xa, an 18-saccharide heparin is the minimum required to allow optimal inhibition of thrombin[5] (figure 2). Physiologically, heparins are not present in plasma, but HSPGs are attached to vascular endothelium. *In vivo*, the activity of antithrombin is greatest in the region adjacent to the endothelium as a result.[6]

1.2 Anti-Inflammatory Function of Antithrombin

Antithrombin has been shown to exert an anti-inflammatory influence both by its inhibition of coagulation and directly via interactions with the endothelium.[7] The two main proteolytic substrates of antithrombin, thrombin and factor Xa (FXa), are thought to play a role in amplification of the acute-phase response. Thrombin induces the release of cytokines interleukin (IL)-6 and IL-8 from endothelial cells and monocytes via protease-activated receptors. It has been implicated in endothelial adhesion and rolling of neutrophils, a critical stage in their activation. FXa also interacts with the endothelium stimulating the release of cytokines and soluble adhesion molecules.

Independent of the coagulation system, antithrombin interacts with the vascular endothelium via HSPGs resulting in increased production of the anti-inflammatory cytokine prostacyclin. In the presence of exogenous heparin, these direct effects of antithrombin are diminished and the overall anti-inflammatory effect of antithrombin is markedly reduced. This appears to be as a result of the saturation of antithrombin binding by heparin resulting in reduced binding to endothelial HSPGs.

Many of the inflammatory effects of thrombin and FXa and the inhibitory actions of antithrombin occur on the surface of intact vascular endothelium, a region in which antithrombin is at its most effective. Therefore, it seems likely that local inhibition of thrombin and FXa by endothelial antithrombin plays an important role in the regulation of inflammation.[8]

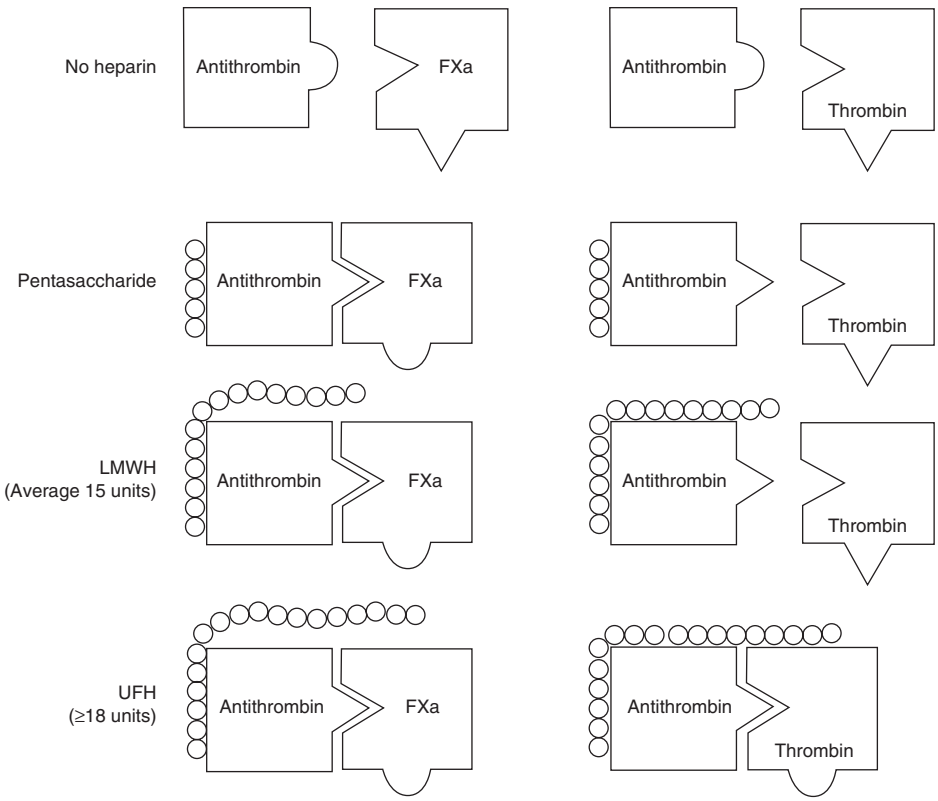

Fig. 2. The interactions of antithrombin with factor Xa (FXa) and thrombin in the presence of various sized heparins. In the absence of heparin, antithrombin does not inhibit FXa or thrombin significantly. In the presence of pentasaccharide heparin, FXa is effectively inhibited, but thrombin is not. Only heparins of 18 saccharide length or greater are able to potentiate the inhibition of thrombin by antithrombin. Low molecular weight heparins (LMWH), which have an average size of 15 saccharide units, contain a much lower proportion of 18 saccharide units than unfractionated heparin (UFH) and are, therefore, less able to facilitate the interaction of antithrombin with thrombin.

2. Epidemiology

2.1 Congenital

Since its original description[9] there has been a steady stream of reports of mutations in the antithrombin gene responsible for hereditary thrombophilia, with >150 described to date. These mutations can affect antithrombin protein production in a number of ways, resulting in a spectrum of antithrombin deficiency phenotypes. These are best summarised using the Antithrombin Mutation Database system that refers to type I quantitative and type II qualitative antithrombin deficiencies.[10] Type I deficiency is the result of a complete lack of gene product, and in the heterozygous state results in approximately 50% antithrombin activity and antigen levels. Type II deficiencies are a result of production of altered antithrombin protein with loss of function, this is characterised by reduction in antithrombin activity but not necessarily any reduction in antithrombin antigen. Type II deficiencies can be further defined by the site of the abnormality in the variant protein: (i) the effect on the reactive site; (ii) the effect on the heparin binding site; and (ii) the effect on both sites – pleiotropic effect.

Type I antithrombin deficiency is present almost exclusively in the heterozygote state; homozygosity being almost always fatal *in utero*. Rare cases of homozygous type II antithrombin deficiency have been reported, but the great majority of cases are also heterozygous. Thus, irrespective of mutation

type, hereditary antithrombin deficiency is almost always present in the heterozygous state and can be considered to have autosomal dominant inheritance.

2.1.1 Prevalence

Historically, reports on prevalence of antithrombin deficiency have ranged widely from 1 : 2000 to 1 : 20 000;[11,12] however, more recent estimates focussing on type I hereditary antithrombin deficiency have suggested that its prevalence lies between 1 : 2000 and 1 : 3000.[13] In patients presenting with venous thrombosis, the prevalence of hereditary antithrombin deficiency is between 1 : 20[14] and 1 : 200.[15]

In studies of the general population, often of blood donors where the overall prevalence has been higher, type II mutations outnumber type I mutations by a ratio of 2 : 1 or more.[16] However, among symptomatic patients and their families, type I mutations are much more common, representing approximately 80%.[17] This suggests that the venous thromboembolism (VTE) risk posed by type I mutations is substantially greater than that by type II mutations and also that the majority of cases of type II antithrombin deficiency are unidentified within the population. The exception to this is that type II reactive site mutations also carry a high risk of thrombosis.[18]

2.2 Acquired

Acquired antithrombin deficiency can arise in a number of circumstances. Production can be reduced as a result of impaired synthesis secondary to liver disease, malnutrition or premature infancy. Intracellular accumulation of the nascent molecule can occur associated with asparaginase therapy.[19] Alternatively, antithrombin may be lost directly in conditions such as nephrotic syndrome or consumed at an increased rate. Heparin therapy is a common cause of antithrombin consumption as a result of greatly enhanced formation of irreversible thrombin-antithrombin complexes in the plasma. More clinically relevant is the antithrombin depletion caused by the consumptive coagulopathies associated with disseminated intravascular coagulation (DIC), thrombotic micro-angiopathy, acute haemolytic transfusion reactions and malignancy.[4,8]

The level at which antithrombin deficiency becomes clinically relevant is not clear and may depend on the cause of deficiency; however, levels <50–60% in the presence of sepsis are associated with poor outcome. There is an almost universally fatal outcome in patients with antithrombin <20%.[5]

2.2.1 Pregnancy

It has been widely reported that antithrombin levels remain stable in normal pregnancy.[20] However, this view has been challenged recently by a Scandinavian study that shows antithrombin to be decreased slightly during the third trimester and even further postpartum.[21] A Japanese case series has also shown slight reductions in twin pregnancies and more marked reductions in triple pregnancies toward the end of gestation.[22] Among almost 2500 female blood donors a small but significant reduction in antithrombin of 4 IU/dL was noted in those taking an oral contraceptive.[23] Taken together, this suggests that while hormonal influences may cause small changes in antithrombin levels, these are unlikely to be clinically relevant in an otherwise healthy individual.

3. Pathogenesis

3.1 Congenital

Patients with congenital antithrombin deficiency have around 50% normal levels of antithrombin activity. This level is reasonably constant throughout life and is little influenced by pregnancy or hormonal replacement. During childhood, a period which carries an inherently low thrombotic risk, VTE is uncommon even in antithrombin deficiency.[24] However, with increasing age and the presence of other risks such as pregnancy, surgery or immobility, the risk of thrombosis rises markedly.[17]

The lifetime risk of VTE in hereditary type 1 antithrombin deficiency is at least 50%, with some estimates as high as 85%. For type II antithrombin deficiency, the risk depends on the site of the abnor-

mality with reactive site defects carrying a higher risk than those affecting the heparin binding site.[18] There is a clear age-dependent pattern with few thromboses seen before the third decade then a steady increase in risk with age.[25] Interestingly, despite this, normal life expectancy has been shown in a population with antithrombin deficiency or at least 50% chance of antithrombin deficiency.[26]

The most common presentation is with DVT; however, uncommon sites of thrombosis such as upper limb deep veins, mesenteric veins, vena cava, renal veins and retinal veins are overly represented. Less commonly seen are cerebral venous thrombosis and Budd-Chiari syndrome, and while arterial thrombotic events are rare, they have been reported.[25]

The incidence of spontaneous VTE has been reported as 1.6% per year in hereditary antithrombin deficiency.[27] A slightly lower incidence of VTE has been reported from a family study in which 27 of 85 antithrombin-deficient patients aged from 20–60 years have developed VTE. From this, a lifetime risk of eight times normal and an annual incidence of 1% were calculated.[17] Another group correlated the frequencies of antithrombin deficiency in the general population with those presenting with VTE to generate a relative risk of 20.[25] In summary, for type 1 and some type II reactive sites, the risk of thrombosis appears to be approximately 1% per year from age 15 years. Other type II deficiencies have lifetime risks as low as 20%.[28]

The incidence of pregnancy-related VTE may be >50% in untreated women with antithrombin deficiency. Robertson et al.[29] reported on three studies that in combination showed VTE in 8 of 11 women with antithrombin deficiency compared with 242 of 815 women without (odds ratio 4.69; 95% CI 1.3, 16.9).

It has been widely accepted that antithrombin deficiency in pregnancy poses a significantly greater risk of VTE than other thrombophilic defects. On a background risk of 1 : 1000 for pregnancy-related VTE, the risk associated with hereditary antithrombin deficiency has been calculated as 1 : 2.8 for women with type 1 deficiency and 1 : 42 for those with type 2 deficiency.[30]

Current evidence suggests that there is no increased risk of early pregnancy loss associated with antithrombin deficiency, while there are conflicting data regarding late pregnancy loss. A large retrospective study showed a 5-fold increased risk of stillbirth in pregnancies to women with antithrombin deficiency,[31] although a subsequent meta-analysis was unable to confirm this.[32]

3.2 Acquired

3.2.1 Sepsis

In sepsis, antithrombin levels are reduced for a number of reasons. While acute-phase proteins are upregulated, there is a downregulation of antithrombin production. Further reductions occur as a result of its increased plasma turnover in this setting. Antithrombin deficiency is, therefore, a predictable consequence of sepsis, and the degree of deficiency correlates with severity of illness and clinical outcome.[33] In animal studies, the use of large doses of antithrombin have been shown to reduce inflammatory markers and end-organ damage and improve outcome.[34,35] There appears to be a dose effect with supra-physiological doses associated with the best results. In one of these studies, the co-administration of LMWH reversed any outcome advantage and a delay of 24 hours in antithrombin administration reduced its effectiveness significantly.[34] It is speculated that the presence of heparin may increase antithrombin consumption and limit its potential benefits. These data also suggest that the influence of antithrombin therapy is greatest if given early.

A number of unknowns remain in this field. While it is likely that the anti-inflammatory effect of antithrombin is most pronounced on the surface of the endothelium, the extent to which plasma antithrombin activity correlates to endothelial antithrombin activity in sepsis remains unclear. In addition, the precise mechanism of action of supra-physiological antithrombin remains to be investigated.

3.2.2 Pregnancy

The coagulation system is altered in pregnancy in preparation for the major haemostatic challenge of childbirth. Coagulant factors VIII and von Willebrand factor are elevated, while the natural anticoagulant protein S is reduced. There is also an increase in fibrin turnover akin to mild chronic DIC.[36] It is not yet clear whether there is a physiological change in antithrombin level towards the end of pregnancy or whether pre-eclampsia is associated with a reduced antithrombin level.

Paternoster et al.[37] showed antithrombin to be significantly lower in 17 pre-eclamptic compared with 18 normal pregnancies, although a further study by the same group in 212 women failed to show a significant association. A recent Turkish study evaluated 80 pregnant women of whom 57 had eclampsia or pre-eclampsia, and found no reduction in antithrombin in these patients.[38]

3.2.3 Surgery

Cardiopulmonary bypass (CPB) is associated with reductions in plasma antithrombin activity to 40–50 U/dL.[39] This is due to haemodilution, coagulation activation within the extra corporeal circuit and possibly pre-treatment with heparin. Ranucci et al.[40] identified five independent factors for antithrombin depletion post-CPB: (i) preoperative antithrombin level; (ii) older age; (iii) diabetes mellitus; (iv) combined operation; and (v) length of CPB. In this setting, the major adverse effect of antithrombin deficiency is heparin resistance, which exaggerates the coagulopathic effect of CPB and often results in a bleeding tendency.[41] A study of 647 intensive care unit (ICU) admissions post-CPB showed a significant inverse relationship between antithrombin level on admission and length of ICU stay.[42] An antithrombin level <58 U/dL was predictive of an ICU stay of >1 week.

4. Treatment

4.1 Congenital

4.1.1 Primary Prophylaxis

Currently, primary prophylaxis with anticoagulant therapy is not recommended in asymptomatic antithrombin deficiency. The risk of fatal VTE is significantly less than that of fatal haemorrhage associated with long-term anticoagulation.[43]

4.1.2 Prophylaxis of High-Risk Events

Short-term thrombo-prophylaxis is recommended for patients with congenital antithrombin to cover periods of increased VTE risk such as surgery, trauma, plaster casts or immobilisation irrespective of personal history of thrombosis.[43] This guideline does not specify the prophylaxis to be used. For many minor procedures, LMWH would be the treatment of choice.

Plasma-derived antithrombin (pdAT) concentrate has been used in high-risk patients for >25 years; however, there is no randomised trial evidence to confirm its benefit. Within the American Red Cross study, six patients received pdAT to cover surgical procedures, no episodes of thrombosis were recorded.[44] When three of these patients underwent further surgery without pdAT prophylaxis, two developed VTE, one fatally. Despite the inherent risks associated with the use of pooled plasma products, its use has been considered appropriate in patients undergoing procedures with a high VTE risk,[45] even for just the few days when it is unsafe to administer therapeutic doses of anticoagulants.

The use of recombinant human antithrombin (rhAT) replacement in this setting has been described in a small series including six procedures in five patients.[46] All the patients described had a significant thrombotic history and underwent major surgical procedures without further VTE or major bleeding.

4.1.3 Treatment of Venous Thromboembolism

The initial management of VTE in those with antithrombin deficiency should generally be no different from its management in those without.[43]

Occasionally in severe thrombosis or if heparin resistance develops, the use of antithrombin concentrate (pdAT) may be considered.[45,47] On an individual patient basis, the length of anticoagulation may be adjusted for those perceived to be at an increased risk of recurrence. The risks and benefits of prolonged secondary prophylaxis need to be considered in light of the fact that the incidence of recurrent VTE is around 10% per year in patients with antithrombin deficiency.[48] Following two or more spontaneous episodes of VTE, indefinite anticoagulation would definitely be recommended.

4.1.4 Pregnancy

The 7th American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy[49] recommends that antithrombin-deficient women without a history of VTE use active ante-partum prophylaxis. This can be achieved with twice daily subcutaneous LMWH (dalteparin sodium 5000IU or enoxaparin sodium 40mg) or twice daily subcutaneous unfractionated heparin (UFH) titrated to an anti-Xa level of 0.1–0.3 U/mL at 4 hours post-dose. For those with a history of VTE, twice daily dose-adjusted LMWH (dalteparin sodium 100 IU/kg or enoxaparin sodium 1 mg/kg) or therapeutic dose-adjusted UFH are recommended. Graduated compression stockings are advised for those with a history of VTE.

The British Committee for Standards in Haematology (BCSH) guidelines on the investigation and management of hereditable thrombophilia[43] class women who have type I or type II (reactive site) antithrombin deficiency as high risk for antenatal or postnatal thrombosis irrespective of VTE history. Dose-adjusted LMWH or dose-adjusted UFH are recommended. For 12-hourly dalteparin sodium, a dose of 75 IU/kg is suggested, aiming for a peak plasma anti-Xa activity of 0.35–0.5 U/mL 3 hours after injection. For UFH, the target range is slightly higher at 0.35–0.7 U/mL anti-Xa activity at 4 hours post-dose. Women in this high-risk group are advised to wear graduated compression stockings throughout and for 6–12 weeks after pregnancy. Post-partum anticoagulation is advised in both guidelines, but choice of agent is not discussed; the BCSH guideline suggests 6 weeks of therapy.

LMWH is now established as the anticoagulant of choice both for thrombo-prophylaxis and treatment of VTE in pregnancy. Greer and Nelson-Piercy[50] reviewed 64 studies including 2777 pregnancies assessing outcome and adverse effects. VTE occurred at a rate of 0.84% in those receiving prophylaxis and recurrent VTE at a rate of 1.15% in the treatment group. Bleeding >500mL occurred in 1.98%, while allergic skin reactions were seen in 1.8%. No episodes of heparin-induced thrombocytopenia with thrombosis were reported in the studies reviewed in this article. No single LMWH has been shown to be superior in this setting; however, enoxaparin sodium and dalteparin sodium are the most widely used. For once-daily subcutaneous administration of LMWH in high-risk prophylaxis in pregnancy dalteparin sodium 5000IU or enoxaparin sodium 40mg are considered appropriate.[51]

Because of concerns over bleeding following delivery or in relation to epidural anaesthesia, anticoagulants are often withheld during labour. There may be a role for antithrombin replacement in this setting, although published evidence to support its use is limited.[52]

4.2 Acquired

4.2.1 Sepsis

To date, seven clinical studies have investigated the role of antithrombin in the clinical setting of intensive-care management of sepsis. A meta-analysis of three early studies including 122 patients was able to show a nonsignificant trend towards improved 28-day survival (45% vs 35%).[53] More recently, the larger Kybercept study was unable to show any difference in 28-day all-cause mortality (38.7% vs 38.9%) in 2314 patients.[54] Despite this overall result, a number of subset analyses have identified groups of patients who may benefit. In the initial publication, it was noted that patients at moderate risk of death by Simplified Acute Physiology Score (SAPS) gained a greater survival advantage from antithrombin therapy than those with less or more severe illness. Further analysis of the SAPS

high-risk group has suggested that concomitant use of heparin may lessen any benefits of antithrombin therapy.[55] Within 563 patients throughout the study who did not receive heparin, there was a significant survival advantage to receiving antithrombin in those shown to have DIC.[56] With the caveat that much of the data comes from subset analysis, this large study suggests that in some patients at moderate risk and in the absence of heparin, antithrombin may have a therapeutic role. This said, there remains a general consensus that the role of antithrombin therapy in sepsis is not yet fully clarified and that its use should be confined to appropriate clinical studies.[8,57]

4.2.2 Surgery

In the management of heparin resistance during CPB, pdAT concentrate has been shown to improve heparin responsiveness.[58,59] However, neither of these studies showed any outcome advantage from the use of antithrombin replacement. More recently, rhAT therapy has been shown to be safe in the setting of CPB surgery and to reduce markers of coagulation activation; again though, no clinical benefit has been shown.[39,60]

Aortic aneurysm has been shown to be associated with a degree of coagulopathy, with the size of aneurysm correlated to plasma thrombin-antithrombin complex levels.[61] When pdAT was administered pre- and post-aortic aneurysm repair surgery, there was a rise in antithrombin and a significant reduction in thrombin-antithrombin complex, D-dimer and IL-6.[62] No clinical outcome data are presented.

4.2.3 Acute Lymphoblastic Leukaemia

The antithrombin deficiency associated with asparaginase use in the treatment of acute lymphoblastic leukaemia is well recognised and is associated with an increased risk of VTE. Two studies have investigated the use of antithrombin replacement (pdAT) in this setting.[63,64] Neither reports any adverse response to therapy; however, while a predictable rise in antithrombin level has been demonstrated, no outcome benefit has yet been demonstrated.

4.2.4 Other Scenarios

The pdAT concentrate has been used in the management of venous occlusive disease of the liver following bone marrow transplant with some evidence of improved organ function but no survival benefit.[65] In the neonatal setting, two studies have shown antithrombin therapy to be of no benefit. In 122 neonates with respiratory distress syndrome, which is associated with decreased antithrombin activity, those randomised to pdAT showed a poorer outcome.[66] Similarly, pdAT failed to reduce intracranial bleeding rates among 60 premature infants.[67]

It is not within the scope of this article to advise on the dosage of antithrombin replacement; however, guidance is published in the settings of congenital deficiency[47] and sepsis.[8]

5. Differences Between Plasma-Derived and Recombinant Human Antithrombin

A rhAT (ATryn®)[1] is now available, produced in the milk of transgenic goats. A comparison of this product with an established pdAT, Thrombate III®, has identified some minor differences between the products.[68] The rhAT protein has a different glycosylation pattern from the native human protein resulting in a greater heparin affinity. The effect this has on bio-distribution and efficacy are under investigation. There is concern that these novel epitopes will induce an immune response in recipients, although no antibodies have been reported to date.[39] Studies in healthy volunteers[69] and in patients undergoing CPB[46] have established that the half-life of rhAT appears to be considerably shorter than that of pdAT (10.5 vs approximately 60 hours). While the authors are confident that single dose administration will be adequate for CPB, more frequent administration regimens will be needed to maintain target plasma antithrombin levels for longer procedures.

In the era of transfusion-transmitted disease, this recombinant product clearly has advantages over plasma-derived alternatives, despite assertions of

1 The use of trade names is for identification purposes only and does not imply endorsement.

the latter's safety.[44,70] Concerns regarding the transformation to inactive L-forms of antithrombin by heat treatment viral inactivation of plasma[71] may not be relevant to rhAT, depending on the production methods used.

6. Conclusion

The role of antithrombin replacement therapy in congenital or acquired antithrombin deficiency states remains largely unsupported by any robust evidence base. On the one hand, congenital antithrombin deficient patients are few, but are very likely to experience venous thrombosis as a result of their deficiency. This scarcity of patients has prevented any randomised treatment studies, and therefore recommendations are based on extrapolation and consensus of expert opinion.[43,49,72]

Acquired antithrombin deficiency appears to be frequent, particularly in the ICU setting, yet the clinical relevance of deficiency is still not fully established.

There is evidence of an association between reduction in antithrombin and coagulation activation, inflammation and clinical outcome in the settings of sepsis and CPB. While a therapeutic role for antithrombin is suggested, the extent to which its reduction is causative in relation to clinical outcome is not yet clearly established. It could be argued that antithrombin use in states of acquired antithrombin deficiency is not truly a replacement but rather an active therapy as in both animal and clinical studies any benefit noted has been with supra-physiological doses.

For those uncommon situations when antithrombin replacement therapy appears justified (mostly in congenitally deficient patients facing high thrombotic-risk surgery or delivery of pregnancy without the protection of full dose anticoagulation), the recent availability of a rhAT may further improve the risk **:** benefit ratio for use of replacement treatment.

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