Experience of Danaparoid to Treat Vaccine-Induced Immune Thrombocytopenia and Thrombosis, VITT

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Research Article

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Abstract

Background: Vaccine-induced immune thrombocytopenia and thrombosis (VITT) is triggered by nCOV-19 adenovirus-vectored vaccines against SARS-CoV2. Pathogenesis has been mainly related to platelet activation via PF4-reactive antibodies that activate platelets and cross-react with heparin. Data concerning optimal anticoagulation are anecdotal, and so far, there are scattered reports of danaparoid use in VITT management. Danaparoid has good efficacy and safety in treatment of heparin-induced thrombocytopenia. We report here our experience of the administration and monitoring danaparoid in VITT. *Methods:* We diagnosed six hospitalized cases of definite or probable VITT, based on the international diagnostic guidance. All VITT-related data were from the local electronic medical and laboratory record system and were analyzed with IBM SPSS Statistics. *Results:* Predominately women in their late forties developed VITT on average 24 days (range 9-59) after the first ChAdOx1 dose. Clinical presentation included single or multiple venous and/or arterial thrombosis, moderate thrombocytopenia and high D-dimer levels. After detecting PF4 antibodies subcutaneous danaparoid was our first-line antithrombotic treatment with an average duration of three weeks. The median plasma anti-FXa activity was in the lower part of the therapeutic range and during the first week of danaparoid administration clinical symptoms, platelet counts and fibrin turnover resolved or significantly improved. The average duration of hospital admission was 10 days (2-18). One patient died but the other five recovered completely. *Conclusions:* The clinical outcomes of our small cohort align with the earlier published reports, and support danaparoid as a rational option for the initial anticoagulation of VITT patients.

Introduction

Global outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections emerged early in 2020. From the very beginning of this pandemic development of an effective vaccination has been a great priority. Amongst different possible mechanisms of anti-viral antibody induction, adenovirus-vectored vaccine has been one of the most widely used technologies among manufacturers [1,2]. In Finland, all adenoviral COVID-19 vaccinations have been performed with the ChAdOx1 nCOV-19 (Vaxzevria®, Astra Zeneca). By the end of the May 2021, the number of first ChAdOx1 doses was 358 000 and 55 000 people had completed their vaccination program with the two ChAdOx1 doses[3].

The vaccination program has been critical in control of the pandemic due to its robust efficacy and safety[1,2,4,5]. However, in March 2021, three months after the initiation of the vaccination program, concerns arose over emerging reports of immune thrombotic syndromes after nCOV19 adenoviral vector vaccination[6,7]. Some patients suffered combined thrombocytopenia and a clinical course of multiple and/or unusually sited thrombosis, including cerebral venous sinus (CVST) and splanchnic vein thrombosis, as well as arterial events[6,7,8]. Most typical biomarkers identified included low platelet and high fibrin D-dimer levels and platelet-activating anti-PF4 antibodies (by ELISA method, rapid immunoassays may be negative) without previous heparin exposure[8,9]. Clinical presentation mimicked the condition previously reported as autoimmune or spontaneous heparin-induced thrombocytopenia (aHIT)[10]. After

various initial names the condition is now known as vaccine induced immune thrombocytopenia and thrombosis (VITT) [9] or thrombosis with thrombocytopenia syndrome (TTS) by WHO[11].

Platelet factor 4 (PF4), originating from platelet alpha-granules, is a chemokine with a high affinity for polyanions, including heparin. It has several roles in inflammation, wound repair, and neutralization of endothelial heparin-like molecules[10,12]. Heparin independent antibodies against PF4 may strongly and inappropriately activate platelets via the platelet Fc receptor signaling with procoagulant effects, leading to severe thrombosis[10]. They may also cross-react with heparin if it is used for treatment.

Treatment options of VITT are based on the experience from other anti-heparin/PF4 antibody –related disorders of HIT and aHIT. Anticoagulation with preferably a non-heparin agent is required, and an expert consensus also recommends administration of intravenous immune globulin (IVIG) to restrain the pathological platelet activation[9,10]. The optimal anticoagulant for the initial administration is unclear, direct parenteral thrombin inhibitors, argatroban and bivalirudin, as well as danaparoid and fondaparinux are options, and the direct oral anticoagulants (DOACs) appear to be suitable, at least in the later course of the disease[9,10,11].

Danaparoid sodium is a non-heparin glycosaminoglycan antithrombotic that inhibits thrombin generation. It consists mainly of heparan sulfate with small amounts of dermatan and chondroitin sulfates. Its low overall negative charge density compared with heparin does not allow it to form the ultra-large complexes with PF4 necessary for the spontaneous induction of the platelet activating antibodies that characterize HIT. In addition, the absence of heparin-like domains apart from a minor amount of the pentasaccharide sequence necessary for AT binding, explains its very low propensity to cross-react with anti-PF4/heparin antibodies. It has been successfully used for HIT and its alternative administration routes (intravenous and subcutaneous) provide practical options for both inpatient and outpatient administration[13]. Unlike other agents, danaparoid has been reported to detach PF4 from the platelet surface and disrupt PF4 containing antigen complexes thus interfering with platelet-activation by immune complexes[10]. Hence theoretically, danaparoid should have a direct influence on VITT pathogenesis beyond its anticoagulant action[10,14]. Our local guidance for acute treatment of HIT include danaparoid as an initial option for anticoagulation and it is commonly administered in this indication, the subcutaneous dosing ranging between 750-1500 U 2-3 times a day[15]. There are a few reports of danaparoid use for treatment of HIT during COVID-19[16,17] or thrombosis post vaccination[18-21]. In this study, we want to share our experience of its use to treat VITT.

Patients And Methods

Our adapted diagnostic guidance requires previous nCOV19 adenovirus-vectored vaccination (usually 4-30 days before presentation), evidence of new thrombosis and thrombocytopenia and a positive anti-heparin/PF4 antibody ELISA test to confirm a diagnosis of VITT[22,9].

Our study was accepted by the Helsinki University Ethical Committee (HUS/1238/2020). Written informed consents were received from patients 2 to 6 and from a close relative of patient 1. We collected all

available VITT episode -related clinical and laboratory data from local electronic medical and laboratory record systems (EPIC Apotti, Weblab Clinical). IBM SPSS Statistics 25 was used to describe and analyze the collected data (Descriptive Statistics package) and Prism to visualize the data.

Our main focus was to evaluate all patients' medical history, date of vaccination, prior heparin exposure (< 6 months before current presentation), initial clinical presentation with laboratory and coagulation biomarker statuses, initial antithrombotic medication and detection of anti-heparin/PF4 antibodies (ELISA, Asserachrom HPIA, Diagnostica Stago, France). In addition, administration of intravenous immune globulin (IVIG), clinical course during hospital admission, administration of danaparoid and its anti-FXa -activity (U/mL, HemosIL Liquis Anti-Xa, Mediq

Suomi Oy), and final clinical outcome were recorded when examining the raw health information data. The aim of the anti-FXa –activity levels during subcutaneous danaparoid administration was 0.3-0.5 U/mL.

With respect to the systematic coagulation analysis, we screened coagulation times including prothrombin time (Medirox Owren's PT (%) Medirox, Nyköping, Sweden), activated partial thromboplastin time (APTT (seconds) Actin FSL®, Siemens) and thrombin time (seconds, BC Thrombin reagent, Siemens). Antithrombin activity (AT, (%), was captured with a chromogenic assay (Berichrom Antithrombin III). We also analyzed fibrinogen level (g/L, Clauss method, HemosIL Q.F.A. Thrombin, Werfen, Barcelona, Spain), fibrin D-dimer level (mg/L, HemosIL D-Dimer HS 500), coagulation factor VIII activity (FVIII:C, IU/dL, one-stage clotting assay, Pathromtin SL and FVIII Deficient Plasma)). Furthermore, fibrin D-dimer to fibrinogen ratio was calculated.

We collected available data at following 5 time points: the admission day (time point I) and dynamically from days 1-3 from admission (time point II), days 4-7 (time point III), days 8-14 (time point IV) and days 15-30 (time point V). These time points were matched with the dynamics of platelet count and an acute phase reactant C-reactive protein (CRP).

Patient 1

40-year-old man with history of hypertension, obesity (145 Kg and BMI 40), type 2 diabetes, achalasia, and sleep apnea, was admitted to hospital 9 days after his first dose of ChAdOx1 with complaints of fever, arthralgia, and chest pain. A thrombocytopenia (platelet count 40 $x10^9$/L) and myocardial infarction (NSTEMI) with myocarditis as differential diagnosis were identified

and C-reactive protein was elevated as a sign of inflammation. Coagulation status was pathological because of extreme fibrin turnover (D-dimer > 128 mg/L) and low fibrinogen (1.0 g/L). Patient was transferred to the Cardiac Care Unit (CCU) and the acute coronary syndrome medication was dose-restricted because of the thrombocytopenia.

Later in the CCU, patient´s neurological presentation raised concerns and contrast head CT scan was diagnostic for CVST with extensive clot burden. The scan also showed a secondary intracranial

hemorrhage (ICH) due to increased venous pressure. The platelet count remained low and anti-PF4 antibodies were positive by ELISA. At the time, VITT was a barely known entity.

Anticoagulation was initiated with intravenous danaparoid (loading bolus 1500 U with subsequent infusion of 250 to 330 U / h) and platelets, fresh frozen plasma and fibrinogen were supplemented because of bleeding. However, his clinical course deteriorated, and ICH extended with edematous reaction. After neurosurgical consultation, decompressive hemicraniectomy was performed, proceeded with administration of IVIG. These interventions did not lead to clinical amelioration, and the patient died two days after the admission.

Patient 2

21-year-old woman with BMI of 30.3 (94.5 Kg) was in remission from acute lymphoblastic leukemia (ALL) after allogenic stem cell transplantation. Beyond that, she had type 1 diabetes and chronic chemotherapy-related pain issues. She was admitted to hospital 12 days after her first ChAdOx1 dose with recurrent headache and new thrombocytopenia (platelet count 54 x 10^9/L). Her coagulation screen included elevated D-dimer (12 mg/L) and mildly elevated FVIII (195 IU/dL). Head MRI scan revealed extensive CVST.

She was admitted to the neurological inpatient department with tinzaparin for CVST treatment. However, her platelet count remained low. On day 5 after admission a coagulation specialist advised ELISA testing for anti-PF4 antibodies, which was positive, while a previous rapid immunoassay had been negative. Diagnosis of VITT was confirmed and anticoagulation was switched to subcutaneous danaparoid (1250 U x 2, later 1250 U + 750 U). Beyond that, IVIG 0.4 g/Kg/day for five consecutive days was administered. This co-treatment led to recovery of the clinical course and the thrombocytopenia. Patient was discharged after 15 days of admission with self-injections of danaparoid treatment. Two months later an MRI scan presented complete resolution of CVST and danaparoid was switched to prophylactic dose of fondaparinux for another month. The patient has fully recovered.

Patient 3

52-year-old man had dyslipidemia and aortic stenosis because of a bicuspid aortic valve. He was set to a surgical list of heart valve replacement. BMI was 24 (77 Kg). 9 days after his first ChAdOx1 dose he was admitted to hospital with headache and chest pain. Acute myocardial infarction with inferior ST-elevations was diagnosed and a simultaneous thrombocytopenia (55 x10^9/L) with extremely elevated D-dimer level (101 mg/L) were identified. He was transferred to the cardiological catheterization unit with conventional neoadjuvant antithrombotic drugs (acetylsalicylic acid, ticagrelor and recently started enoxaparin). Despite this medication the cardiologist noticed that blood coagulated extensively and fast during the procedure. Head MRI was negative for CVST, but VITT was considered, based on the experience of the cases 1 and 2, since the anti-PF4 antibody ELISA was also positive. With the VITT diagnosis IVIG 1 g/Kg/day was administered for two consecutive days, and s.c danaparoid (750 U x 2) was initiated with concomitant antiplatelet therapy. At the early phase of the admission, fibrin turnover remained high, and likely new onset portal vein and cephalic vein thrombosis were diagnosed. Danaparoid dosing was intensified (firstly to

1500 U x 2 and then to 1250 U x 2) leading to favorable clinical course with platelet count recovery and D-dimer normalization.

The patient was discharged 18 days after admission with ambulatory self-injected danaparoid and peroral ticagrelor medications. Anticoagulation was switched to fondaparinux after 1 month of treatment and since the initial episode, no thrombotic symptoms occurred. Afterwards, patient was commenced on indefinite apixaban 2.5 mg BD with concomitant ticagrelor.

Patient 4

60-year-old woman had asthma and reflux esophagitis and a history of bilateral pulmonary embolism (PE) 5 years earlier. Her BMI was 29.8 (90 Kg). 19 days after her first ChAdOx1 dose she developed bilateral pulmonary embolism and left tibial vein thrombosis. At this point the platelet count was normal, and dalteparin anticoagulation was initiated.

41 days after vaccination she was re-admitted due to the onset dizziness, headache, and nausea. CVST was excluded by contrast CT scan, but new thrombocytopenia (54 x10^9/L) was detected. Her coagulation profile was quite indifferent with only marginally elevated D-dimer (1.1 mg/L) and FVIII (258 IU/ dL). However, suspicion of VITT with classical HIT as a differential diagnosis was raised, and anti-PF4 antibodies were positive by ELISA.

After subcutaneous danaparoid 1500 U x 2 was started platelet levels normalized and her subsequent clinical course improved in a couple of days without IVIG. The patient was discharged on Day 7 after switching to oral dabigatran since indefinite anticoagulation was recommended because of the recurrent episode of PE. She fully recovered.

Patient 5

68-year-old woman, without medical history, sought medical attention 16 days after the first ChAdOx1 dose with complaints of recurrent headache. New thrombocytopenia (65x10^9/L) and markedly elevated D-dimer level (35 mg/L) were observed. Head MRI scan showed an extended left side CVST, and she had also a small PE with minor symptoms. VITT was immediately suspected. Danaparoid was rapidly initiated after admission and the laboratory confirmed positive anti-PF4 antibodies by ELISA. IVIG was administered and the clinical course, platelet count and D-dimer level responded favorably. One week after admission, she was discharged on ambulatory subcutaneous self-injected fondaparinux. She made a full recovery and anticoagulation was switched later to oral apixaban.

Patient 6

42-year-old woman with sleep apnea and obesity (109 Kg with BMI 38) was admitted to hospital 59 days after her first ChAdOx1 dose with recent symptoms of headache, common cold and myalgia. Initial laboratory evaluation identified a thrombocytopenia (platelet count 73 x10^9/L) and elevated C reactive

protein (70 mg/L) and D dimer (20.4 mg/L). Bilateral pulmonary embolism was diagnosed by contrast CT scan, and she was commenced on enoxaparin.

The platelet count remained low, thrombo-inflammatory activity persisted, and her clinical course did not improve. Head MRI scan revealed a left internal jugular vein thrombosis and abdominal contrast CT scan identified extended portal vein thrombosis. Anti-PF4 antibodies were negative by rapid immunoassay but due to technical reasons initial ELISA samples were lost. However, clinical suspicion of probable late onset VITT was raised and IVIG (1g/Kg for two consecutive days) together with subcutaneous danaparoid were initiated leading to recovery of the thrombocytopenia and thrombotic activity, and her clinical course gradually improved. After two weeks of danaparoid anticoagulation she was switched to oral apixaban, and she recovered fully from the episode.

Results

Clinical Data

We diagnosed five definite and one probable VITT cases in Finland between mid-March and late May 2021, and the use of this vaccine was halted in April 2021. Mean age of our predominately female (4/6) patients was 47 years (range 21-68 years). The mean elapsed time from the first ChAdOx1 vaccination to the Emergency Department contact was 24 (range 9-59) days (Table 1 and 2). Half of the patients had CVST (1, 2 and 3), but mostly also other locations of thrombosis were verified (patients 1, 3, 4, 5 and 6). Arterial events were detected in two male patients, both cases being myocardial infarction, with myocarditis as a differential diagnosis in patient 1. One patient had prior exposure to a heparin with her previous therapeutic dalteparin for a PE. Mean duration of hospital admission was 10 days (range 2-18 days). Five of the six patients fully recovered but one patient had a fatal outcome (patient 1). Thus, case mortality rate of our cohort was 16.7 %, similar to a recent report[23].

Table 1: Baseline clinical characteristics and laboratory observations

Patient	1	2	3	4	5	6
Age	40	21	52	60	68	42
Sex	M	F	M	F	F	F
Admission – days after vaccination	9	12	9	41	16	59
Prior exposure to a heparin	No	No	No	Yes	No	No
Hemoglobin (M134-167, F 117-155 g/L)	147	106	146	116	N/A	N/A
ALT (U/L) (<50 U/L)	127	12	55	55	N/A	N/A
Bilirubin (µmol/L) (< 20 µmol/L)	13	3	14	11	N/A	N/A
Creatinine (µmol/L) (50-100 µmol/L)	61	55	84	73	N/A	N/A
WBC Count (x 10^9/L) (3.4-8.2 x 10^9/L)	6.1	5.5	5.4	5	N/A	N/A
Neutrophilia or monocytosis	Yes	No	Yes	Yes	N/A	N/A
(reference values), N/A = not available						
Nadir since admission to a distant hospital						

Table 2: VITT diagnosis, location of thrombosis, antithrombotic and IVIG therapy

Patient	*1*	2	3	4	5	6
Cerebral venous sinus thrombosis	Yes	Yes	No	No	Yes	No
Multiple thromboses	Yes	No	Yes	Yes	Yes	Yes
Arterial thrombosis	Yes	No	Yes	No	No	No
Anti-PF4 Ab ELISA positivity – Days after admission	1	5	1	0	1	N/A
Initial (1-2 doses) antithrombotic treatment	enoxaparin, aspirin	tinzaparin	enoxaparin, aspirin, ticagrelol	danaparoid	danaparoid	danaparoid
IVIG	Yes	Yes	Yes	No	Yes	Yes
Duration of hospital stay (days)	2	15	18	7	7	N/A
Outcome	Fatal	Recovery	Recovery	Recovery	Recovery	Recovery
N/A = not available						

Laboratory data

The average hemoglobin level was 129 g/L (range 106-147 g/L) and all patients presented with moderate thrombocytopenia with an average count of 57 x10^9/L (range 40-73 x10^9/L, Figure 1). At the time point IV (7-14 days after admission), platelet counts had normalized to an average count of 276 x 10^9 /L (range 127-477 x 10^9 /L). General biomarkers available for 4 of the 6 patients did not identify significant liver or renal impairment. White blood cell counts were normal in all cases, but the differential analysis showed neutrophilia or monocytosis in three patients. Almost every patient presented with inflammation based on the initial CRP levels (mean 55 mg/L; range 5-139 mg/L, Figure 2). By timepoint III, 4-7 days from hospitalization, inflammation was already significantly attenuated (mean CRP 19 mg/L; range 4-50 mg/L), excluding patient 6 whose diagnosis of VITT was delayed in another hospital.

We did not detect abnormalities in coagulation times of PT, APTT, thrombin time or antithrombin levels during and after the admissions. FVIII activity was elevated in all patients, single peak level being 335 IU/dL in patient 3 at time point IV (Figure 3a). Likewise, compared with other reports of VITT coagulation abnormalities[8,9], fibrin D-dimer levels were elevated in every patient, and extensive fibrin turnover (D-dimer exceeding 30 mg/L) was detected in half of the patients (1, 3 and 5 see Figure 4a). In addition, low fibrinogen levels were identified in two patients (Figure 3b). D-dimer to fibrinogen ratio was extreme in patients 1 and 3, suggesting markedly enhanced fibrin degradation (Figure 4b).

Treatment data

Five of the six patients were administered IVIG to reduce and prevent the further pathological platelet activation (Table 2). Danaparoid therapy and its follow up showed a favorable course (Table 3). Subcutaneous danaparoid was generally initiated at the early phase of the hospital admission with an average treatment duration of 20 days (range 1-60 days) with twice daily dosing. Average initial daily dose was 2333 U (range 1500-3000 U). Median anti-FXa activity levels remained at the lower range of recommended scale, 0.3 U/mL (Figure 5). D-dimer levels after one week of danaparoid treatment significantly declined compared with the initial phase, and the one-week mean levels were 5.2 mg/L (range 1.7-11.8 mg/L). One clinically significant bleeding episode was associated with VITT as the CVST of patient 1 was complicated with progressive secondary ICH, already present before danaparoid initiation.

Table 3: Course and outcome of danaparoid treatment

Patient	1	2	3	4	5	6
Danaparoid initiation – Days after admission	1	6	2	0	0	N/A
Route of administration	iv	sc	sc	sc	sc	sc
Initial sc. daily dose (U)	No	2500	1500	3000	N/A	N/A
Anti-FXa (U/mL) Median	0.23	0.31	0.33	0.23	N/A	N/A
D-Dimer after 4-7 days of danaparoid therapy	N/A	1.7	11.8	1.9	5.2	N/A
Bleeding events	Yes	No	No	No	No	No
Outcome	Fatal	Recovery	Recovery	Recovery	Recovery	Recovery
N/A = not available						

Discussion

Our Finnish VITT cohort seems to be aligned with the earlier reports with respect to: clinical presentation, coagulation biomarker status and clinical outcome. Our mortality rate is the equal of the recently published big UK cohort`s rate (16.7 vs 22 %), and the only fatal outcome was the very first VITT case of the nation. At that time, an optimal treatment protocol, including upfront IVIG as a key for pathogenesis control, was only developing. VITT as a condition with remarkable potential for devastating outcomes calls upon rapid recognition of cases. Since the perception of this new syndrome, several thorough interim guidance has been published to help the frontline health workers and clinicians[9,11,22].

Danaparoid, most frequently administered subcutaneously in our cohort, is a reasonable option for initial VITT anticoagulation supported by previously published guidance and experience from other anti-H/PF4 antibody – related disorders [9,10,11,13]. Our study suggests that danaparoid administration together with upfront IVIG was effective for VITT treatment as five of the six patients fully recovered without significant clinical sequelae. Subcutaneous administration is more practical to handle than continuous intravenous infusions, which direct thrombin inhibitor anticoagulants require. The effective initial subcutaneous

treatment is easy extend to the ambulatory mode, if needed. However, intravenous danaparoid, even at low infusion rates provides constant antithrombotic and anti-inflammatory activity levels compared with the peaks and troughs of intermittent subcutaneous injections, and is the preferred option if clinically feasible.
Our patients´ danaparoid was administered and monitored with anti-FXa activities, which were in the lower level of the target therapeutic range. The only bleeding complication which occurred was a progressive ICH which had already presented before danaparoid treatment initiation, and the low-dose intravenous infusion with loading bolus option was probably too intensive. Intracranial bleeding during CVST has previously proved to be a significant risk factor for bad outcome[24], and that trend is also represented in the largest available VITT cohort[23]. Our results also compare favorably with previously reported use of danaparoid to treat VITT[18-21].

Our study has certain limitations. Data are retrospective and observational with some missing data points (especially patients 5 and 6), and the sample size is only six patients. All patients received danaparoid so there is no comparison with other initial anticoagulant options. The availability of danaparoid is a national and tradition-based policy reserved to patients intolerant or allergic to heparin.

We did not use direct oral anticoagulants (DOAC) early on, as multiple, and also arterial thrombi had to be managed. In addition, despite some favoring data[25,26], there is scanty evidence concerning the safety and efficacy of DOACs in the management of these forms of thrombosis (i.e, CVST). Dabigatran has proven at least as good option as warfarin[26], which is not recommended in acute HIT due to its impairment of protein C and S[10,27].

To establish the optimal initial anticoagulation for VITT or later related conditions, more research is needed, also in a prospective mode. Even if the role of adenoviral vector nCOV19 vaccination has diminished in many countries, it is important to gain and publish knowledge of VITT for future occasions. Although we recognize the pathogenetic aspects of VITT, we do not understand who will get it, and the syndrome is not limited to adenovirus vector nCOV19 vaccine exposure only. Rare but potentially disastrous immune thrombotic anti-H/PF4 antibody related syndromes are likely to occur also in other instances outside vaccination front[7]

Conclusions

Our clinical case series supports danaparoid as a rational option for initial anticoagulation of VITT. Its safety, certain pharmacodynamic advantages and efficacy are reported in this study when administered together with upfront IVIG. To establish the optimal first-line anticoagulation of VITT and other PF4 antibody –related conditions, prospective comparative studies are required.

Declarations

Ethics approval and consent to participate: Yes

Consent for publication: Yes

Availability of data and material

We are open for data sharing, please contact the corresponding author (riitta.lassila@hus.fi) if needed.

Competing interests

1,2,4) Nothing relevant to disclosure

3) was involved with the clinical development of danaparoid from 1980 to 2000 and in retirement has provided consultant services to various MAHs including the current license holder Aspen Pharma.

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Authors´ contributions

All authors contributed to the study design and writing process. Authors 1 and 2 collected data from health records and visualized the data.

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Figures

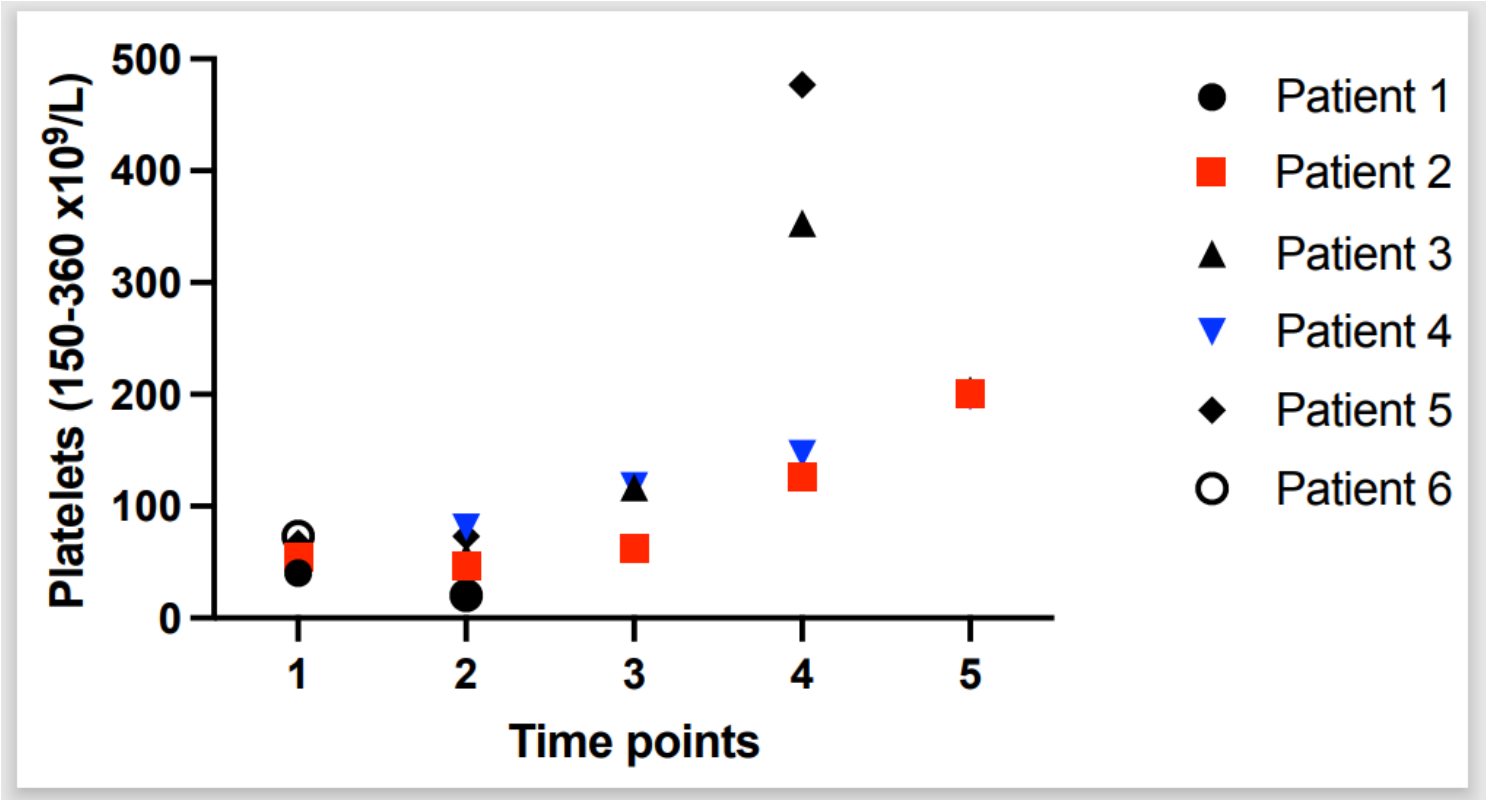


Figure 1

Evolution of platelet counts (normal range 150-360 x 109 / L) before and during danaparoid therapy Time points: 1 = on admission day, 2 = at 1-3 days, 3 = 4-7 days, 4 = 8-14 days, 5= 15-30 days

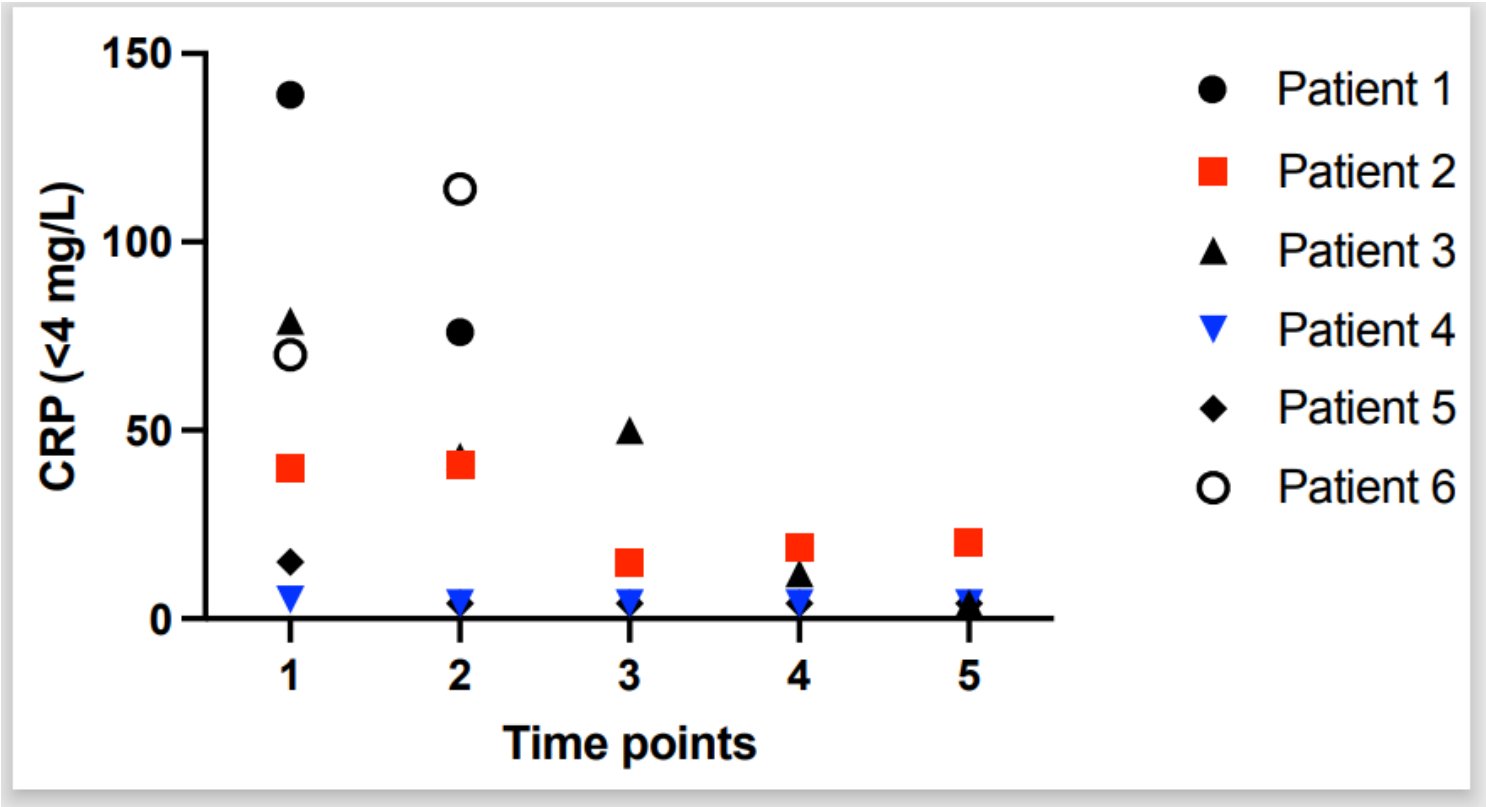
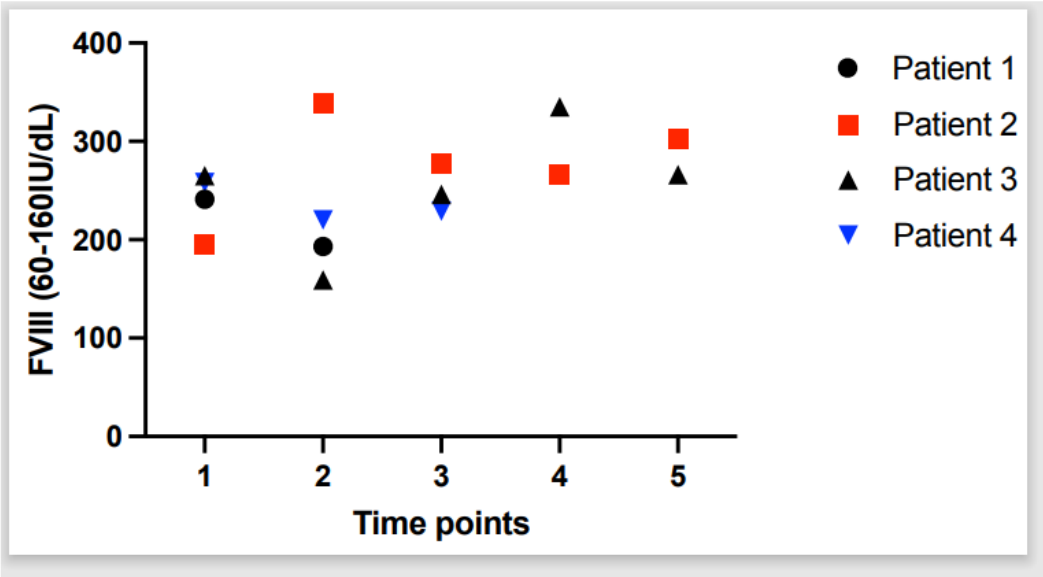
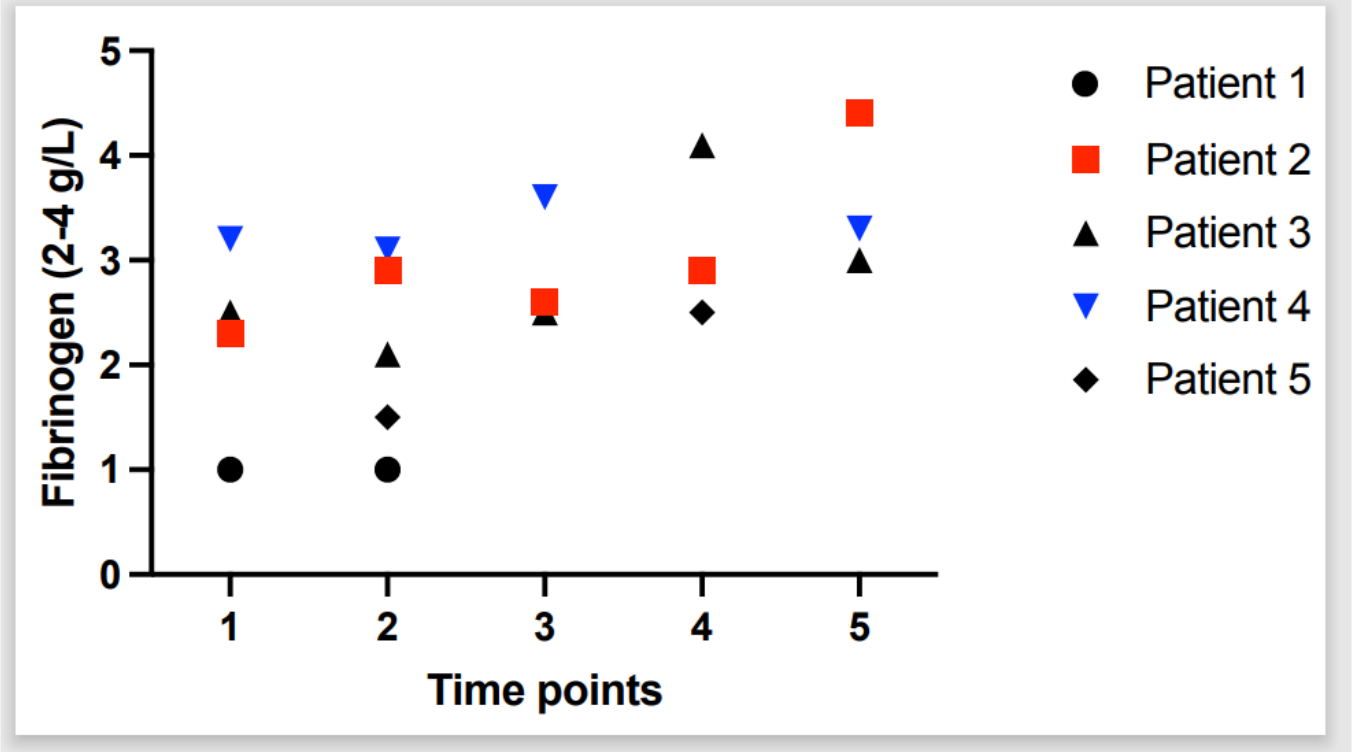


Figure 2

Evolution of C-reactive protein (normal < 4 mg/L) before and during danaparoid Time points: 1 = on admission day, 2 = at days 1-3, 3 = days 4-7, 4 = days 8-14, 5= days 15-30



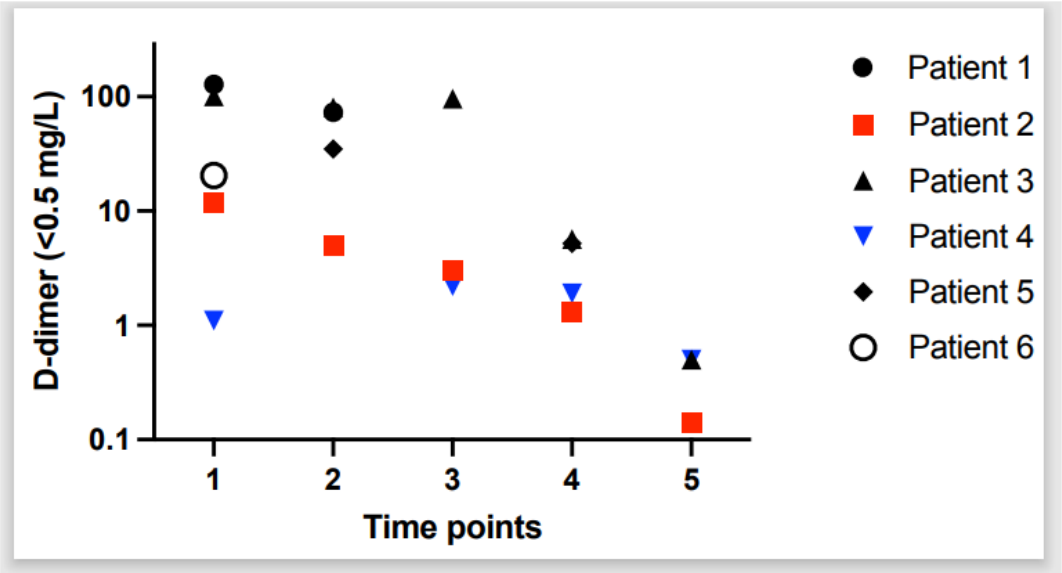
A



B

Figure 3

A and B: Evolution of FVIII (normal 60-160 IU/dL) and fibrinogen (normal 2-4 g/L) before and during danaparoid therapy Time points: 1 = on admission day, 2 = at 1-3 days, 3 = 4-7 days, 4 = 8-14 days, 5= 15-30 days



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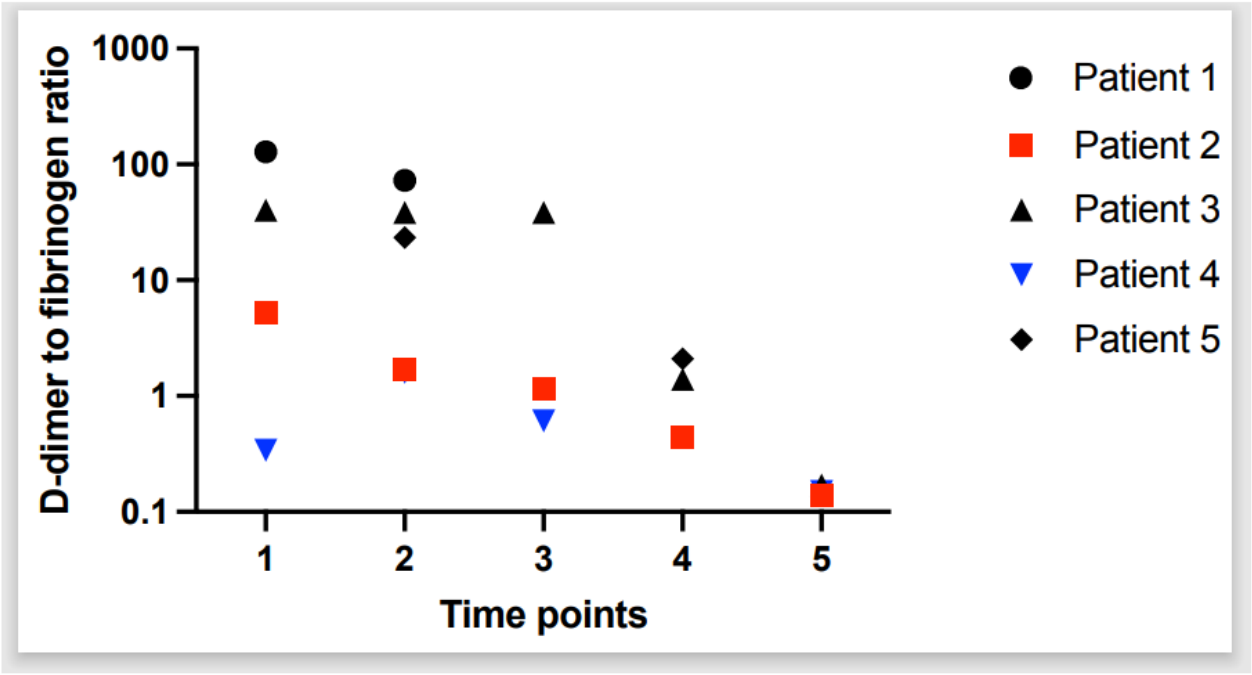

B

Figure 4

A and B: Evolution of D dimer (normal <0.5 mg/L) and D dimer to fibrinogen ratio Time points: 1 = on admission day, 2 = at 1-3 days, 3 = 4-7 days, 4 = 8-14 days, 5= 15-30 days

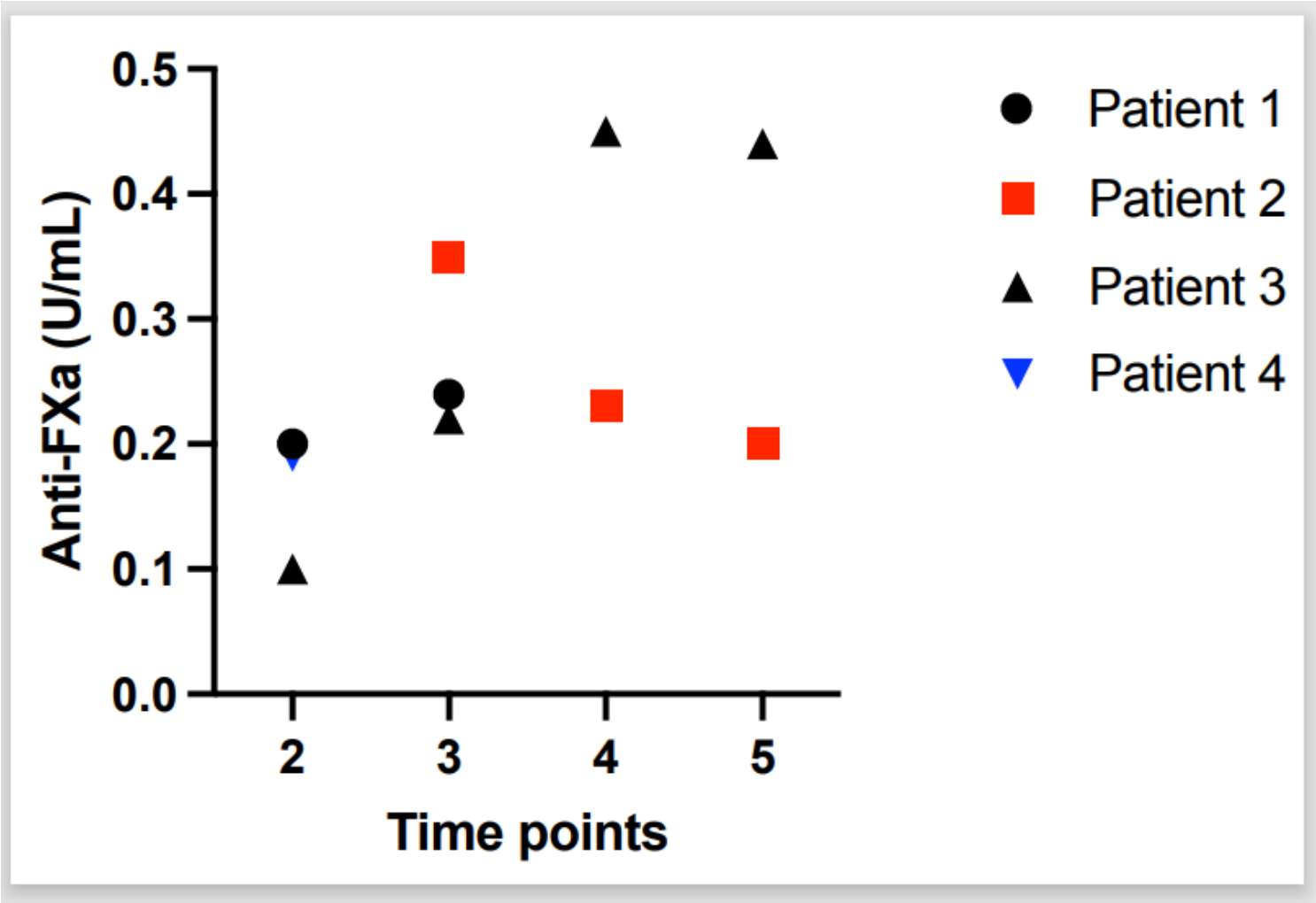

Figure 5

Available anti-FXa activity (U/mL) levels through the danaparoid treatment course Time points: 1 = on admission day, 2 = at 1-3 days, 3 = 4-7 days, 4 = 8-14 days, 5= 15-30 days