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Successful Prophylaxis of Hereditary Angioedema with Human C1 Inhibitor Concentrate: A Collection of Case Reports

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ABSTRACT

Background: Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder (type I or type II, associated with C1 inhibitor [C1-INH] gene defects). Prophylaxis with attenuated androgens, antifibrinolytics and plasma-derived C1-INH concentrates is recommended to reduce the frequency/severity of HAE attacks.

Methodology: These case reports describe the use of a plasma-derived C1-INH concentrate (Berinert®, CSL Behring) for prophylaxis against HAE (type I) attacks in 5 patients who experienced limited/lack of efficacy when using alternative recommended prophylactic agents, 2 of whom required prophylaxis during pregnancy.

Results and Conclusions: Prophylaxis with C1-INH concentrate was associated with a complete cessation or decreased frequency of acute HAE attacks compared with no prophylaxis. C1-INH concentrate prophylaxis also had a positive impact on patient quality of life and professional life, and was effective and well-tolerated, during pregnancy. These reports demonstrate the effectiveness of C1-INH for prophylaxis when alternative options were proven ineffective, not well-tolerated or contraindicated.

INTRODUCTION

Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder that affects an estimated 1 in 10,000 to 50,000 individuals globally.[1] The classic form (type I and II) is caused by defects in the C1 inhibitor (*C1-INH*) gene, with more than 200 mutations identified thus far.[2] Type I HAE (85% of cases) is associated with low levels of C1-INH and reduced function; the less prevalent type II disease (15% of cases) is linked with reduced C1-INH function (but normal or elevated levels of C1-INH).[3]

The disorder manifests as recurrent episodes of severe abdominal pain, cutaneous angioedema, and/or angioedema of the upper airway, which can be life threatening because of the risk of asphyxiation. HAE reduces patients' health-related quality of life (QOL) compared with the general population, impairs physical and mental health, negatively impacts educational attainment, reduces work productivity, and hampers professional development. Consequently, individuals with HAE may also experience a substantial economic burden.[4]

In women of child-bearing age, the effects of pregnancy on HAE symptoms is a further consideration. Pregnancy has a variable impact on the natural history of disease: the condition can reduce the number of HAE attacks or stop them altogether; increase the attack rate, particularly in the second and third trimesters; mitigate clinical symptoms; or have no effect at all.[5-8] In addition, HAE attacks represent a risk to the fetus with the potential to increase the risk of miscarriage or stillbirth.[9]

Management of HAE typically involves treatment of acute attacks, short-term prophylaxis (eg, prior to minor dental work), and long-term prophylaxis.[3,10,11] Long-term prophylaxis against HAE attacks involves continuous, potentially lifelong, therapy and is appropriate for patients with HAE for whom on-demand acute therapy is "inadequate."[10] However, the precise definition of "inadequate" has garnered considerable debate.[10] Depending on the therapy used, treatment can be administered in a medical facility or at home by the patient, a relative, or a friend. At-home therapy may allow earlier treatment of acute HAE attacks and provide better symptom control.[12]

Attenuated androgens (eg, danazol), plasma-derived C1-INH concentrates (Berinert®, CSL Behring GmbH, Marburg, Germany; Cinryze®, ViroPharma, Exton, PA, USA, and ViroPharma Europe, Brussels, Belgium), and antifibrinolytics (eg, tranexamic acid) can be used for long-term prophylaxis against HAE attacks.[3] Efficacy of attenuated androgens and plasma-derived C1-INH concentrates in this setting is supported by strong (high-

level) evidence; conversely, the efficacy of antifibrinolytics in clinical trials has not been confirmed in general practice.[10] Androgen-related adverse effects are numerous (eg, weight gain, hypertension, liver neoplasms); antifibrinolytics commonly cause dyspepsia, together with other adverse effects such as muscle weakness, fatigue, and hypotension.[3] Minimal adverse effects have been reported in controlled trials of plasma-derived C1-INH concentrates, although concerns exist over injection-site infection and the infection risk associated with use of any human blood product.[10] The consensus report on the management of HAE by Cicardi et al published in 2012 stated that 17-alpha-alkylated androgens can be considered for long-term prophylaxis against HAE attacks in certain patients; nevertheless, plasma-derived C1-INH concentrates can be considered for all patients, although treatment regimens should be individualized.[10] Tranexamic acid use is acceptable during pregnancy, but danazol is contraindicated.[13] C1-INH concentrates form the basis of treatment for severe attacks.[13]

Berinert is a highly purified plasma-derived C1-INH concentrate prepared using 3 virus and 2 prion reduction steps, in addition to a recently introduced nanofiltration step.[14] It is approved in more than 30 countries for the treatment of acute HAE attacks as well as short-term prophylaxis, but is not currently licensed for long-term prophylaxis against HAE attacks.[14,15] It is administered by slow intravenous infusion. Clinical trials, case reports, clinical experience, and the monitoring of adverse drug reactions over a period of 26 years support the efficacy and long-term safety of C1-INH concentrate against single HAE attacks, providing rapid onset of relief.[1,15-25] In a recent large placebo-controlled study (International Multicenter Prospective Angioedema C1-INH Trial 2 [IMPACT2]), a total of 1085 HAE attacks (in 57 patients) were each treated with a single dose of C1-INH concentrate (20 U/kg).[15] Study patients were treated in the event of an attack over a median period of 24 months, during which time there were no treatment-related safety concerns. Thus the authors concluded that C1-INH concentrate provided reliable efficacy as a long-term treatment for HAE attacks at any body location.[15]

Here we present 5 case reports of patients with type I HAE presenting with more than one severe attack per month and in need of either long-term prophylactic treatment or prophylaxis during pregnancy (**Table**). Of note, prior to switching to C1-INH concentrate, all 5 patients had previously tried alternative agents

Table. Characteristics of 5 Patients With HAE Described in the Case Reports

Characteristic	Case Report				
	1	2	3	4	5
Sex	Female	Female	Female	Female	Female
Age, y	32	29	26	29	24
HAE type	I	I	I	I	I
Diagnostic tests					
Complement[a]	C1-INH: 31 mg/L C1-INH function: 2.0 U/mL C4: 64 mg/L	C1-INH: 51 mg/L C1-INH function: 5.5 U/mL C4: 40 mg/L	C1-INH: 70 mg/L C1-INH function: 2.8 U/mL	C1-INH: 48 mg/L C1-INH function: 4.2 U/mL C4: 36 mg/L	C1-INH: 51 mg/L C1-INH function: 12.0 U/mL C4: 70 mg/L
Family history	No HAE family history; no children	Familial	Sister, 3 paternal uncles, and paternal grandmother with type I HAE	Maternal grandmother and mother with type I HAE	Father and sister with type I HAE
Attack frequency before treatment with Berinert	1 severe attack/wk	2 attacks/wk	2–3 attacks/mo	At least 1 attack/wk during pregnancy	Every 3 or 4 days during pregnancy
Attack frquency during treatment with Berinert	No attacks since starting prophylaxis	No attacks since starting long-term prophylaxis	No attacks since starting prophylaxis (initially twice weekly, then reduced to 1 injection prior to menstruation)	One attack per week during once-weekly treatment; no attacks when increased to twice-weekly injections	One attack per week during twice-weekly treatment (at the 4th day, not the 3rd); no attacks when increased to an injection every 3 days

C1-INH, C1 inhibitor; HAE, hereditary angioedema.

[a]Normal reference ranges: C1-INH, 160–330 mg/L; C1-INH function, 17.2–22.4 U/mL; C4, 14–54 mg/L.

recommended for prophylaxis and found them inadequate for controlling HAE attacks. These patients were included in a registry and oral consent was obtained at inclusion.

CASE REPORT 1

Case report 1 involves a 32-year-old woman with type I HAE who works for emergency services (front line), so she needs to be rapidly restored to health after an attack. The patient experiences peripheral, abdominal, and upper airway angioedema during an attack, accompanied by syncope, ascites, cystalgia, and fatigue. Prior to starting prophylaxis with C1-INH concentrate, the patient experienced one severe attack per week (score >8 on a visual analog scale [VAS] of 1–10 for assessment of pain; a score >5 is considered a severe abdominal attack). The attacks were typically located abdominally or peripherally (foot, hand, face, or genitals); however, she experienced an average of one attack per year involving upper airway edema.

She received prophylactic tranexamic acid (3 g/day) for 3 months in 2007 (from August to November) but experienced digestive discomfort and dizziness. Tranexamic acid is therefore no longer part of her regular treatment regimen. She is similarly intolerant to danazol, which she received as one 200-mg tablet on alternate days for 2 years in 1998 and 1999, and experienced amenorrhea and weight gain. The patient developed antithyroid peroxidase and antithyroglobulin autoantibodies (which increased to 573 IU/mL and 787 IU/mL [reference values <100 IU/mL for both], respectively), and Hashimoto's thyroiditis with struma was diagnosed. As a result, she began receiving levothyroxine (50 µg) at the end of July 2011, and her thyroid dysfunction subsequently resolved.

Following the failure of tranexamic acid and danazol for the prophylactic treatment of HAE attacks, no preventative treatment was administered from August 2011 to February 2012, and the patient once again experienced more than one severe attack per week, in the same body locations as previously described. The patient received "on-demand" treatment of C1-INH concentrate (1000–1500 U) and icatibant (30 mg) for these attacks. Subsequently, long-term prophylactic treatment with C1-INH concentrate was proposed to limit acute attacks.

Since February 2012, the patient's regimen has involved prophylaxis with C1-INH concentrate (1250 U, twice weekly). She has experienced no attacks since starting prophylaxis with C1-INH concentrate, and has been advised to continue with the regimen, as it is an effective therapy. Importantly from the patient's perspective, prophylaxis with C1-INH concentrate has allowed her to continue with her intensive work. She is satisfied with her current therapy, and has a high degree of confidence in C1-INH concentrate treatment (she does not trust treatment with icatibant after lack of efficacy following an upper airway attack). However, the patient is anxious about the need for lifelong prophylaxis.

CASE REPORT 2

The second case report describes a 29-year-old woman whose type I HAE disease manifests as subcutaneous, peripheral, facial, upper airway, and abdominal angioedema. Due to the nature of the head and neck attacks she experiences, it is important for her to achieve symptom relief as quickly as possible. In addition, her condition leads to a high level of work absenteeism and substantially affects her QOL. Her diagnosis occurred as a result of familial screening at 6 months of age; however, it was during puberty that her condition worsened and manifested in the skin, larynx, and abdomen.

After her diagnosis, she received acute treatment with morphine and a corticosteroid, and tranexamic acid maintenance therapy was initiated. Prophylactic treatment with tranexamic acid (3 g/day) was administered for 6 months and found to be ineffective. During childhood, oral androgens were used only for surgery prophylaxis (for 7 to 10 days) but not for long term prophylaxis.

Opioid treatment for acute attacks was continued throughout her childhood to provide her with relief for frequent and severe abdominal attacks. This treatment led her to a severe opioid addiction.

At puberty, she experienced numerous abdominal attacks, which were treated with morphine sulfate (60 mg), prednisone (20 mg), and tranexamic acid. The corticosteroid treatment was found to be ineffective and discontinued in 2004. In 2007, the tranexamic acid maintenance therapy was discontinued due to a lack of efficacy, and maintenance treatment with progestin was initiated (levonorgestrel 0.03 mg/day) in 2008. In 2009, she began to receive icatibant (30 mg) for acute attacks, but she experienced a "rebound effect" and attacks continued a few hours after administration. Rebound attacks were treated with additional administration of icatibant.

In June 2012, the patient began receiving prophylaxis with C1-INH concentrate (1500 U, twice weekly). Prior to starting prophylaxis with C1-INH concentrate, she experienced 2 attacks of the abdomen or face per week; since receiving C1-INH concentrate, attack frequency has decreased significantly and her QOL has improved. The patient continues to carry icatibant (30 mg) and C1-INH concentrate (20 U/kg) in the event she experiences an acute attack. However, since the beginning of long-term prophylaxis with C1-INH concentrate, after decreasing dramatically, attacks stopped totally and the patient has not required emergency treatment again.

CASE REPORT 3

This third case is a 26-year-old woman who has been experiencing peripheral angioedemas and abdominal crises since the age of 10 years. Her current symptoms include angioedemas of the face, backs of the hands and feet, and genitalia, as well as dysphagia, dysphonia, and abdominal crisis with vomiting. Furthermore, her attacks are more pronounced immediately prior to menstruation. She had been experiencing about 2 or 3 attacks per month since 2006. Oral danazol (600 mg/day) was prescribed between 2006 and 2009, but was discontinued due to intolerance and lack of efficacy. Similarly, oral tranexamic acid (3 g/day), which was administered from 2009 to 2012, was found to be ineffective. Icatibant (30 mg) was, and continues to be, prescribed in cases of abdominal crises. However, since 2007, about 10 attacks per year have been managed with C1-INH concentrate (1000 U) when icatibant at home was not sufficient.

In line with the recommendations of the National Reference Centre of Angioedema (CREAK), prophylactic treatment with C1-INH concentrate (1000 U twice weekly) was initiated in June 2012 and was shown to be efficacious, with no attacks reported between June and September 2012. Following patient-reported worsening of attacks prior to menstruation, prophylaxis was reduced to a single injection of C1-INH concentrate (1000 U) before menstruation in September 2012, and this was found to be sufficient to prevent attacks. The patient continues to be treated with prophylactic injections of C1-INH concentrate (1000 U) prior to menstruation.

Her treatment satisfaction was described as “good” and no adverse effects were reported. The intravenous dosing was found to be of negligible inconvenience to this patient and did not reduce her QOL.

CASE REPORT 4

The fourth case report involves a 29-year-old woman in whom type I HAE was first diagnosed through familial screening at the age of 5 years (in 1988). She experienced her first HAE symptoms at 3 years of age, had her first attack at 5 years of age, and experienced an increase in attack frequency at the onset of puberty. Her attack symptoms, triggered by stress, consist of severe abdominal angioedema (score frequently >8 on a VAS for assessment of pain) and peripheral angioedema, accompanied by rash, but no edema in the head or neck region.

The patient was prescribed Ogyline® (a progestin contraceptive no longer available) between 2002 and 2006. Since then, she has had 2 successful pregnancies conceived at the age of 26 years (in 2009) and 28 years (in 2011). Both pregnancies were accompanied by an increase in the frequency of HAE attacks (from 2 per month to at least 1 per week), and therefore the patient required maintenance therapy to control her condition and protect the fetus.

Prior to her first pregnancy, she was prescribed tranexamic acid to treat attacks (1 g every 4 hours, over 24 hours), but the low frequency and mild symptoms did not justify prophylaxis with C1-INH concentrate. She became pregnant in June 2009 and was prescribed maintenance therapy with tranexamic acid (1 g/day) in October 2009 (ie, during her second trimester). The tranexamic acid dose was increased during an attack to 1 g every 4 hours. In December 2009 (ie, during her third trimester), attack therapy was changed to C1-INH concentrate (20 U/kg). Prophylaxis of HAE was discontinued in April 2010, after childbirth. Moderate attacks were subsequently treated with tranexamic acid (1 g every 4 hours, over 24 hours); C1-INH concentrate (20 U/kg) was recommended for severe symptoms.

In June 2010, maintenance treatment was instigated with tranexamic acid (3 g/day); icatibant (30 mg) was used during attacks. This maintenance regimen was continued when the patient became pregnant again in December 2011, but the attack treatment was changed to C1-INH concentrate (20 U/kg). More frequent attacks led to the addition of C1-INH concentrate (1500 U/week) to the maintenance regimen, which was then increased to 1500 U twice weekly in May 2012 to limit attack frequency (which had occurred at a rate of around one attack per week on the once-weekly regimen) and intensity. No attacks subsequently occurred and the patient was able to stop tranexamic acid maintenance therapy in June 2012, thus simplifying treatment.

The patient was reluctant at first to begin prophylaxis with C1-INH concentrate during her second pregnancy, but she was ultimately very satisfied with its efficacy. The ability of the C1-INH treatment to completely stop attacks was reassuring for the patient and important for protection of the fetus. Furthermore, C1-INH concentrate was well tolerated, facilitating its use during pregnancy.

After delivery, the patient still required long-term prophylactic treatment with C1-INH concentrate 1500 U twice weekly. The dose was decreased after 2 months to 1500 U once weekly and finally discontinued in September 2013. Since then, she has experienced only one severe acute attack per month (or even less frequently), which has been treated with C1-INH concentrate. Currently, the patient’s preference is to not receive long-term prophylactic treatment, which is in accordance with international guideline recommendations.

CASE REPORT 5

A similar case report involves a 24-year-old woman who experienced her first type I HAE attack, involving the foot and ankle, at the age of 8 years. Her attacks became more frequent by 11 years of age and started to affect her

face. She continued to experience one attack per year, mostly of the hands or feet and less often the face, until 2007 when her attacks, which were not related to menstruation, extended to several locations and increased in frequency. Between 2007 and 2009, approximately 4 attacks per year affected her face or neck and went untreated. In addition, she lost her sight during this 2-year period. Her current attack symptoms consist of facial, neck, peripheral, abdominal, and epigastric angioedema.

Initial treatment with tranexamic acid (1.5–3 g/day) was administered between the ages of 11 and 14 years, and at the age of 15 years an edema of the uvula and larynx (with swallowing difficulty and dysphonia) was treated with C1-INH concentrate (20 U/kg/day). Short-term prophylaxis with C1-1NH concentrate (1000 U) was also administered between 2007 and 2009 to cover dental care. In 2010, icatibant (30 mg) was used; however, administration caused extreme pain at the injection site (VAS score 8). In addition, in June 2010, the combined contraceptive pill led to numerous attacks and although chlormadinone acetate was prescribed, it was not taken due to an intention for pregnancy. The patient had a miscarriage in October 2010 and afterwards experienced frequent attacks affecting the hands, periphery, and sometimes the face or oropharynx, prior to menstruation. These attacks were treated on demand with C1-INH concentrate, and in the case of facial attacks or functional disturbance before work, one injection of 500 U/week was administered by a nurse at home.

During her second pregnancy, which began in March 2012, the frequency of attacks increased severely, with a total of eight in April 2012. These were treated with 12 vials of C1-INH concentrate at a dose of 500 U due to the patient's fear of venous capacity. However, the prescribed dose was 1500 U and this underdosing of treatment was found to induce attack repetition. To minimize attacks during her pregnancy, prophylactic treatment with C1-INH concentrate (1500 U twice weekly) was initiated in May 2012. This treatment was effective; however, she experienced prodromal symptoms prior to receiving the second weekly dose on day 4 and therefore the administration frequency was increased to every 3 days in July 2012. This increased prophylactic treatment frequency was efficacious during pregnancy and the only reported adverse effect was a warming sensation of the infused vein. Overall, the patient was satisfied with the treatment. To prepare for childbirth, the woman received a 1500-U dose of C1-INH concentrate to prevent an attack during labor. After delivery, the patient has continued to receive long-term prophylactic treatment (C1-INH concentrate 1500 U twice weekly).

DISCUSSION

In these case reports, prophylaxis with C1-INH concentrate, either alone or with tranexamic acid, was associated with a complete cessation or significantly reduced frequency of acute HAE attacks. C1-INH concentrate prophylaxis also improved patient QOL and had a positive impact on patients' professional lives. Furthermore, patients were satisfied with C1-INH concentrate prophylaxis, indicating that intravenous administration was not an obstacle to treatment, and no patients discontinued treatment. No adverse events were reported by the patients, suggesting that tolerability was acceptable.

These results are consistent with earlier studies on the prophylaxis of HAE with plasma-derived C1-INH concentrates.[1,26-32] As early as 1989, Bork et al reported a case in which C1-INH concentrate (Berinert; 500 U), every 4 or 5 days for 1 year, resulted in a patient with HAE becoming symptom free.[1,26] More than 2 decades later, Tallroth showed that C1-INH concentrate (Berinert; 1000–1500 U), 3 times weekly for 5 years, was effective and well tolerated in a patient with HAE, producing a dramatic improvement in symptoms and better QOL.[29] The patient was free from swelling for 4.5 years at the time of the report. In a retrospective case-cohort review, 6 patients self-administered C1-INH concentrate (Berinert or Cinryze; 1000 U once or twice weekly, every 3 or 4 days) over an average of 18.1 months.[27] The mean monthly attack rate was 0.34/patient. The study by Bork et al published in 2011 is of particular interest.[28] A total of 14 patients with HAE received long-term prophylaxis with C1-INH concentrate (Berinert; 500–2000 U, 1–7 times weekly), for 5 to 19 years.[28] In 8 patients, attack frequency was lower at the end of the study compared with the prestudy period; however, the frequency of attacks increased in 5 patients and did not change in 1 patient.[28] Two patients were attack free, 6 patients experienced mild or very mild attacks, while 6 patients had predominantly mild attacks, although a few severe, sudden attacks occurred.[28] Although the authors acknowledged the benefits of receiving one or more injections of plasma-derived C1-INH concentrate per week (eg, less frequent, less severe, or absence of attacks), they stressed that potential risks should also be considered (eg, an increased number of attacks and injections).[28] In this case collection, 2 patients required an adjustment from their initial prophylaxis regimen to an increased frequency of dosing to control the frequency and intensity of acute attacks. In both cases, this change led to an acceptable level of control and was well tolerated.

The 2 case reports on pregnant patients demonstrated that C1-INH concentrates were successfully used as

maintenance therapy to control HAE attacks in a situation in which danazol was contraindicated and tranexamic alone was ineffective. They add to the small but growing evidence base supporting the use of C1-INH concentrates for prophylaxis against HAE attacks during pregnancy.[6,7,33-36] For example, in a retrospective analysis of 118 pregnancies (82 full-term and 36 abortions) in 41 women with HAE, C1-INH concentrate (91 vials in total) was well tolerated and effective in all cases when used to relieve acute attacks, or as short- or long-term prophylaxis.[7] The weaknesses of these case reports are relevant to all such studies, including the potential for selection bias.

Long-term prophylactic treatment is recommended in France, following international consensus guidelines,[10] when patients have more than one severe acute attack a month. The main goal for long-term prophylactic treatment is to limit acute attacks (especially severe acute attacks) and to improve patients' QOL.[37]

During pregnancy, some women experience an increase in HAE attacks, and, in these cases, we recommend the use of long-term prophylaxis with C1-INH concentrate. Apart from pregnancy, a similar approach is also taken in patients who suddenly experience an increase in attacks during certain periods of their life, for which long-term prophylaxis is recommended for weeks or months if necessary. Because autoantibody development against C1-INH in some patients receiving C1-INH concentrate has been previously reported,[15] potential autoantibody development should be investigated for all patients.

We choose to use short-term prophylaxis just before identified triggers (eg, surgical and dental procedures), as described in international consensus guidelines.[10] This also includes short-term C1-INH prophylaxis prior to delivery, as we consider this a trigger for HAE attacks.

SUMMARY

In conclusion, this collection of case reports not only provides further evidence of the efficacy of C1-INH concentrate for long-term prophylaxis of HAE but, importantly, also provides hope for patients who are intolerant of, or have a poor response to, other prophylactic therapies, or who want a safe pregnancy. In light of the current recommendations for consideration of long-term prophylaxis using C1-INH concentrates against HAE attacks, this approach warrants further clinical investigation.

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