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Chapter
Danaparoid Sodium: A Review of Its Use in Hepatic Thrombotic Disorders

Harry N. Magnani

Abstract

Danaparoid sodium is an antithrombotic isolated from porcine mucosa. Its main constituent is a mixture of heparan sulphates that inhibits thrombin generation and also possesses anti-inflammatory and immune-modulatory activity. It has shown safety and efficacy in its main indications of deep venous thrombosis prophylaxis, heparin-induced thrombocytopenia treatment and disseminated intravascular thrombosis treatment. In addition, there are reports of its off-label use for the treatment of portal vein thrombosis in adults and for prevention of the hepatic thrombotic microangiopathies haematogenous that complicate recovery after stem cell transplantation in adults and children. The results of these studies provide further support for its safety and efficacy even in subjects with cirrhosis and/or severe hepatic dysfunction. In this chapter the rationale for danaparoid use is presented and the collated results of comparative studies and case reports are compared with those of other pharmaceutical options for managing these hepatic thrombotic disorders.

Keywords: danaparoid, PVT, SOS, TA-TMA, HSCT, hepatic thromboses

1. Introduction

The liver is the largest organ in the body, and while it only accounts for about 3% of the total body weight it receives 25% [1, 2] of the cardiac output via the hepatic artery and portal vein. This is due to its multifunctionality in regulating glucose and amino acid homeostasis, detoxifying the blood, processing of lipoproteins and their fats, synthesis of bile and proteins, storage of glycogen and vitamins and filtering of bacteria, etc.

Hepatocytes produce many of the proteins involved in normal regulation of the clotting cascade and fibrinolytic system. These, with platelets, achieve a balanced haemostasis system with fine controls and checks at many levels to maintain free flow of blood within the circulation, prevent uncontrolled clotting of the blood and quickly plug blood vessel wall breaches to limit blood loss. Toxins and pathogens can not only cause hepatocyte injury but also damage hepatic sinusoidal cells and endothelial cells (ECs) throughout the circulation. The injury results in reduced synthesis of clotting factors but due to compensating changes in additional factors that regulate the clotting and fibrinolytic cascades, haemostasis and thrombin generation remain...
in balance [3] and any bleeding is usually due to the presence of varices. This new haemostasis balance is more sensitive to perturbation because synthesis and release of proteins and proteases responsible for its fine tuning, that come not only from hepatocytes but also sinusoidal cells and ECs, are also disrupted. The initial result is more likely to be a procoagulant state, but if hepatic dysfunction worsens the balance may tip the other way with predomination of fibrinolysis, thrombocytopenia and worsening platelet dysfunction causing bleeding.

2. Portal vein thrombosis

The haemostasis disruption may lead to macro-vascular thromboses involving the complex circulation around the liver, i.e. the portal venous system (PVS) that includes the intra-hepatic portal vein branches, the splenic and superior mesenteric veins. Portal vein thrombosis (PVT) commonly occurs in patients with hepatic cirrhosis and/or carcinoma, while splenic vein thrombosis may also be found as an extension of a PVT or develop as a complication of splenectomy [4, 5]. PVT may also develop in the absence of primary liver disease [6] and has recently been described in patients with COVID-19 [7, 8] and in patients suffering vaccine-induced immune thrombocytopenic thrombosis (VITT) following COVID-19 vaccination [9].

In patients with cirrhosis the frequency of PVT increases with disease severity [10] from about 3%–25% [11]. In post-splenectomy patients with cirrhosis the frequency may reach 36% in the absence of anticoagulation and rates as high as 70%–85% have been found in the presence of malignancy (hepatoma, lymphomas, solid tumours, myeloproliferative neoplasms). Although at first PVT may be almost symptomless and many spontaneously disappear, persistence and recurrence result in significant or complete obstruction of one or more vessels of the PVS and portal hypertension with increasing morbidity. Formation of collateral circulations and varices are prone to rupture with often major blood loss. PVT can present either acutely with abdominal pain, diarrhoea and ileus—occasionally as an acute abdomen or chronically often with signs of portal hypertension.

Persistent/recurrent PVS thrombosis (PVST) may eventually be fatal, hence there is frequently a need for effective antithrombotic management. Especially if acute non-occlusive PVST or a thrombotic risk factor is present, e.g. sepsis, cancer, antiphospholipid antibody or an acquired or hereditary thrombotic risk (factor V Leiden, prothrombin mutation G20210A, protein C and/or S deficiency, etc.) then anticoagulation should be considered [12, 13]. The aims of anticoagulation are thrombus recanalisation, reduction of portal hypertension to lower the bleeding risk and prevention of PVST recurrence. The use of anticoagulants has been reviewed and several meta-analyses of the results are available [5, 14]. Despite the heterogeneity of the included studies, there appears to be a growing consensus that use of anticoagulants for the treatment of PVT increases the rate of recanalisation compared with non-anticoagulated patients, but there is too little evidence concerning their benefit to risk balance with emphasis on bleeding complications.

3. Sinusoidal obstruction syndrome and transplant associated thrombotic microangiopathy

The sinusoidal cells, which share many features of ECs, are particularly at risk of toxic injury. Both hepatic sinusoidal obstruction syndrome (SOS) and transplant
associated thrombotic microangiopathy (TA-TMA) are examples of sinusoidal cell and EC injury. Detoxification of chemotherapeutic drugs and other toxins, including pathogen induced endotoxins, is mediated by the hepatic cytochrome P450 complex and any toxic side-products produced are neutralised by the glutathione enzymatic system (GSH). The centrilobular cells of the sinusoids have the least GSH and the lowest oxygen supply thus they are at most risk of toxic injury. If the activity of the P450 and/or GSH is impaired or overwhelmed, e.g. in hepatic disorders and/or the presence of high intensity chemotherapy, then toxic side-products accumulate leading to sinusoidal and EC injury. The resultant disruption of local haemostasis and immune system control result in microvascular thromboses the development of SOS [15] (formerly known as veno occlusive disease or VOD). The injury may extend beyond the sinusoids allowing toxic chemotherapeutic drugs and their side products to access ECs in the general circulation and other organs. If these are already injured by prior total body radiation and/or infections or by graft v host disease (GvHD) following haematogenous stem cell transplantation (HSCT), then further endothelial damage will develop with gradual or sudden emergence of the clinical and pathological picture of TA-TMA. Both SOS and TA-TMA occur most frequently as complications of HSCT as a result of the chemotherapy used to prepare for the transplant, the use of allogeneic in place of autologous transplants and post-transplant use of further chemotherapy and a cocktail of drugs to prevent or control infection, transplant rejection and GvHD. Both SOS and TA-TMA are associated with a high mortality. Table 1 shows risk factor associated with one or both complications.

Complement cascade proteins also originate in the liver. In health the immunological/anti-inflammatory and haemostatic systems are finely tuned and, because of their cross-talk via various interacting pathways, maintain a finely balanced vascular homeostasis ready to repel ‘foreign’ invasion and seal damaged vessels to limit blood loss and procoagulant products (including PAI-1, thrombomodulin, vWF and microparticles). However, sinusoidal cell and EC injury related to HSCT injury leads to release of a cocktail of cytokines and mitogens, the so-called ‘cytokine storm’. Unregulated complement activation [16–20] ensues and the balance and cross-talk between haemostasis and the immune systems is disturbed. The result is further EC damage with fibrin deposition and thrombi feeding into the pathogenesis of both SOS and TA-TMA.

SOS usually manifests within 21 days but may present late, with thrombocytopenia and signs of portal hypertension due to fibrous obliteration of the sinusoids and central venules. Endothelial injury underlies both disorders but for some [21] this is insufficient to consider SOS as a vascular endothelial syndrome. However, others [22] disagree since TA-TMA, with its mixed endothelial/immune origin is included [21]. Furthermore, immunological involvement in the pathogenesis of SOS is also very likely since injured ECs release cytokines and mitogens and these are capable of complement cascade activation and disruption [23]. These can also activate the coagulation cascade via the intrinsic pathway further increasing thrombin production. Observations that the frequency of SOS increases with the use of mis-matched and unrelated donor cells and is reduced in T-cell depleted HSCT also point to an immunological connection. The overall frequency of SOS development after bone-marrow transplantation (BMT) is about 14% (range 5%–50%), depending upon the chemotherapeutic drug and/or conditioning regimen used for cancer treatment and transplantation, and the clinical diagnostic criteria used [24, 25]. Children appear to be more prone to SOS but the wide range is greatly influenced by diagnostic imprecision, clinical status of the patient at BMT, and the conditions of the transplant, particularly the type of conditioning used. SOS is associated with a 40% mortality but in the presence of organ dysfunction this may rise to 80%.
TA-TMA usually presents at any time within the first 3 months of transplantation but may appear up to several years after the HSCT. The overall frequency of TA-TMA is about 5% but up to 76% [26] has been reported (see Table 1). Mortality may reach 80% and is related to the number of risk factors present, e.g. the type of cytotoxic agent, particularly methotrexate, cyclophosphamide, etc., used in the conditioning regimens for transplantation, presence of active infection, use of matched unrelated donors, transplant mismatches, presence of GvHD and previous BMT. Survivors may suffer long term morbidity due to chronic organ damage.

Perhaps TA-TMA represents a vascular form of GvHD since it may precede the appearance of GvHD and its frequency increases with the severity of GvHD [21] and they share similarities in pathophysiology [27–29]. These considerations may explain the overlaps and differences between SOS and TA-TMA in their risk factors (see Table 1) and their distribution, clinical presentation and sequelae (see Table 2). In addition, it may account for their presence together in some patients and the continuing controversy over their diagnostic criteria that confounds early recognition and treatment of both disorders.

It is possible that SOS and TA-TMA are different clinical presentations of the same problem. Their pathogenesis is similar and the resulting sinusoidal and EC injury triggers release of many factors resulting in disruption of both haemostasis and immune systems. In this respect both SOS and TA-TMA are similar to the general group of microangiopathies [22, 30].

Table 1.
Risk factors for SOS and TA-TMA.

<table>
<thead>
<tr>
<th>Risk factor cited for occurrence and severity</th>
<th>SOS</th>
<th>TA-TMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F &gt; M)</td>
<td>+</td>
<td>(+)</td>
</tr>
<tr>
<td>Age at HSCT &lt;10 years</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Use of: alkylating cytostatic agents, platinum complexed agents, pyrrolizidine plant alkaloids</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Immunotherapies for acute leukaemias: gemtuzumab, inotuzumab, ozogamicin,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor mismatch</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Platelet transfusion mismatch</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Number of prior stem-cell transplants</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Fungal or viral infections/sepsis</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Pre-existing hepatic injury (viral, cancer)</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Active co-morbidity</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Prior abdominal radiotherapy</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Immunodeficiency syndrome</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Presence of an autoimmune disorder</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>The interval between malignancy diagnosis and the HSCT</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Presence of acute GvHD</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Inherited thrombophilia (FVL, G20210A)</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Post HSCT cyclosporine, tacrolimus, serolimus</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>After autologous as well as allogeneic BMT</td>
<td></td>
<td>(+) (+)</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
It is clear that both antithrombotic and immune modulating drugs are indicated to prevent or treat both conditions. However, prevention is always better than cure if the right product is available. The ability of a single product to attenuate the effects of both systems without causing further damage would be a desirable bonus especially if this can be done safely and relatively cheaply.

4. Danaparoid

Danaparoid sodium is a mixture of linear glycosaminoglycuronans (GAGs) with a MW_{ave} of 4500 Da (range 2500–10,000 Da). It is extracted from porcine mucosa.
after heparin removal and ultrafiltration. The final product consists of heparan sulphate (HS) 85% with about 12% dermatan sulphate (DS) and traces of chondroitin sulphates 4 and 6 (CS). The HS appears to be more concentrated in the lower MW<sub>ave</sub> chains and the DS and CS in the longer chains. The main structural difference between danaparoid and the heparins is the presence of glucuronic acid in place of iduronic acid. Enzyme degradation of danaparoid GAG chains produces disaccharides (see Figure 1) with a low degree of sulphation and acidification. Hence the GAG chains in danaparoid a low overall negative charge density compared with the heparins [unfractionated (UFH) and the fractionated low molecular weight heparins (LMWHs)]. However, about 5% by weight of the HS fraction of danaparoid [the so-called high affinity HS (HA-HS)] consists of more highly sulphated chains because like those of UFH they contain an antithrombin (AT) binding pentasaccharide sequence that includes a triple sulphated glucosamine residue. Only this specific AT binding site possesses a higher overall negative surface charge density than the rest of danaparoid chains that do not bind AT.

Danaparoid is an antithrombotic that inhibits thrombin generation by both AT mediated inhibition of factor Xa by the HA-HS subfraction and direct inhibition of thrombin activation of factor IX by the major non AT binding HS. In addition, a minor inhibition of thrombin activity is produced by the HA-HS, mediated via AT, and by the DS fraction mediated via heparin-cofactor II.

Danaparoid is not a heparin but a heparinoid and further, unlike the heparins, it is not an anticoagulant because the recommended therapeutic dose regimen hardly affects the routine clotting tests (aPTT, PT, ACT and TT). A lack of spontaneous platelet activation and the weak inhibition of thrombin-induced platelet activation is associated with virtually normal primary haemostasis and hence low bleeding risk.

Three biological effects of danaparoid can be assayed—its anti-Xa activity, anti-thrombin activity and TGI. These have plasma half-lives of 24.7, 2.0 and 6.7 h respectively. However, the anti-thrombin activity is too weak for monitoring and at the time of its clinical development (1980s) there was no simple TGI assay. Hence the pharmacokinetics of danaparoid was based on the effect of the smallest subfraction.

**Principal Disaccharide – Repeating Units**

![Figure 1](Comparison of heparin and danaparoid disaccharide structures.)
of danaparoid (HA-HS) that represents only 5% by weight of the total product and is responsible for only half of its anti-thrombotic activity.

Plasma anti-Xa activity measurements have shown that at least the HA-HS subfraction is cleared via the kidneys and that the liver plays no role in its elimination from the blood. In the absence of overall labelling studies it is assumed that the remaining fractions of danaparoid undergo a similar fate. Although useful for estimating plasma levels of danaparoid the anti-Xa activity shows poor correlation with bleeding or thrombotic events reflecting the fact that this assay, unlike thrombin generation inhibition (TGI), does not measure all actions contributing to danaparoid’s effect on haemostasis.

Only 5% of the HS chains in danaparoid contain the trisulphated disaccharide required for AT binding. The remaining chains are low in both sulphate and acidic groups hence the overall negative charge density of danaparoid is low compared with the heparins (see Figure 1). Thus danaparoid is unable to bind to the many positively charged ‘heparin-binding’ proteins in the circulation and without this ‘neutralising effect’ danaparoid is 100% bioavailable for antithrombotic activity compared with 30% for UFH and about 80% for the LMWHs. This is also the reason why the anti-Xa activity units (U) of danaparoid are not equivalent to the IU of the heparins.

Clinical development of danaparoid led to widespread approval for deep venous thrombosis (DVT) prophylaxis hip following hip orthopaedic and general cancer surgery and in Japan for the treatment of disseminated intravascular thrombosis (DIC). The absence of heparin making it unlikely to cross-react with the specific antiplatelet antibody led to its approval for the treatment of heparin-induced thrombocytopenia (HIT), including the prevention or treatment of thrombosis in patients with renal failure requiring use of an extracorporeal circuits, in children and in pregnancy, if these patients also have HIT or other forms of heparin intolerance. Table 3 compares some PK and PD aspects of danaparoid with those of the heparins.

Apart from its antithrombotic activity, animal and isolated tissue experiments revealed that like heparin danaparoid has both immune-modulatory and anti-inflammatory activities [32], with both similarities and differences from the heparins (see Table 4).

The first indication of this came when danaparoid prevented heparin from activating platelets in the presence of plasma from patients with HIT [33]. In addition, it was found that while the isolated HA-HS subfraction (4% by weight of danaparoid) showed 100% cross reactivity with the specific HIT antibody this was totally prevented by addition of the remaining 96% of danaparoid with no affinity for AT [34]. Finally it was shown that danaparoid is unique among currently available antithrombotics in interfering with the interactions of the specific HIT antibody with heparin and its platelet and monocyte targets [35]. In addition, it was shown that danaparoid is unable complex with platelet factor 4 (PF4, a platelet derived cytokine to which heparin binds to induce HIT) to form the ultra-high molecular weight complexes with neo-antigenic sites [36] required to induce the specific antiplatelet antibody underlying the pathogenesis of HIT. Other experiments [37–49] (summarised in Table 4, where it is compared with the effects of the heparins) have shown that danaparoid inhibits or attenuates anti-inflammatory effects induced by various triggers, including endotoxin, ischaemia, reduction of ischaemia/reperfusion-induced hepatic injury in animals and a pilot endotoxin study in volunteers. Many of these actions occurred at the equivalent of its usual therapeutic dosing intensities. They appear to be independent of danaparoid’s antithrombotic activity, since they occur in the absence of AT or other clotting cascade constituents. From independent studies of synthetic GAGs or chemically modified heparin the resultant chemical structure of its oligosaccharide chains is of great importance. The low degree of sulphation with fewer acid groups and
the absence of the 2-O sulphate group on the glucosamine (see Figure 1) appear to be responsible for many of the immune-modulatory/anti-inflammatory activities summarised in Table 4 [31, 32, 50–53].

Thus fine structural differences between the many HSs within the body are responsible for myriad interactions that are site-specific with roles in haemostasis, inflammation, leukocyte transmigration, immune homeostasis, lipid metabolism, cell attachment, angiogenesis, migration, invasion and cell differentiation.

Based on the combination of antithrombotic activity and immune/modulatory actions danaparoid has been successfully used to treat patients with sepsis, DIC and HIT. In addition its low bleeding inducing capacity has led to off label use to prevent post-HSCT SOS and TA-TMA and to treat patients with PVT.
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DOI: http://dx.doi.org/10.5772/intechopen.103851

4.1 Danaparoid treatment of portal vein thrombosis

4.1.1 Population exposure

Danaparoid exposure in relation to PVT is available for 559 patients. Five retrospective comparative studies treated 177 patients with danaparoid only v UFH [54], v danaparoid + AT [55, 56] or v danaparoid + AT and AT only [57] and danaparoid + AT v AT only [58]. In addition, 383 patients received danaparoid in reports of retrospective case series and single case reports [57, 59–91] in which danaparoid was used alone or combined with AT and finally 2 single case reports of danaparoid administered with UFH [92] or urokinase [93]. Danaparoid was given to treat the PVT in 41 of the 43 reports. In the remaining 2 it

<table>
<thead>
<tr>
<th>Inhibition or reduces:</th>
<th>Heparin</th>
<th>LMWHs</th>
<th>Danaparoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotoxin lung injury:</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Local</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulopathy Inflammation</td>
<td>No</td>
<td>nd</td>
<td>No</td>
</tr>
<tr>
<td>Fibrinolysis systemic</td>
<td>No</td>
<td>nd</td>
<td>No</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reperfusion injury</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Endothelial glycocalyx damage</td>
<td>(yes)</td>
<td>(yes)</td>
<td>Yes</td>
</tr>
<tr>
<td>Growth factor production</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Interferon</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Burn/smoke inhalation injury</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Endothelial injury</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Intimal hyperplasia</td>
<td>Yes</td>
<td>(yes)</td>
<td>(yes)</td>
</tr>
<tr>
<td>Cell proliferation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Annexin binding</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tissue and/or organ damage</td>
<td>Yes</td>
<td>(yes)</td>
<td>nd</td>
</tr>
<tr>
<td>Leucocyte activation and adhesion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>NET formation</td>
<td>Yes</td>
<td>Yes</td>
<td>nd</td>
</tr>
<tr>
<td>Effects of HMGB-1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Immunogenic binding with PF4</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Virus transduction</td>
<td>Yes</td>
<td>(yes)</td>
<td>weak⁴</td>
</tr>
<tr>
<td>Spontaneous ‘HIT’ induction</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>HIT antibody interactions</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

HIT = heparin-induced thrombocytopenia, HMGB-1 is a chromatin protein and cytokine mediator of inflammation, NET = neutrophil extracellular trap, PF4 = platelet factor 4.

¹However highly dependent on the specific annexin and degree of sulphation of the GAG involved.
²Single report using recombinant adeno-associated virus - type 2⁴.
nd—no data, brackets indicate action is weaker or only occurs under certain circumstances.

Table 4.
GAG immune-modulatory effects at therapeutic dose levels.
was given for PVT prophylaxis. Table 5 shows some patient characteristics that could be identified with the treatment given.

Hepatic PVT was present in 524 of the 558 patients exposed to danaparoid (including those receiving AT and the 3 receiving concomitant antithrombotics—UFH, warfarin or a thrombolytic). In 33 patients thrombus was also present in the splenic vein and in 33 in the superior mesenteric vein, but only 11 single case reports stated the exact distributions when 2 or more sites were implicated, i.e. PV + SMV 6 cases, PV + SV 1 case, PV + SV and SMV 3 cases and PV + B-Ch 1 case and one publication mentioned that in 16 of 41 patients the PVT was present in more than 1 site.

The frequencies of some relevant presenting parameters were inconsistently provided in the study reports, e.g. hepatic failure was hardly mentioned but one study [60] reported a mean MELD score of 8.6, encephalopathy was only mentioned in four reports, the Child-Pugh status was provided for 10 comparative studies and 6 case reports as either scores (range 5–12) or classes A, B and C—118, 166 and 49 respectively, bleeding (in all cases gastrointestinal, 3 due to varices) was only mentioned in 6 single case reports and severe infection in only 3 reports, mean plasma AT levels available in only 8 publications were low normal or <60% of normal levels in 7 and platelet counts provided in only 5 single case reports and 4 comparative studies or case series were a median 80 G/L (range 17–655). It is not known if these parameters were therefore normal, absent or not considered, hence their absence from the pooled overview shown in Table 5.

Patients were followed-up after danaparoid discontinuation for at least 3 months and in some studies events up to 2 or 3 years were recorded. During this follow-up period at least 210 patients had been transitioned to a warfarin to continue anticoagulation. One study [66] found that long-term edoxaban succeeded but warfarin failed to sustain successful initial danaparoid treatment of PVT.

### 4.1.2 Danaparoid dosing for PVT

All studies, apart from three single cases [72, 81, 94], were performed in Japan. In two cases, HIT [72, 81] was also present and in three cases the PVT was accompanied by hepatic vein thrombosis (HVT, Budd-Chiari syndrome) [72, 81, 87]. Because treatment and prevention of PVT is an off label indication for danaparoid the dosing regimen used in Japan was that approved for DIC treatment, i.e. 1250–2500 U/day as 1 or 2 i.v. bolus

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**Table 5.**

General characteristics of PVT of danaparoid treated patients and non-danaparoid controls.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Danaparoid use in comparative studies</th>
<th>Danaparoid use in case reports</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alone</td>
<td>With AT</td>
</tr>
<tr>
<td>N2</td>
<td>75</td>
<td>64</td>
</tr>
<tr>
<td>Age (range in years)</td>
<td>23–85</td>
<td></td>
</tr>
<tr>
<td>M/F distribution (%)</td>
<td>35.1/64.9</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>67/67</td>
<td>7/7</td>
</tr>
<tr>
<td>Varices</td>
<td>105/107</td>
<td>197/283</td>
</tr>
<tr>
<td>Hepatocellular cancer</td>
<td>65/107</td>
<td>113/274</td>
</tr>
</tbody>
</table>

AT = Antithrombin.

1Not all studies had complete information hence the different denominator.

2Danaparoid was compared in most studies with danaparoid + AT. In Ref. [31] the number receiving dan alone or + AT is only specified in an interim analysis for 28 of the final 55 patients. Three additional case reports of dan + UK, dan + UFH and dan + warfarin are not included in table but are discussed in text.
injections (or short infusions) respectively. For most patients the higher dose 1250 U b.d., i.v. was chosen. In the three non-Japanese single case reports [72, 81, 91] the danaparoid regimen was ‘therapeutic’ (i.e. >2250 U/day) to treat HIT resulting from initial use of a heparin for the PVT and/or the HVT. In one of these patients it was used safely up to and after orthotopic liver transplant and to anticoagulate the cell saver during surgery [81]. For the other HIT patient no precise dosing information is available and for the third non-Japanese patient [93], the dose was also not mentioned but it was administered with warfarin until the patient could be discharged on warfarin only. Danaparoid exposure lasted a median 14 days (range 4 days to 2 months). In addition, sporadic reports state its successful re-use when PVT recurred during long-term warfarin use [55, 59, 67, 70].

Fifteen reports showed that AT was used concomitantly with danaparoid in 180 patients and in 2 studies AT was used alone as a comparator in 93 patients. In some studies comparing danaparoid alone with danaparoid + AT the AT was only used in patients presenting with plasma levels below 60%. The AT regimen was usually 1500 U daily for 3 days, but in one comparative study [56] and one case report [88] it was administered for 5 days. Administration of AT was often dependent upon the patient’s AT status but in two studies danaparoid alone was compared with danaparoid + AT.

4.1.3 Results

The efficacy of danaparoid treatment assessed as complete, ≥70%, 50%–70%, <50% recanalisation/no change or as a new/progressive thrombosis, are summarised in Table 6.

Danaparoid treatment was associated with complete recanalisation in 46% of the patients and clinically significant thrombosis management in 72.6% (i.e. ≥70% PVT resolution) of the patients (although some investigators considered >50% reduction as clinically significant). An ineffective outcome was recorded in 10.7% of the patients including one with progression of thrombosis. Two studies assessed vessel volume reduction as a measure of recanalisation. One [61], involving 41 patients treated with danaparoid only, expressed the result as the mean reduction of 55.1% ± 40.2% at

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Outcome of PVT treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Degree of PVT resolution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complete</td>
</tr>
<tr>
<td>Danaparoid only all studies</td>
<td>270</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34.8%</td>
</tr>
<tr>
<td>Danaparoid + AT all studies</td>
<td>87</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27.6%</td>
</tr>
<tr>
<td>All danaparoid</td>
<td>370</td>
<td>173</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46.8%</td>
</tr>
<tr>
<td>AT only</td>
<td>24</td>
<td>11/24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45.8%</td>
</tr>
</tbody>
</table>

nc = no change, AT = antithrombin, nd = no data.

Table 6.
Pooled outcomes of PVT treatment.
2 weeks, the other [66], involving 55 patients also treated with danaparoid only, found a reduction from median 3.43 cm$^3$ to 1.42 cm$^3$, also at 2 weeks. Incidental presenting thromboses were: SSST and ovarian vein in one patient and two PEs, all resolved during danaparoid treatment, but only one of the three concomitant hepatic vein thromboses responded favourably to danaparoid. In all reports providing data on coagulation markers d-dimer, TAT and fibrinogen the plasma levels normalised by 2 weeks. All platelet counts (including the two patients with HIT) also increased to normal except for one patient, but no reason was given. In addition, plasma AT levels, whether above 60% before danaparoid treatment initiation or supplemented with injected AT, did not deteriorate during danaparoid use. The only study with a group of non-anticoagulated controls showed.

Three bleeding events (0.8%) developed, one each in three patients, during danaparoid treatment initiation: two from varices (one following endoscopic ligation), and one peritoneal haemorrhage. Danaparoid was restarted in one. No problem was recorded during the transition from danaparoid to warfarin.

No patient death was reported within 3 months of stopping danaparoid treatment. Other adverse events reported were the development of ascites in two patients (one with diarrhoea) and one case of thrombocytoopenia that was not considered serious but no other details were provided. Despite one investigator [56] calculating that warfarin doubled the time of PVT recurrence from 1 to 2 years, eight others [55–59, 61, 66, 67] reported that follow-up treatment with warfarin failed to maintain PVT reductions achieved when danaparoid was discontinued.

### 4.1.4 Indirect comparison of danaparoid with other anticoagulants

Due to the lack of adequate non danaparoid and or AT controls an indirect comparison of pooled PVT treatment outcomes with various other drug treatment strategies has been made in Table 7. These data [95–107], however, lack consistency in describing PVT treatment outcomes. Hence it was necessary to express the results as complete and $\geq 50\%$. Despite this restriction it appears that clinically relevant PVT resolution, i.e. complete or $\geq 70\%$ recanalisation, occurred in 73% of danaparoid treated patients compared with $<42\%$ for no treatment, $<62\%$ for sulodexide and $<67\%$ for the LMWH. It is not possible to calculate for warfarin but it is also in likely to be in the region of 70%. Thus the efficacy of danaparoid is at least as good as warfarin and the LMWH. However the frequencies of no change or progression of the PVT and bleeding was much lower with danaparoid.

Comparison with non-danaparoid controls other than AT is confounded by: the fact that only two small studies [54, 58] used such controls. One study tested danaparoid prophylaxis and found that no PVTs in the 11 danaparoid treated patients but 2 in the 32 patients receiving AT only. The two PVTs and seven from a prior ‘testing’ cohort in this study were successfully treated with danaparoid. In a study of cirrhosis related PVT [54] danaparoid successfully managed all eight PVTs in its treatment group but of the seven UFH + Urokinase controls only five (71.4%) responded favourably and the two non-responders died of liver failure within 3 months of treatment. While there is little evidence from non-danaparoid controls in the danaparoid studies there is evidence based on the use of the heparins and VKA that anticoagulation increases the chance of recanalisation of PVT. However if recurrences are to be prevented it is also necessary to follow-up with long term outpatient anticoagulation. This has largely been left to the VKAs but more recently the oral direct oral anticoagulants (DOACs) have also become available.
Danaparoid Sodium: A Review of Its Use in Hepatic Thrombotic Disorders
DOI: http://dx.doi.org/10.5772/intechopen.103851

5. Danaparoid prophylaxis of post-transplant thrombotic disorders

The diagnosis of SOS is usually based on the Baltimore or Seattle criteria, and not every publication—especially single case reports or meeting abstracts, reveals which was used. The main difference between these two diagnostic guidelines is the inclusion of hyperbilirubinemia in the former. This seemingly small difference can result in great differences in important outcome events such as TRM, OS and MOD/MOF frequencies [108] when applied within the same population cohort. The European Society for Blood and Marrow Transplantation (EBMT) has attempted to rationalise this by applying the two sets of criteria to early and late SOS since hyperbilirubinemia is often absent in late SOS but a grey area remains and the change has yet to be clinically validated. Such validation is necessary since it appears to have a great influence on disease progression and the outcomes of specific treatment modalities.

5.1 Population exposure

Danaparoid has been evaluated in at least 524 patients for the prevention of SOS and/or TA-TMA after HSCT. All eight reports [108–115] come from Japan. Malignancies, particularly haematogenous cancers, formed about 80% of the reasons for HSCT. The non-malignant reasons were mainly aplastic anaemia, adrenoleukodystrophy and mucopolysaccharidoses. The subjects presented with a wide spectrum of underlying clinical disorders and had followed a course of chemotherapy (the conditioning regimen) or radiotherapy. In addition they had or were still receiving prophylaxis against GvHD and a cocktail of prophylactic medication.

<table>
<thead>
<tr>
<th>Antithrombotic treatment</th>
<th>n</th>
<th>Outcome of PVT treatment</th>
<th>Bleeding events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Extent of PVT resolution</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complete</td>
<td>≥70%</td>
</tr>
<tr>
<td>LMWHs²</td>
<td>298</td>
<td>86</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31.6%</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>121</td>
<td>82</td>
<td>83.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.2%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Sulodexide</td>
<td>32</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23.8%</td>
<td>38.1%</td>
</tr>
<tr>
<td>None</td>
<td>209</td>
<td>7</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.6%</td>
<td>38.6%</td>
</tr>
<tr>
<td>Danaparoid</td>
<td>357</td>
<td>118</td>
<td>158</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33.1%</td>
<td>44.3%</td>
</tr>
</tbody>
</table>

nc = no change, TE = thrombi, LMWHs = low molecular weight heparins.
⁴LMWH unspecified, enoxaparin and nadroparin.
³Only >50% resolution data for all studies.
²In one study of 20 patients data for <50% resolution and recurrence were combined (12 = 60.0%) hence the study has been excluded from the calculation.

Table 7.
Comparison of pooled published non-danaparoid PVT outcomes with pooled danaparoid outcomes.
to prevent BMT rejection and infection. Many of these drugs cause SOS or TA-TMA because of their hepato- and renal toxicity.

Japanese investigators have compared danaparoid use in both indications with standard prophylaxis using AT and/or ursodeoxycholic acid (UDCA) with or without antithrombotic co-medication. Defibrotide (DF) the standard therapy for SOS/TA-TMA treatment is also increasingly used for their prevention but there has not been a direct comparison with danaparoid.

The 197 patients in 2 comparative studies were adults [108] or mostly adults (median age 48 years, range 16–70 years) [109], as was one of the single cases reported [115]. The remaining studies and case reports of 326 patients were performed exclusively or mostly in children (age range < 1–18 years). In the only two studies with data males appeared to predominate (64.2%).

5.2 Study

The dosing regimens for danaparoid (provided in all but one case series and a single case report), dalteparin and UDCA in adults and children in the remaining reports are shown in Table 8. For danaparoid the adult regimen 2500 U/day follows that approved for DIC treatment in Japan and is close to the lower limit of the recommended dosing range for thrombosis treatment. This has been adapted for use in children and the 60–70 U/Kg/day is similar to that used for paediatric (V)TE treatment [116]. However this is equivalent to 4200–4900 U/day for a 70 kg adult, twice the dosing intensity received by adults for SOS/TA-TMA prevention.

5.3 Results

Many studies concentrated on SOS without mention of TMA, hence it is not known if TA-TMA was absent or not considered. The efficacy outcomes of these prophylactic studies with danaparoid were usually mainly expressed as outcome survival (OS) and treatment related mortality (TRM). All efficacy and bleeding outcomes are summarised in Table 9.

<table>
<thead>
<tr>
<th>SOS/TA-TMA prophylaxis regimen</th>
<th>Dosing regimens of danaparoid and active controls used for SOS/TA-TMA prophylaxis¹</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Dosing regimen</td>
<td>n</td>
</tr>
<tr>
<td>Danaparoid used alone</td>
<td>164</td>
<td>1250 U b.d., i.v.</td>
<td>0</td>
</tr>
<tr>
<td>Danaparoid (+ UDCA)</td>
<td>33</td>
<td>1250 U o.d., i.v.</td>
<td>223</td>
</tr>
<tr>
<td>Dalteparin used alone</td>
<td>59</td>
<td>3000 IU/day as i.v. infusion</td>
<td>0</td>
</tr>
<tr>
<td>Dalteparin (+ UDCA)</td>
<td>52</td>
<td>2500–3500 IU/day</td>
<td>96</td>
</tr>
<tr>
<td>UDCA used alone</td>
<td>195</td>
<td>600 mg/day</td>
<td>0</td>
</tr>
<tr>
<td>UDCA + antithrombotic</td>
<td>85</td>
<td>300–600 mg/day</td>
<td>210</td>
</tr>
</tbody>
</table>

b.d. twice daily, o.d. once daily, i.v. = intravenous, UDCA = ursodeoxycholic acid.

¹for 1 adult and 103 children no dosing regimen is available.

Table 8.

Dosing regimens used for danaparoid and controls for SOS/TA-TMA prophylaxis.
Danaparoid Sodium: A Review of Its Use in Hepatic Thrombotic Disorders
DOI: http://dx.doi.org/10.5772/intechopen.103851

Not all parameters were addressed in each of the seven studies therefore % frequency calculations have been corrected by the available data. This indirect comparison suggests that danaparoid reduces SOS/T-A TMA frequency in patients undergoing HSCT at least as well as a LMWH and UDCA with a lower frequency of bleeding at the dosing regimen used. More importantly it appears that danaparoid ± UDCA reduced TRM. Unfortunately the study with a UDCA treatment only control [99] did not provide information on TRM or OS development and for an unexplained reason halved the dose of danaparoid to 1250 U o.d.

### 5.4 Adverse events

The frequency of major bleeding events was lowest in patients receiving danaparoid. The development of GvHD was only mentioned in two study reports with grossly disparate results (see Table 9) between anticoagulant alone or combined with UDCA. One dalteparin treated subject developed HIT [105] but there is no record of how this was treated. Two danaparoid treated patients developed DIC. Of the 16 patients undergoing allogenic SCT for Adrenoleukodystrophy [108] transient haemolytic anaemia (2), engraftment syndrome (9) and viral reactivation developed all of which improved with specific treatment or supportive care while danaparoid treatment continued.

Of the 5 specifically paediatric studies three [110, 111, 114] reported no post-BMT complications and two [112, 113] reported 27 patients (8.3%) with SOS, TA-TMA or DIC associated with sepsis or engraftment syndrome. All were successfully treated with recombinant thrombomodulin.

<table>
<thead>
<tr>
<th>Antithrombotic and/or UDCA</th>
<th>n</th>
<th>SOS</th>
<th>TA-TMA</th>
<th>TRM</th>
<th>OS</th>
<th>GvHD</th>
<th>MB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danaparoid only</td>
<td>255</td>
<td>23/255</td>
<td>11/255</td>
<td>14/255</td>
<td>191/255</td>
<td>51/164</td>
<td>4/164</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.0%</td>
<td>4.3%</td>
<td>5.5%</td>
<td>74.9%</td>
<td>31.3%(^3)</td>
<td>2.4%</td>
</tr>
<tr>
<td>Danaparoid + UDCA</td>
<td>268</td>
<td>24/202</td>
<td>nd</td>
<td>2/114</td>
<td>188/235</td>
<td>5/77</td>
<td>6/211</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.9%</td>
<td>1.8%</td>
<td>18.0%</td>
<td>6.5%(^2)</td>
<td>2.8%</td>
<td></td>
</tr>
<tr>
<td>Dalteparin only</td>
<td>59</td>
<td>13/59</td>
<td>nd</td>
<td>12/59</td>
<td>29/59</td>
<td>24/59</td>
<td>6/59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22.0%</td>
<td>20.3%</td>
<td>49.2%</td>
<td>40.7%(^2)</td>
<td>10.2%</td>
<td></td>
</tr>
<tr>
<td>Dalteparin + UDCA</td>
<td>148</td>
<td>22/148</td>
<td>nd</td>
<td>17/86</td>
<td>56/96</td>
<td>13/86</td>
<td>4/47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14.9%</td>
<td>19.8%</td>
<td>58.3%</td>
<td>15.1%(^4)</td>
<td>8.5%</td>
<td></td>
</tr>
<tr>
<td>UDCA only</td>
<td>195</td>
<td>28/195</td>
<td>nd</td>
<td>16/195</td>
<td>nd</td>
<td>nd</td>
<td>10/195</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14.4%</td>
<td>8.2%</td>
<td></td>
<td></td>
<td></td>
<td>5.1%</td>
</tr>
</tbody>
</table>

Dan = danaparoid, (LMW)/H = low and unfractionated heparins, MB = major bleeding, nd = no or unclear data, OS = outcome survival, SOS = sinusoidal obstruction syndrome, TA-TMA transplant associated thrombotic microangiopathy, TRM = treatment related mortality, UDCA = urso-deoxycholic acid.
\(1\) early and late refer only to TA-TMA <2 weeks or ≥4 weeks respectively, and to TRM ≤3 months or 2-5 years respectively, according to the publications with data on either or both.
\(2\) nd = no data or in some cases insufficient clarity of data (mortality rate compared in terms of p values or cumulative frequency charts).
\(3\) total is for only acute GvHD (grade II-IV) at 3 months.
\(4\) total is for acute GvHD (grade II-IV) at 3 months plus chronic GvHD.

Table 9. Pooled treatment outcomes of SOS/TA-TMA prevention in danaparoid studies.
6. Other treatments for SOS/TA-TMA

Currently while several drugs for SOS prophylaxis are available there is no clear treatment to prevent TA-TMA.

6.1 The heparins

Despite some reports of successful prophylaxis with UFH and LMWHs a meta-analysis and systematic review of their use [117] found no significant reduction in risk of SOS. Safety also appeared to be an issue when used in patients with gastrointestinal varices or thrombocytopenia or renal dysfunction, especially when they were combined with lipo-prostaglandin E1 or UDCA. Hence heparin is no longer recommended for SOS prophylaxis [20].

6.2 Ursodeoxycholic acid

UDCA, currently the most widely used drug for SOS prevention, is a natural bile acid that is capable of reducing the toxicity of its companion bile acids in cholestatic liver diseases. In inflammatory disorders it can ‘attenuate the pro-inflammatory cytokine environment through decreased expression of TNF-α, interleukins 1 and 2, and interferon-γ, thereby minimising endothelial injury occurring in HSCT associated with the cytokine storm [117]. UDCA is safe and not only lowers the frequency of SOS but also of TRM and appears to have a small effect in reducing the development of GvHD.

<table>
<thead>
<tr>
<th>Antithrombotic and/or UDCA</th>
<th>n</th>
<th>SOS</th>
<th>TRM</th>
<th>OS</th>
<th>GvHD</th>
<th>MB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danaparoid only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>255</td>
<td>9.0%</td>
<td>5.5%</td>
<td>74.9%</td>
<td>31.1%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Adults</td>
<td>164</td>
<td>10.4%</td>
<td>8.6%</td>
<td>65.2%</td>
<td>31.1%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Children</td>
<td>91</td>
<td>6.8%</td>
<td>0.0%</td>
<td>92.3%</td>
<td>nd</td>
<td>0.0%</td>
</tr>
<tr>
<td>Danaparoid + UDCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>268</td>
<td>11.9%</td>
<td>nd</td>
<td>74.6%</td>
<td>6.5%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Adults</td>
<td>33</td>
<td>15.2%</td>
<td>nd</td>
<td>65.2%</td>
<td>nd</td>
<td>3.0%</td>
</tr>
<tr>
<td>Children</td>
<td>235</td>
<td>4.1%</td>
<td>1.8%</td>
<td>80.0%</td>
<td>9.1%</td>
<td>1.5%</td>
</tr>
<tr>
<td>UDCA only</td>
<td>1441</td>
<td>14.4%</td>
<td>8.2%</td>
<td>nd</td>
<td>nd</td>
<td>5.1%</td>
</tr>
<tr>
<td>DF ‘only’</td>
<td>1371</td>
<td>4.9%</td>
<td>19.0%</td>
<td>72.3%</td>
<td>22.2%</td>
<td>22%</td>
</tr>
<tr>
<td>DF + UDCA</td>
<td>56</td>
<td>1.9%</td>
<td>1.9%</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
</tbody>
</table>

Dan = danaparoid, DF = defibrotide, GvHD = graft v host disease, (LMW)H = low and unfractionated heparins, MB = major bleeding, nd = no or unclear data, OS = outcome survival, SOS = sinusoidal obstruction syndrome, TA-TMA transplant associated thrombotic microangiopathy, TRM = treatment related mortality, UDCA = ursodeoxycholic acid.

1 From Table 9 and additional data from non-danaparoid studies.
2 Assessed at D + 100 and/or 2–5 years after HSCT.
3 Assessed at D + 100 after HSCT.
4 From Refs. [119, 120].
5 From Ref. [121].

Table 10. Pooled results of SOS prophylaxis studies.
of GvHD [118]. It is occasionally used in combination with UFH and LMWHs but there is little evidence that they improve its efficacy. Outcomes of UDCA use shown in Table 10 are derived from several studies and reviews [117–120, 122].

6.3 Defibrotide

This oligodesoxyribonucleotide extracted from porcine intestinal mucosa has numerous antithrombotic, EC protective, fibrinolytic, anti-ischaemic and angiogenic activities. Its clear benefits for the treatment of SOS have led to approval by the FDA for this indication. More recently DF has been investigated for SOS prevention with mixed results [121, 123–127]. The inter-study variance may be due to the different dosing regimens used (including occasional co-medication with UDCA) and different intervals between diagnosis and DF treatment initiation. Greater success has been reported using initiating DF earlier [128] after SOS diagnosis or combining it with UDCA [129].

6.4 Results

The outcomes of non-danaparoid studies with UDCA and DF for the prevention of SOS (and where mentioned TA-TMA) are summarised and compared with danaparoid in Table 10. The data for danaparoid only and in combination with UDCA have been separated because of the apparent greater. Impact of comedication with UDCA on the frequencies of TRM and GvHD. For many studies it is unclear to what extent TA-TMA might have been present and therefore contributed to caused morbidity or death since it was mentioned. In addition not all parameters were assessed in all studies hence percentages are based only on the available data. The frequency of haemorrhages with DF in several studies [130, 131] has been as high as 22%, but in one study [130] was the same as the unspecified controls. So there remains some confusion regarding its safety.

Interestingly the danaparoid efficacy appears to be better in children than in adults, perhaps related to the use of a higher dosing intensity/kg body weight.

7. Discussion

7.1 Danaparoid dosing

Danaparoid dosed at 1250 U b.d., i.v. in adults and 30 U/kg body weight b.d., i.v. in children, appears to be effective and safe for the treatment of PVT or prevention of SOS and TA-TMA. Despite the relatively high danaparoid dosing intensity used in children there were no reports of bleeding complications in any of the studies and case reports supporting its safety in these vulnerable subjects.

Nevertheless, the intermittent dosing regimen based on DIC treatment used for both adults and children is unlikely to be optimal since it takes 2–3 days to reach steady state drug levels, produces post-injection peak levels of drug that could cause bleeding in high risk patients and pre-injection troughs with insufficient thrombosis protection. The antithrombotic action of danaparoid is shared between the 5% by weight HA-HS and the 80% by weight NA-HS subfractions of danaparoid with greatly different half-lives—25 and 7 h respectively. Hence by the time the next 12 hourly danaparoid injection is due there is much less of the NA-HS left in the circulation even at steady-state pharmacokinetics. This subfraction is largely responsible for the
anti-inflammatory and immunosuppressive actions of danaparoid [34]. Hence for TE treatment PK modelling was used to determine a dosing regimen that provided circulating therapeutic danaparoid levels as quickly as possible and maintained the natural ratios of the HS-HS and NA-HS constituents continuously. The ideal regimen was found to be an i.v. loading dose of 2250 U (body weight adjusted—1250 U if <55 kg and 3000 U if >90 kg), followed by a continuous i.v. infusion of 400 U/h × 4 hours, followed by 300 U/h × 4 hours, followed by the maintenance infusion rate of 150–200 U/h for as long as considered necessary. This regimen immediately attains and maintains the target plasma anti-Xa activity range of 0.4 and 0.8 U/mL and outside Japan is approved for patients with thrombosis. This can be important for increasing the efficacy of danaparoid not only for PVT treatment but also for SOS/TA-TMA prevention since the inflammatory disturbances should respond better to the continuous presence of the NA-HS subfraction of danaparoid. If a bleeding risk is present then the daily danaparoid dosing intensity, can be lowered by reducing the loading dose size by 25%–50% and the maintenance infusion rate to 100–125 U/h.

7.2 PVT treatment

Due to differences in detail between guidelines for the management of PVT, some confusion remains surrounding attempts to evaluate and compare its alternative treatment strategies. Many clinical factors such as the distribution of Child-Pugh status, the cause of cirrhosis, the frequency of cirrhosis, varices or hepatocellular carcinoma, the distribution of PVST and grade of vessel obstruction at the time of antithrombotic initiation, the age of the thrombus, the presence of infection, the inclusion of different antithrombotics and their combination with either AT or UDCA. Furthermore there is a need to standardise what is considered a ‘good clinical treatment outcome’ for PVT. Is it complete recanalisation only [94], or ≥70% partial recanalisation [58] or is ≥50% [95] sufficient. What assessment criteria for an effect on PVT is best—reduction thrombus size, in vessel volume or in portal hypertension or a combination of these possible outcomes? For how long should study end-points be assigned to the original treatment drug—2 weeks, 4 weeks or 3 months after switching to an alternative long-term antithrombotic? Such details are crucial for adequate drug comparisons. Even age and gender distributions of studies are not usually considered in the choice of studies included in meta-analyses but can have a profound effect on the clinical responses to treatment. For these reasons I am not convinced of the value of treatment assessment meta-analyses that are more concerned with the mechanics of study design [5, 14] than many of the above clinical issues.

The pooled results of danaparoid treatment suggest that it possesses at least the same efficacy as AT and its performance does not seem to be enhanced by the addition of AT. Danaparoid appears to be safe even in patients with moderate to severe hepatic dysfunction and extensive varices. A Japan-wide survey performed in 2018 [132], revealed that 46% of the 539 patients included in the responses were treated with danaparoid alone or + AT. A comparison of the outcomes of the six most common treatment regimens i.e. heparin, warfarin, danaparoid, heparin + warfarin, danaparoid + antithrombin and no anticoagulant, showed that warfarin produced the highest complete PVT disappearance rate (about 50% compared with danaparoid at 30%). However, the rate of PVT disappearance plus reduction (not defined) was highest for danaparoid about 80% compared with just over 70% for warfarin. The rates of no change and PVT extension were both lowest for danaparoid at about 18% and 2%
respective. Furthermore, PVT disappearance rates with danaparoid + AT while better than those of heparin were inferior to those achieved with danaparoid alone.

7.3 SOS/T A-TMA prevention

Apart from one study [108] there appears to be agreement on the prophylactic dosing regimens of danaparoid used for adults or children to prevent SOS/TMA. Children above 2 years appear to require almost double the dosing intensity used in adults to achieve the same plasma anti-Xa levels [116], but it does not appear to have compromised safety in terms of bleeding and side-effects.

The study [109] that did not use UDCA co-medication recorded a higher rate of acute GvHD (grades II–IV) for both danaparoid alone and dalteparin alone compared with the much lower rates recorded for both drugs when combined with UCDA in the other major comparative study [110]. Whether this reveals a true effect of UDCA or a centre/patient cohort treatment bias requires further investigation. Acute GvHD is a risk factor for TA-TMA, thus it is unfortunate that the investigators [109] comparing a low intensity danaparoid + UDCA with dalteparin + UDCA and UDCA alone, although detailing measures taken to prevent GvHD, did not refer to it again.

Two comparative studies concluded that danaparoid: ‘reduces the incidence of transplant associated microangiopathies’ in adults [105] or ‘lowers TRM after stem-cell transplantation in children’ [110] since in both studies danaparoid was superior to dalteparin with or without UDCA. Whether or not these results are due to the antithrombotic action of danaparoid alone or a combination with its anti-inflammatory effects has not been investigated. The latter is likely in view of the positive results of danaparoid use in HIT [133], sepsis [134], APS [135, 136] and paroxysmal nocturnal haemoglobinuria [137].

7.4 HIT development

Although one patient exposed to danaparoid developed thrombocytopenia it was not reported to be due to HIT. However, of 214 control patients receiving UFH or a LMWH in the danaparoid studies a case of HIT was recorded [109].

7.5 Alternative therapies

Long term antithrombotic treatment appears to be crucial for preventing PVT recurrences and the VKAs have until recently been the method of choice. However, despite one investigator [56] calculating that warfarin doubled the time of PVT recurrence from 1 to 2 years, eight others [55–59, 61, 62, 67] reported that follow-up treatment with warfarin after initial danaparoid failed to maintain PVT reductions achieved when danaparoid was discontinued. A comparison of warfarin v edoxaban following danaparoid PVT reduction showed that only edoxaban maintained or reduced the already achieved vessel volume reduction.

Whether any pharmaceutical prophylaxis for SOS/TATMA is effective remains controversial, but it appears possible with current therapy options and UDCA is now recommended by the EBMT Handbook and the British Committee for Standards in Haematology/British Society for Blood and Marrow Transplantation guidelines. It is unclear if UDCA improves the efficacy of danaparoid but it appears to improve the safety of DF in patients with a high risk of developing SOS. It is also unclear who should receive prophylaxis and which treatment is most likely to offer the best
risk–benefit ratio so it is interesting that danaparoid is especially effective in reducing both SOS and TRM in children and increases their OS. DF appears to be efficacious in preventing SOS but at the expense of a high bleeding rate (perhaps related to its pro-fibrinolytic activity). A large prospective Phase III controlled trial of DF v best management without DF was discontinued in 2018. The manufacturers report of the interim analysis of that study concluded ‘it would be highly unlikely to reach statistical significance for the primary end-point of SOS survival at Day +30 post HSCT in the final analysis if the study were to complete enrolment’ [138]. So that there remains confusion around the evidence for DFG suitability for SOS prophylaxis. Danaparoid however, appears to be safe even when compared with UDCA.

7.6 Cost calculations

It is difficult to generalise about the cost effectiveness of different pharmacological strategies for SOS prevention due to the unclear duration of drug administration and inter-country differences in basic drug and hospitalisation costs. In Europe the current price of 10 × 750 U ampoules of danaparoid sodium varies between € 975 and € 1250 (price discounting not considered), having been much less when originally approved for DVT prophylaxis. Thus per patient treatment of PVT at 3 A/day for 2 weeks could cost about € 5250. For SOS/TA-TMA prophylaxis danaparoid administration at 3–4 A/day for the median 2 months treatment duration would cost between € 17,500 and € 30,000. This assumes long term follow-up treatment with a VKA or DOAC to prevent recurrence of the PVT. For DF dosed at 25 mg/kg/day divided into 4 doses the drug cost is about the same as danaparoid. DF is known to reduce hospital stay but this effect is somewhat offset by the fact that unlike danaparoid many patients do not complete their treatment due to adverse events, particularly bleeding and these events incur the costs of additional investigations and treatment. One single centre study [139] found an SOS incidence of 7.4% and a TRM of 19%. Their cost effectiveness analysis led to the conclusion that ‘prophylactic DF for children at risk of SOS was not cost-effective with respect to TRM and length of hospital stay’. By contrast the UDCA cost per patient (in 2013) was about € 400 for 2 months treatment [140]. UDCA can be a lifelong treatment but its cost price may have risen since then. Which is the most cost-effective for the management of SOS/TA-TMA hinges on the desired outcome—mere prevention or reducing TRM and increasing OS.

8. Conclusions

Problems associated with study design, diagnostic criteria, end-point choice and evaluation, and use of single or several pharmacological agent, make it difficult to evaluate and compare the outcomes of different drug trials in hepatic thrombotic disorders. Despite the absence of studies against placebo/no treatment to establish absolute efficacy, comparative studies versus a LMWH suggest that danaparoid is effective and safe for the treatment of PVT and not only prevents SOS and TA-TMA but reduces TRM and increases OS after HSCT. It is unclear if the efficacy of danaparoid is improved with the addition of AT or UDCA. Danaparoid has a high cost of treatment but a cost-efficacy analysis has not been performed. Its safety, particularly the low haemorrhagic risk, may offset some of these costs.
Given the potentially fatal outcomes of hepatic thrombotic disorders, the ease of administration of danaparoid, its apparent efficacy and safety in patients with a high bleeding risk, danaparoid merits further investigation in the management of hepatic thrombotic disorders. However, the dose of danaparoid needs to be optimised.

There remains a great need for sufficiently powered, double-blind, randomised controlled trials, with well-defined end-points relevant for clinical practise, to evaluate the short and long-term effects of currently available antithrombotics used in the management of hepatic thrombotic disorders.

**Conflict of interest**

The author declares no conflict of interest.
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