



Letter

Real-life experience with long-term prophylactic C1 inhibitor concentrate treatment of patients with hereditary angioedema

Effectiveness and cost

Hereditary angioedema (HAE) is a rare genetic disease with recurrent angioedema that usually becomes symptomatic early in life. When the upper airways are involved, asphyxiation can occur. Complement C1 inhibitor (C1INH) deficiency causes an uncontrolled activation of the contact system with excessive bradykinin formation. Current consensus statements on HAE treatment suggests that long-term prophylactic treatment is warranted if the patient cannot achieve adequate benefit from on-demand therapy of attacks.¹ C1INH concentrate and attenuated androgens are the mainstays of long-term prophylaxis (LTP). C1INH can be used in all age groups and during pregnancy.² Only one brand of C1INH, Cinryze (C1INH-C), is currently licensed for LTP in Europe. Because of high cost and intravenous administration, the indication needs to be rather stringent.

A prospective observational study on the effectiveness of C1INH-C, 1,000 U twice weekly as LTP, in 6 Danish adults diagnosed as having HAE was performed. The included patients had 1 to 2 attacks per week or intolerable adverse effects when using attenuated androgens or on-demand therapy with C1INH or icatibant. All patients were taught to self-inject C1INH. The patients filled in a disease-specific diary and came for follow-up by a physician after 3 months and subsequently every 6 months. The severity of attacks was scored on a numerical scale. The study was approved by the Danish Data Protection Agency, which serves as an institutional review board.

Six patients met the inclusion criteria. All patients were white and had HAE type 1; the mean age was 36.7 years (range, 25–48 years) at the time of inclusion. The male-female ratio was 1:1.

The overall attack rate was reduced with 63 % in the study period (Table 1). The potentially life-threatening attacks in the head and neck area were reduced by 80%. One patient conceived during the study period, and thus her attack rate might have been higher because of the pregnancy.

The mean duration of an attack during LTP with C1INH-C was reduced by 52%. Severity, as per the numerical scale, was not significantly affected by introduction of prophylactic therapy with C1INH-C (Table 1). All patients used 1 or more different medications to treat a total of 67 breakthrough attacks during the study period (Cinryze, Firazyf, Ruconest, or Berinert), depending on availability and personal preferences. The treatment delay and absence from school or work and social events were reduced

(Table 1). The drug was generally well tolerated because only 1 patient reported an adverse reaction as “feeling unwell after injection.” No objective pathologic findings were visible.

The main challenge encountered by patients was to obtain correct injection technique. One patient had troubles with the injection technique at times; however, the patient’s attack frequency was still reduced by more than 80%. One patient ran out of C1INH-C supply and was not able to travel to the HAE center to collect more medication. During the 3-week break from LTP, the patient experienced 6 attacks as opposed to 1 attack in 10 months while using C1INH-C.

The expense of LTP with C1INH-C in Denmark was calculated to be approximately €182,829 per year. For comparison, a typical Danish patient with a mean of 4 attacks per month treated with icatibant would cost approximately €93,792 per year when using a single dose per attack (€1,984 per dose). The price of LTP with attenuated androgens is approximately 370 times less than that of C1INH-C.

HAE is a disease with different phenotypes, and some patients need LTP.³ In this study, the overall frequency of attacks decreased by 63% after administration of C1INH-C; however, large variations among patients were observed. This finding is in concordance with previous findings.^{2,4} The cohort size is a limitation, and therefore firm conclusions are not possible. The mean duration of an attack and the number of hours lost from school or work were reduced remarkably. It has previously been suggested that C1INH concentrate might reduce the number of abdominal and head and/or neck attacks.⁵ Our study supports this suggestions. One minor adverse event was observed. Attenuated androgens in a low dosage can be used as an effective LTP in selected, mainly male, adult patients under close observation because attenuated androgens might cause potentially serious adverse effects. For some women, an effective and cheap alternative is progestins, but in Denmark this treatment option has traditionally not been much explored because of the availability of other effective alternatives.⁶

Patients and society benefit from home therapy because the mean number of hospital visits can be reduced with as much as 84% and patients have a significantly higher general health-related quality-of-life score.^{7,8} LTP with C1INH, however, poses a substantial economic burden on the health system, which has to be taken into consideration. The cost of emergency department visits and admissions should also be included in the calculation because a previous study found that emergency department visits and hospital admissions accounts for 68% of the cost when treating a patient with severe HAE. In addition, the indirect cost of lost productivity, missed work, and lost income has so far been estimated to be approximately €15,000 in the typical patient with HAE.⁹ Thus, newer and more costly drugs have a much higher effectiveness and lower risk profile, which justifies the use of them in selected patients.

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Table 1
Characterization of angioedema attacks

Characteristic	Before C1INH-C Prophylaxis	During C1INH-C Prophylaxis
Follow up, mo	61 (mean, 10.1; median, 11; range, 6–13)	50 (mean, 8.3; median, 8.5; range, 4–15)
Attack frequency, mean/mo	4.6 (range, 3.5–8)	1.7 (range, 0.1–3.7)
Duration, mean, h	38.7 (range, 14–44) ^a	20 (range, 6–44)
No. of treated breakthrough attacks with rescue medication		63 (range, 1–36 per patient)
		Cinryze: 39
		Firazyr: 24
		Beriner: 3
		Ruconest: 1
Treatment delay, mean, h	3.9 (range, 0–15.2)	2.2 (range, 0–8.5)
Severity score on a scale of 0 to 3 (3 being the worst), mean	2.1 (range, 1–3) ^a	2.3 (range, 0.5–3)
Absence from work, school, or social events, mean, h	7.6 (range, 1–3) ^a	4 (range, 0–12)
Localization of attacks, No. (%)		
Peripheral	62 (22)	19 (22)
Abdominal	123 (44)	37 (43)
Multifocal	59 (21)	23 (27)
Head and neck	15 (5)	4 (5)
Genital	3 (1)	1 (1)
Unknown	19 (7)	2 (2)

Abbreviation: C1INH-C, Cinryze brand of C1 inhibitor.

^aOnly 1 patient had registered these data in the period before initiation of long-term prophylaxis with C1INH-C.

Most patients with HAE are otherwise healthy people, and with the correct individualized treatment plans, they will be able to lead normal productive lives. LTP should be considered at the time of diagnosis if the disease severity indicates so, but on-demand therapy will often be sufficient.¹⁰ However, no type of LTP should stand alone, and an optimal treatment plan includes an on-demand option and clinical follow-up. In conclusion, LTP is indicated in patients with HAE with frequent or severe angioedema attacks. The benefit from LTP with C1INH-C should be well considered in each patient because the cost of the treatment is significant.

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