

Risk of thromboembolism in patients with hereditary angioedema treated with plasma-derived C1-inhibitor

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ABSTRACT

Background: Plasma-derived C1-inhibitor (C1-INH) concentrates (pdC1-INH) have been used as safe and effective treatments for hereditary angioedema with C1-INH deficiency (C1-INH-HAE) for >30 years. Notwithstanding this, sporadic reports and a study into the high-dose therapy of neonates with C1-INH concentrate administered in an off-label indication raised concerns that this drug might increase the risk of thromboembolism.

Objective: To investigate the incidence of thromboembolism and the background of the risk factors related to treatment with pdC1-INH.

Methods: Our retrospective cohort study of 144 patients with C1-INH-HAE compared the incidence of thromboembolism and its risk factors in patients who received pdC1-INH with those who did not receive pdC1-INH as well as with those treated with danazol or with tranexamic acid.

Results: During the observation period (29 years), 104 of the 144 subjects received pdC1-INH. The average dose per treatment was 573.59 IU. None of the patients used an indwelling central venous catheter. Multiple risk factors for thromboembolism were identified in 93 of the 104 patients treated with pdC1-INH. The incidence rate of thromboembolism was 0.0019/100 person-years in patients treated with pdC1-INH, whereas it was 0.0211/100 person-years in the not-treated group.

Conclusion: Our cohort study did not find any evidence for an increased risk of thromboembolism during treatment with pdC1-INH, despite the presence of multiple predisposing factors.

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Hereditary angioedema (HAE) with deficiency of the C1-inhibitor (C1-INH-HAE) is a rare, autosomal dominant disorder that belongs to the group of bradykinin-mediated angioedemas.¹ In the absence of functional C1-INH, the plasma enzyme cascades, such as the complement, contact-kinin, coagulation, and fibrinolytic systems, undergo uncontrolled activation, which leads to the production of bradykinin, and to enhanced vascular permeability, which may cause angioedema that involves the subcutis and/or the submucosa.^{2,3} The management of C1-INH-HAE consists of acute treatment and edema prophylaxis (short-term or preprocedural or long-term prophylaxis).⁴ The drugs for acute therapy inhibit bradykinin release by

replacing the missing protein with human, plasma-derived, nanofiltered C1-INH (pdC1-INH) concentrate^{5,6} or with recombinant human C1-INH.^{7,8} Further alternatives include administering a kallikrein inhibitor,⁹ or blocking the effect of bradykinin on its receptor.¹⁰ The drugs most often used for prophylaxis include antifibrinolytics, attenuated androgens, and pdC1-INH concentrates. The intravenous administration of pdC1-INH concentrate (Cetor [Sanquin, Amsterdam, the Netherlands], or Berinert [CSL Behring GmbH, Marburg, Germany]⁵ and Cinryze [Shire Pharmaceuticals, Wayne, PA]⁶) is a safe and effective option, both for acute treatment and for prophylaxis. Notwithstanding this, sporadic reports, and a study into the off-label use of high-dose pdC1-INH in neonates raised concerns that this drug might increase the risk of thromboembolism (TE).^{11–13} Our aim was to investigate the risk factors and the occurrence of TE in patients with C1-INH-HAE treated with pdC1-INH.

METHODS

Patients

Our retrospective study surveyed the period between 1986 and 2015 in 144 patients with C1-INH-HAE (79 women and 65 men; mean age, 38.82 years [range, 2–84 years]) followed up at the Hungarian Angioedema Center. The observation period started at the

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time of diagnosis of the individual patients and ended in 2015 or on the date of death in the case of six patients. C1-INH-HAE was established by pedigree analysis as well as by the clinical manifestations and complement parameters (C1-INH antigenic and functional levels, C1q, C4). All the subjects had been diagnosed at the Hungarian Angioedema Center, and, then, all underwent follow-up at least once according to a standardized protocol. During these follow-up visits, their clinical and laboratory data were collected and entered into the Hungarian HAE Registry.¹⁴ After diagnosis, all the patients were supplied with Berinert because this was the only pdC1-INH concentrate available in Hungary during the observation period. All the patients kept their C1-INH concentrate at home. Alternatively, they could obtain it from the Hungarian Angioedema Center or from major regional hospitals. Whenever pdC1-INH was administered to a patient, the name and the batch number of the product were recorded in the patient diary, to maintain a link between the patient and the product batch.

The dosage of pdC1-INH (Berinert) was as follows: The patients received 500–1000 IU pdC1-INH as acute treatment as well as for short term and for intermittent prophylaxis. Starting from 2011, the recommended dose of C1-INH changed to 20 IU per body weight. In all cases, the patients received intravenous pdC1-INH by peripheral venipuncture. We monitored the possible occurrence of the following arterial and venous TE events: deep venous thrombosis, pulmonary embolism, stroke, myocardial infarction. At each yearly visit, the patients were asked about the occurrence of these TE events.

Risk Factors for Venous and Arterial Thrombosis

We monitored the incidence of TE and its predisposing factors in patients who received and those who did not receive pdC1-INH. The following groups of risk factors were identified. We took into account the predisposing factors for cardiovascular diseases, such as hypercholesterolemia, hypertriglyceridemia, smoking, hypertension, diabetes, and obesity. These parameters were ascertained at the follow-up visit in 2015. “Hypercholesterolemia” and “hypertriglyceridemia” were defined as cholesterol and triglyceride levels, respectively, higher than normal on at least two occasions during follow-up.

We explored the predisposing factors for deep vein thrombosis and pulmonary embolism, including the age of patients (in 2015), major orthopedic surgery, oncologic surgery, oral contraceptive use, pregnancy, and previous venous TE documented in the medical history of the patients. Inherited, acquired, and coagulation risks were screened for the following: lupus anticoagulant (LA), diluted Russell viper venom time

and LA-sensitive partial thromboplastin time, anticardiolipin antibody and anti- β_2 -glycoprotein I antibody, Factor Leiden mutation, and prothrombin G20210A mutation, which were tested in 2014.¹⁵ Also, we took into account whether the patient had undergone long-term prophylaxis with an antifibrinolytic (tranexamic acid) or an attenuated androgen (danazol).

Laboratory Methods

Coagulation studies (with the Siemens BCS-XP coagulation automate [Siemens HealthCare Diagnostics Product GmbH, Marburg, Germany]) and molecular genetic testing (Genosign kit [Microtrade, Budapest, Hungary], real-time polymerase chain reaction, Light-Cycler Roche [Roche Diagnostics, Mannheim, Germany]) were performed in all the patients. If these tests indicated an abnormality, then we completed the assessment of thrombotic risk by measuring the activity of antithrombin (Innovance chromogenic assay [Siemens HealthCare Diagnostics Product GmbH]; anti-activated factor X), along with the levels of Protein C, and Protein S. The study protocol was approved by the institutional review board of Semmelweis University of Budapest, and informed consent was obtained from each patient in accordance with the Declaration of Helsinki. H. Farkas and K.V. Kóhalmi contributed equally to this study.

RESULTS

During the observation period, 104 of the 144 patients (62 women and 42 men; median age, 38.1 years [range, 25.9–51.5 years]) received, and 40 patients (17 women and 23 men; median age, 36.6 years [range, 16.4–57.8 years]) did not receive pdC1-INH (Table 1). The average dose per treatment was 573.59 IU (500 IU in 3155, 1000 IU in 434, 1500 IU in 38, 2000 IU in 7 occasions, and 2500 IU in 1 patient). The median (25th to 75th percentile) pdC1-INH exposure was 10.5 years (5.0 to 14 years), and the cumulative number of years was 1031 in the exposed group. In a single patient, the maximum cumulative dose over a year was 136,500 IU during pregnancy. The cumulative number of the years of observation was 365 in the patients who did not receive pdC1-INH. None of the patients used a central line or port for administering pdC1-INH.

There are many risk factors to explore, both in the pdC1-INH-exposed and in the nonexposed groups of the patients (Table 2). In both groups, nearly half of the patients were > 45 years of age and had hypercholesterolemia. Both groups were similar with regard to the other risk factors, with several exceptions. In the group treated with Berinert, four women took a progesterone-containing oral contraceptive, whereas the female patients in the other group did not. Similarly, obesity was more common in the group that received pdC1-

Table 1 Baseline characteristics, exposure time (time at risk), and incidence of thromboembolism of pdC1-INH treated vs not-treated patient groups

Demographics	Received pdC1-INH (104 patients)	Did Not Receive pdC1-INH (40 patients)
Age, y	38.1	36.6
Sex, no. women/men	62/42	17/23
No. with HAE type I/II	95/9	38/2
pdC1-INH exposure, median (Q1, Q3), y	10.5 (5.0, 14)	—
Years of observation, median (Q1, Q3), y	—	8.5 (4.0, 13.5)
No. (%) patients with risk factor for thromboembolism	93 (89)	27 (68)

pdC1-INH = plasma-derived C1-inhibitor concentrate; HAE = hereditary angioedema.

Table 2 Risk factors for thromboembolism among patients who received or did not receive pdC1-INH

Risk Factors	Received pdC1-INH, no. (% of 104)	Did Not Receive pdC1-INH, no. (% of 40)
Cardiovascular*		
Hypercholesterolemia	52 (50)	17 (43)
Hypertriglyceridemia	17 (16)	6 (15)
Smoking	22 (21)	7 (18)
Hypertension	13 (13)	10 (25)
Diabetes mellitus	3 (3)	2 (5)
Preobesity (25 kg/m ² < BMI < 30 kg/m ²)	35 (34)	10 (25)
Obesity (BMI > 30 kg/m ²)	20 (19)	4 (10)
DVT and PE		
Age (>45 y)*	40 (38)	17 (43)
Major orthopedic surgery	0 (0)	2 (5)
Oncologic surgery	2 (2)	1 (3)
Oral contraceptives (desogestrel)	4 (4)	0 (0)
Pregnancy	26 (25)	4 (10)
Previous venous thromboembolism	2 (2)#	1 (3)
Inherited, acquired, and coagulation		
LA positivity	8 (8)	0 (0)
β_2 GP positivity	5 (5)	1 (3)
ACA positivity	4 (4)	0 (0)
Leiden mutation HZ	4 (4)	2 (5)
Prothrombin G20210A	8 (8)	0 (0)
Protein C % (<54)	0 (0)	0 (0)
Protein S % (<59)	4 (4)	0 (0)
Antithrombin % (<80)	0 (0)	0 (0)
VIII, IX, XI factor hyperactivity	1 (1)	2 (5)
Drugs		
Tranexamic acid	28 (27)	3 (8)
Danazol	57 (55)	8 (20)

pdC1-INH = plasma-derived C1-inhibitor concentrate; BMI = body mass index; DVT = deep vein thrombosis; PE = pulmonary embolism; LA = lupus anticoagulant; β_2 GP = β_2 -glycoprotein I; ACA = anticardiolipin antibody; HZ = heterozygous.

**Ascertained in 2015.*

#One patient received pdC1-INH after his DVT and PE.

INH. Also, the number of patients on long-term prophylaxis was three to four times higher in the latter group. The comparison of the risk factors identified in

patients who took danazol or tranexamic acid showed that cardiovascular risk factors were more common in the former than in the latter group. Age > 45 years,

Table 3 Risk factors for thromboembolism in patients who received danazol, and in those who took tranexamic acid*

Risk Factors	Received Danazol, no. (% of 65)	Received Danazol (n = 65)		Received Tranexamic Acid, no. (% of 31)	Received Tranexamic Acid (n = 31)	
		Received pdC1-INH, no. (% of 57)	Did Not Receive pdC1-INH, no. (% of 8)		Received pdC1-INH, no. (% of 28)	Did Not Receive pdC1-INH, no. (% of 3)
Cardiovascular#						
Hypercholesterolemia	42 (65)	37 (65)	5 (63)	14 (45)	13 (46)	1 (33)
Hypertriglyceridemia	13 (20)	10 (18)	3 (38)	4 (13)	3 (11)	1 (33)
Smoking	13 (20)	11 (19)	2 (25)	7 (11)	5 (18)	2 (67)
Hypertension	15 (23)	11 (19)	4 (50)	5 (16)	4 (14)	1 (33)
Diabetes mellitus	2 (3)	1 (2)	1 (13)	0 (0)	0 (0)	0 (0)
Preobesity (25 kg/m ² < BMI < 30 kg/m ²)	28 (43)	26 (46)	2 (25)	11 (36)	11 (39)	0 (0)
Obesity (BMI >30 kg/m ²)	16 (25)	14 (25)	2 (25)	3 (10)	3 (11)	0 (0)
DVT and PE						
Age (>45 y)#	37 (57)	33 (58)	4 (50)	12 (39)	11 (39)	1 (33)
Major orthopedic surgery	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Oncologic surgery	2 (3)	2 (4)	0 (0)	1 (3)	1 (4)	0 (0)
Oral contraceptives (desogestrel)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Pregnancy	18 (28)	17 (30)	1 (13)	15 (48)	13 (46)	2 (67)
Previous venous thromboembolism	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Inherited, acquired, and coagulation						
LA positivity	6 (9)	6 (11)	0 (0)	0 (0)	0 (0)	0 (0)
β_2 GP positivity	3 (5)	3 (5)	0 (0)	2 (6)	2 (7)	0 (0)
ACA positivity	3 (5)	3 (5)	0 (0)	1 (3)	1 (4)	0 (0)
Leiden mutation HZ	2 (3)	1 (2)	1 (13)	4 (13)	3 (11)	1 (33)
Prothrombin G20210A	6 (9)	6 (11)	0 (0)	0 (0)	0 (0)	0 (0)
Protein C % (<54)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Protein S % (<59)	1 (2)	1 (2)	0 (0)	2 (6)	2 (7)	0 (0)
Antithrombin % (<80)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
VIII, IX, XI factor hyperactivity	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

pdC1-INH = plasma-derived C1-inhibitor; BMI = body mass index; DVT = deep vein thrombosis; PE = pulmonary embolism; LA = lupus anticoagulant; β_2 GP = β_2 -glycoprotein I; ACA = anticardiolipin antibody; HZ = heterozygous.

*Based on the incidence of the risk factors in these two groups; two subsets were defined according to the administration or nonadministration of pdC1-INH.

#Ascertained in 2015.

pregnancy, oral contraceptive use, and previous venous TE were also more common among patients who took danazol (Table 3). Thrombophilic abnormalities constituted the most important risk factors for TE. Fifteen of 144 patients tested positive for LA and prothrombin G20210A. Two were high-risk cases (with HZ Leiden plus HZ FII polymorphisms and a high-positive LA plus HZ FII polymorphism), whereas nine patients had a moderate risk for developing TE (three

high-positive LAs, three HZ Leidens, and three HZ FII polymorphisms). Except for a single patient with the HZ FII polymorphism, all these 11 patients received pdC1-INH.

We observed TE events in five patients; two of these patients received pdC1-INH. Patient no. 1, with multiple risk factors (chronic alcohol abuse, hypercholesterolemia, advanced age, and long-term danazol prophylaxis), had an arterial (infarctus cerebri) TE after 9

months of dosing with Berinert. During the 14 years before the occurrence of cerebral infarction, this patient had received a cumulative dose of 2500 IU pdC1-INH. Treatment with pdC1-INH was no longer necessary after the TE, because the patient did not experience further HAE attacks. Patient no. 2 had venous TE, which involved the left external iliac vein, the common femoral artery, and the great saphenous vein as well as the superficial femoral veins 7 months after the administration of the last 500 IU dose pdC1-INH. Moreover, this patient also had arterial cerebral infarction 3 years later, 5 months after the administration of the last 500 IU dose of pdC1-INH. This patient also had a number of risk factors for TE, *viz.* hypercholesterolemia, preobesity, age, long-term danazol prophylaxis, and previous venous TE. Over 15 years, this patient received 4000 IU pdC1-INH until the occurrence of deep vein thrombosis, along with an additional 3000 IU thereafter. Moreover, another 500 IU of pdC1-INH was administered, without further TE events, after the cerebral infarction, which the patient contracted 3 years later. Both patients with TE events were treated with fixed (500 IU) doses of pdC1-INH.

We would like to point out the example of a female patient with C1-INH-HAE. She received the highest cumulative dose of pdC1-INH (136,500 IU per year); as well, tranexamic acid was administered concomitantly during pregnancy and breast-feeding; however, thromboembolic events did not occur.

DISCUSSION

According to our long-term follow-up study, treatment with pdC1-INH, administered either as an acute treatment or as short-term or intermittent prophylaxis did not increase the risk of TE. This is remarkable in view of the presence of multiple predisposing factors in 93 of the 104 patients treated with pdC1-INH and of the use of high cumulative doses in some cases. The incidence rate of TE among the patients treated with pdC1-INH was 0.0019 per 100 person-years, and it was 0.0211 in the group not treated with pdC1-INH. Thus, the incidence rate of TE was 10 times lower among patients treated with C1-INH. However, the two instances of TE in the treated group were possibly unrelated to treatment with pdC1-INH. In particular, several months elapsed between treatment with pdC1-INH and the occurrence of TE. Moreover, the half-life of pdC1-INH in patients with C1-INH-HAE is as short as 1 to 3 days.

A review of the studies published so far revealed a number of factors (in addition to C1-INH administration) that might have influenced the occurrence of TE events; moreover, a variety of factors have not been considered. In the study by Horstick *et al.*,¹⁶ 13 neonates and infants received off-label treatment with

high-dose pdC1-INH concentrate (up to 500 IU per kg body weight) administered intravenously. All the patients developed severe great-vein thrombosis, and nine children died of emboli.¹³ This population differed from ours in several properties, such as age, underlying disease, off-label use, the mode of dosing with C1-INH, and the administered dose. In this study, TE was possibly related to the excessive doses, which were 25 times higher than recommended (500 IU per kg body weight versus 20 units per kg body weight, or versus the fixed dose of 500–1000 IU before 2012). In conformity with the current label, we prescribed a 20 IU/kg dose of pdC1-INH.

Nevertheless, a proportion of our patients still administered the fixed dose with success. It should be noted that, despite the high cumulative doses used in several cases, particularly during pregnancy, when only pdC1-INH may be administered, we did not observe any TE events.¹⁷ The importance of the dose has been explored by *in vitro* and *in vivo* thrombogenicity studies^{16,18} conducted with pdC1-INH in animals. Some of these studies showed a potential for clot formation with higher doses (>100 IU/kg). The researchers hypothesized that high doses of C1-INH inhibited factor XIa, thrombin, and plasmin, along with the tissue-type plasminogen activator.^{16,18} However, Tassani *et al.*¹⁹ demonstrated the clinical benefit of administering C1-INH in a 100 IU/kg dose to neonates who were undergoing arterial switch operations. The researchers did not observe any procoagulant effect of the pdC1-INH concentrate.¹⁹ Schurmann *et al.*²⁰ did not detect any prothrombotic risk associated with C1-INH treatment in rabbits, even at supratherapeutic doses (up to 800 IU/kg). Relan *et al.*²¹ analyzed multiple coagulation and fibrinolytic parameters after the infusion of recombinant human C1-INH in doses up to 100 IU/kg to patients with C1-INH-HAE and who are symptomatic. They did not find any significant effect of recombinant human C1-INH on coagulation or on fibrinolysis, and neither observed TE events in these patients.

Further, the mode of administration might have had a great influence. In the study by Horstick *et al.*,¹⁶ the patients received pdC1-INH concentrate through a central venous catheter, whereas, in routine practice, a peripheral venous cannula is used for this purpose. The use of central venous access might increase the risk of thrombosis. In their study into the risk of catheter-related thrombosis, Baskin *et al.*²² found that thrombosis occurs in up to 50% of children and in 66% of adults with a long-term indwelling central venous catheter, which indicates that these catheters predispose to thrombosis. The findings of Kalaria and Craig²³ also confirmed this observation. These researchers published a survey conducted among 66 physicians, who followed up 856 patients who received different pdC1-INH products. Five of these 856 patients experienced

an abnormal clotting episode, and 3 of them had an indwelling central venous catheter. The researchers did not disclose the distribution of other predisposing factors for thrombosis in their study population.²³ The observation by Gandhi *et al.*²⁴ also emphasizes the importance of identifying prothrombotic factors. They found 10 potential signals of thrombotic events associated with the use of C1-INH when reviewing an adverse event reporting system. These researchers stress that this data base is not suitable for determining the true frequency of any given adverse event associated with a drug.²⁴ Crowther *et al.*²⁵ reviewed TE events associated with the use of pdC1-INH in patients with C1-INH-HAE, as recorded in the U.S. Food and Drug Administration Adverse Event Reporting System data base. They found that TE was uncommon in patients who received pdC1-INH, and it was particularly infrequent in those with underlying TE risk factors.²⁵

With regard to the appraisal of any possible relationship between treatment with C1-INH concentrate and TE, our study was the first to explore both the predisposing factors for TE events and the use of laboratory screening for inherited risk factors. As evidenced by the nearly 30-year-long experience accumulated since it was first introduced, pdC1-INH is characterized by an excellent safety profile, which also was confirmed by our previous study.²⁶ New C1-INH preparations have been introduced, and the therapeutic indications have been expanded during the last decade. As recommended by the international guidelines, all attacks are eligible for treatment (irrespective of their location) as soon as they are clearly recognized by the patient. Treatment should commence preferably before visible or disabling symptoms develop.²⁷ The pdC1-INH preparation has been licensed for long-term prophylaxis.²⁸ Dosages have changed, the fixed dose used earlier has been replaced by 20 IU/kg per body weight for Berinert, whereas Cinryze 1000 IU twice a week is recommended for long-term prophylaxis.^{29,30} The escalating use of long-term prophylaxis has been accompanied by an increase in the number of patients with an indwelling central venous catheter. Moreover, off-label use is on the rise in other types of bradykinin-mediated edema, particularly in nC1-INH-HAE and in the acquired form of C1-INH deficiency.^{31,32} The more-extensive and frequent administration of pdC1-INH in progressive doses was not accompanied by any increase in the incidence of TE events. With regard to the documented cases of the latter, a large proportion of the affected patients had an indwelling central venous catheter. In other instances, no data could be identified in the medical history to support a scientifically sound conclusion that a direct relationship exists between treatment with this agent and the occurrence of the complication observed.

CONCLUSION

The long-term follow-up of patients in specialist centers (with at least one follow-up visit per year, the use of patient diaries, and the accumulation of clinical and laboratory information in an HAE register) is essential for identifying adverse effects. These data might prove the existence of any possible relationship between the therapy and the adverse events. Our observations support that the use of pdC1-INH concentrate (Berinert) in therapeutic doses for C1-INH-HAE is not associated with an increased rate of TE events compared with the rate seen in the group of patients not treated with pdC1-INH, even in those with preexisting risk factors.

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