

Self-administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency

Marcel Levi, MD,^a Goda Choi, MD,^a Charles Picavet, MA,^b and C. Erik Hack, MD^{c*}

Amsterdam, The Netherlands

Background: Administration of C1-inhibitor concentrate is effective for prophylaxis and treatment of severe angioedema attacks caused by C1-inhibitor deficiency. The concentrate should be administered intravenously and hence needs to be administered by health care professionals, which might cause considerable delay in treatment and inconvenience for patients.

Objective: The aim of this study was to investigate the feasibility, efficacy, and safety of on-demand and prophylactic self-administration of C1-inhibitor concentrate in patients with frequent attacks of angioedema.

Methods: Patients with hereditary or acquired C1-inhibitor deficiency who had very frequent angioedema attacks were trained to self-administer C1-inhibitor concentrate. The study consisted of 31 patients using on-demand treatment and 12 patients using prophylaxis with C1-inhibitor concentrate. Mean follow-up was 3.5 years.

Results: All patients were capable of self-administering the concentrate, with technical failure rates of self-injection being less than 2%. Times between the onset of the attack and the initiation of relief or complete resolution of symptoms in the on-demand group were significantly shortened (2.2 hours and 7.9 hours, respectively) compared with the situation before the start of self-administration. In the prophylaxis group self-administration of C1-inhibitor concentrate decreased the angioedema attack rate from 4.0 to 0.3 attacks per month.

Conclusion: Intravenous self-administration of C1-inhibitor concentrate is a feasible and safe option and results in more rapid and more effective treatment or prevention of severe angioedema attacks in patients with C1-inhibitor deficiency. **Clinical implications:** Self-administration of C1-inhibitor concentrate could be a valuable and convenient treatment modality to prevent or treat angioedema attacks in patients with C1-inhibitor deficiency. (*J Allergy Clin Immunol* 2006;117:904-8.)

Key words: C1-inhibitor deficiency, C1-inhibitor concentrate, hereditary angioedema, acquired angioedema

Deficiency of C1-inhibitor leads to recurrent angioedema attacks and can be an incapacitating disorder that might even result in life-threatening situations.¹⁻⁴ The deficiency might be due to an inherited (autosomal dominant) or spontaneously occurring genetic defect. It also might be caused by an acquired condition, such as the formation of autoantibodies toward C1-inhibitor or the formation of anti-idiotypic antibodies in patients with lymphoproliferative disease, leading to consumption of C1-inhibitor. The angioedema attacks might occur at various sites of the body (often the extremities), but in particular, angioedema attacks in the orofacial region and upper airways (leading to airway obstruction and the risk of asphyxia) and in the abdomen (leading to severe symptoms of pain and vomiting, mimicking an acute abdomen) require immediate medical attention. Angioedema attacks might be prevented by administration of androgenic steroids, such as danazol.⁵ However, this agent is sometimes not well tolerated by women, apart from its adverse effects on blood lipids and the risk of liver tumors on long-term use.⁶⁻⁸ Alternatively, administration of lysine analogues, such as ϵ aminocaproic acid or tranexamic acid, is in some, although not all, patients effective as a preventive strategy or in case of an (imminent) angioedema attack.^{9,10} The most rational form of treatment, however, is administration of C1-inhibitor. Purified concentrates of C1-inhibitor derived from human plasma have been available for many years, are licensed in Europe and under study in the United States, and have shown to be effective in the treatment of severe angioedema attacks in patients with hereditary and acquired C1-inhibitor deficiency.¹¹⁻¹⁴ A limitation of this treatment is that it can only be administered by means of intravenous injection, which might result in dependency on emergency departments or general practitioners and hence in a considerable physician delay and inconvenience for the patient. Therefore the ability that patients could self-administer the C1-inhibitor concentrate might hypothetically result in earlier and therefore more effective treatment and increased patient independence and treatment satisfaction. The feasibility, efficacy, and safety of self-administration of C1-inhibitor concentrate has not been reported in the literature thus far. We here report our experience with the preventive or therapeutic self-administration of C1-inhibitor concentrate in patients with hereditary or acquired C1-inhibitor deficiency and frequently occurring severe attacks of angioedema.

From ^athe Department of Internal Medicine, Academic Medical Center, University of Amsterdam; ^bThe Netherlands Patient Association of Hereditary Angio-edema and Quincke's Edema; and ^cthe Landsteiner Laboratory, Academic Medical Center, University of Amsterdam, and the Department of Clinical Chemistry, Free University Medical Center, Amsterdam.

*Dr Hack is currently affiliated with Crucell Holland BV, Leiden, The Netherlands.

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Reprint requests: Marcel Levi, MD, Department of Medicine (F-4), Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105AZ Amsterdam, The Netherlands. E-mail: m.m.levi@amc.uva.nl.

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METHODS

Patients

The diagnosis of hereditary angioedema was based on the clinical presentation, with recurrent attacks of angioedema and a low functional level of C1-inhibitor (<0.5 U/mL, chromogenic assay; Dade Behring, Marburg Germany) and C4 (<100 mg/L, nephelometric assay; Sanquin, Amsterdam, the Netherlands) in plasma. A family history of C1-inhibitor deficiency was an additional (but optional) criterion to establish a diagnosis of hereditary angioedema. In addition, in the majority of patients, genetic analysis was performed, revealing a mutation in the C1-inhibitor gene. Acquired angioedema was diagnosed when the onset of the angioedema attacks occurred at an age of more than 25 years, when there were low levels of C1q (<80 IU/mL, nephelometric assay, Sanquin) in combination with the low levels of C1-inhibitor and C4 (as above), (optionally) when the presence of anti-C1-esterase inhibitor antibodies (by means of ELISA)¹⁵ could be demonstrated, or (optionally) when a diagnosis of a lymphoproliferative disorder was made.

In this study 2 types of patients were included: (1) patients who, despite preventive medication regularly (>1 per 3 weeks), presented with severe angioedema attacks (see definition of severe attacks below) and therefore frequently required administration of C1-inhibitor concentrate (on-demand treatment) for an observation period of more than 2 years, and (2) patients who, despite preventive medication or without preventive medication because of intolerance, had very frequent attacks of angioedema (>1 per 10 days) and who were therefore eligible for prophylactic administration of C1-inhibitor concentrate (prophylactic treatment) for an observation period of longer than 1 year.

The study was approved by the institutional review board, and patients provided informed consent on inclusion in the study.

Treatment

Regular preventive treatment in patients with C1-inhibitor deficiency consisted of danazol (100-400 mg daily) alone or in combination with tranexamic acid (2-3 g/d) in case of (imminent) angioedema attacks. When danazol was not tolerated, tranexamic acid was administered as prophylactic treatment on a daily basis. If, despite this treatment, a severe angioedema attack occurred, patients were treated with intravenous administration of 1000 U of plasma-derived C1-inhibitor concentrate (Cetor; Sanquin, Amsterdam, The Netherlands). C1-inhibitor is a highly purified product that is prepared from screened volunteer donor plasma from which the cryoprecipitate and prothrombin complex factors are removed. C1-inhibitor is obtained from the plasma through ion exchange chromatography and subsequent polyethylene glycol precipitation of the eluate. The C1-esterase inhibitor concentrate obtained is pasteurized in solution (10 hours at 60°C). The elimination half-life of this C1-inhibitor concentrate in patients with hereditary angioedema was shown to be 48 hours after a single intravenous administration of 1000 U in previous studies. These studies indicated that with a dose of 1000 U, patients would have an increase in plasma levels of greater than 0.3 U/mL for at least 4 days, which is thought to be sufficient to treat or prevent angioedema attacks. On the basis of this elimination half-life, patients eligible for prophylactic C1-inhibitor were assigned to a regimen of administration of C1-inhibitor concentrate every 5 to 7 days.

Self-administration of C1-inhibitor was done after extensive education of patients. This included additional background information on the disease and its treatment, the indications for administration of C1-inhibitor concentrate, and the requirement of proper documentation of symptoms and administration of the agent. Although the administration of C1-inhibitor has never been reported to cause allergic responses thus far, patients were nevertheless instructed how

to handle such a reaction in case it might occur. Furthermore, patients were educated on how to prepare the lyophilized medication with sterile water for injection (total volume of 10 mL after reconstitution) and how to properly work with syringes and needles. Subsequently, patients were taught how to perform a self-venipuncture with a butterfly needle (mostly in an antecubital vein). Education on self-treatment consisted of 2 or 3 individual sessions of 1 hour each performed by a physician or a nurse specialized in intravenous self-administration of medical agents.

Outcome

A severe attack of angioedema was defined as an attack of angioedema in the orofacial region or in the upper airway or a serious abdominal attack (severe abdominal pain with nausea and vomiting). Other attacks, such as swelling of the extremities or angioedema in the genitourinary region, were recorded as less severe angioedema attacks.

Patients receiving on-demand treatment were asked to record the time from the onset of a severe angioedema attack to the time they received the intravenous injection of C1-inhibitor concentrate (attack-to-treatment time). Also, the time to improvement of symptoms, as well as the time to complete resolution of symptoms, was recorded.¹³ As a control, patients reported on their regular attack-to-treatment time and time to improvement and resolution of symptoms at the 5 previous occasions of severe angioedema before they started with self-administration of the C1-inhibitor concentrate. This information was requested at the beginning of self-administration and again at the end of the follow-up period to minimize recall bias. In addition, 10 patients with angioedema caused by C1-inhibitor deficiency who were not participating in the self-administration program served as additional control subjects.

The mean follow-up of patients in the on-demand group was 3.8 years (range, 0.9-5.1 years), and the mean follow-up in the prophylaxis group was 3.5 years (range, 1.6-4.3 years).

Statistical analysis

Data are presented as means \pm SD. Statistical analysis was performed by means of Kaplan-Meier survival analysis with a log-rank test and the Mann-Whitney *U* test. A *P* value of less than .05 was considered statistically significant.

RESULTS

Study population

The on-demand group consisted of 31 patients, 28 with hereditary C1-inhibitor deficiency and 3 with acquired C1-inhibitor deficiency. The prophylaxis group included 10 patients with hereditary C1-inhibitor deficiency and 2 patients with acquired C1-inhibitor deficiency (total of 12 patients). Five of the 12 patients in the prophylaxis group had very frequent (>1 per 10 days) angioedema attacks despite full treatment with danazol and tranexamic acid and were therefore considered for C1-inhibitor concentrate prophylaxis. The other 7 patients did not receive danazol because of intolerable virilization effects in women ($n = 5$), severe dyslipidemia in a patient with a history of cardiovascular disease ($n = 1$), and nonspecific side effects ($n = 1$). In these patients prophylaxis was started because all of them had very frequent (>1 per 10 days) angioedema attacks. Clinical characteristics of patients in both groups are given in Table I.

TABLE I. Characteristics of patients on on-demand treatment and prophylaxis with C1-inhibitor concentrate

	On-demand treatment	Prophylaxis
Total	31	12
Hereditary C1-inhibitor deficiency	28	10
Acquired C1-inhibitor deficiency	3	2
Age, y (\pm SD)	43 \pm 8	38 \pm 12
M/F ratio	14/17	4/8
Years from diagnosis (\pm SD)	24 \pm 4	22 \pm 7
Frequency of severe attacks (\pm SD)*	1 per 16.6 (\pm 4.1) days	1 per 7.9 (\pm 2.0) days
Site of attacks		
Orofacial	15%	18%
Laryngeal	2%	1%
Abdominal	31%	37%
Genitourinary	8%	10%
Extremities	44%	34%
Medication		
Danazol	94%	58%
Tranexamic acid	16%	50%

*During an observation period of at least 1 year.

Feasibility of self-administration of C1-inhibitor concentrate

All patients in both groups completed the education and instruction program without problems. All patients were capable of performing the self-venipuncture and self-injection of C1-inhibitor. They all kept adequate records, including the date of self-administration of C1-inhibitor concentrate, the reason for the injection, the lot number of the concentrate used, and any adverse effects. During the follow-up period, in the on-demand group a mean number of 21.4 \pm 5.3 injections were self-administered per patient, with a reported mean technical failure rate of 1.8% (range, 0% to 5.7%) per patient. In the prophylaxis group the mean number of injections per patient during the follow-up period was 185.3 \pm 28.4, with a reported mean technical failure rate of 0.8% (range, 0% to 3.1%) per patient.

Efficacy of self-administration of C1-inhibitor concentrate in the on-demand and prophylaxis groups

The time between the onset of a severe attack and the self-administration of C1-inhibitor (attack-to-treatment time) was 1.4 \pm 1.0 hours compared with 3.4 \pm 2.1 hours before the start of the self-administration when patients relied on medical professionals for administration ($P = .01$). As shown in Fig 1, the time to improvement of symptoms and complete resolution of symptoms after the onset of a severe angioedema attack was proportionally shorter after self-administration compared with during the historical control period. Fig 2 shows the mean time to initiation of relief and complete resolution of symptoms for patients with hereditary and acquired C1-inhibitor deficiency, respectively. Interestingly, the time to complete resolution

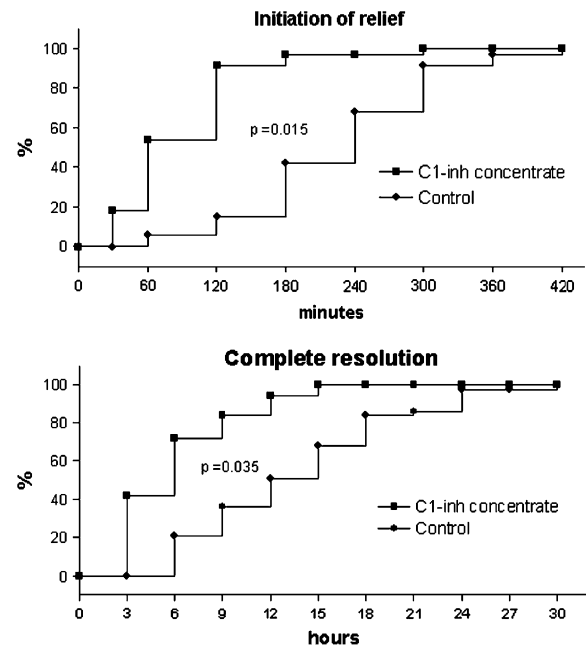


FIG 1. Effect of self-administration of C1-inhibitor (C1-inh) concentrate on the initiation of relief and the complete resolution of symptoms after the onset of the angioedema attack. Controls refers to historical control subjects before the start of self-administration of C1-inhibitor concentrate.

of angioedema from the start of an attack was markedly more reduced (5.9 \pm 2.2 hours in self-treated patients compared with 13.8 \pm 2.9 hours in patients after conventional treatment) than could be explained by the earlier administration of C1-inhibitor concentrate. There were no significant differences between patients with hereditary C1-inhibitor deficiency and patients with acquired C1-inhibitor deficiency regarding clinical responses to C1-inhibitor. Data from the historical control period were virtually identical with data from the 10 control patients who did not participate in the self-administration program (mean time to initiation of relief in historical control subjects of 171 minutes vs 185 minutes in control subjects and mean time to complete resolution in historical control subjects of 13.8 hours vs 14.3 hours in control subjects). In the prophylaxis group the number of angioedema attacks was dramatically reduced after the start of prophylaxis, both in patients with hereditary C1-inhibitor deficiency and in patients with acquired C1-inhibitor deficiency (Fig 3). The mean interval between 2 prophylactic injections was 6.8 \pm 1.0 days. Seven (58%) of 12 patients were completely free of angioedema attacks after the start of prophylaxis, whereas 5 patients had occasional angioedema attacks despite prophylaxis but not more frequently than once per 6 months (3 patients [25%]) or once per 3 months (2 patients [17%]). Mean peak plasma levels of C1-inhibitor after the intravenous administration of 1000 U of C1-inhibitor concentrate were 1.1 \pm 0.2 U/mL. At 48 hours after the administration, plasma levels were 0.7 \pm 0.2 U/mL, and at 5 days after the administration, C1-inhibitor levels were 0.3 \pm 0.1 U/mL. In case of a severe angioedema attack

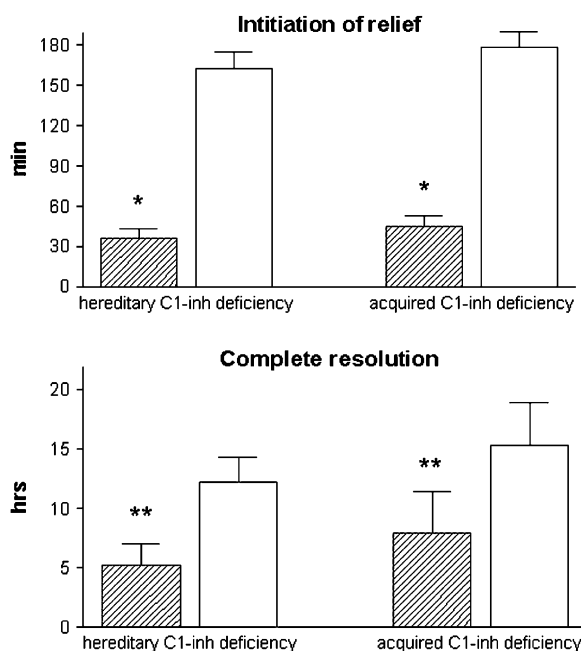


FIG 2. Mean time to initiation of relief and complete resolution of symptoms in patients with hereditary and acquired deficiency of C1-inhibitor (*C1-inh*) after the onset of the angioedema attack when patients self-administer C1-inhibitor concentrate (striped bars) compared with the situation before they started self-management (open bars). Mean values and SDs are given. * $P < .01$, ** $P < .05$.

during the prophylaxis period, patients used additional C1-inhibitor concentrate, which was successful in all instances. There was no need to seek medical attention for any of these episodes during the follow-up period. Patients with acquired C1-inhibitor deficiency had similar results as patients with hereditary deficiency, and in this series there were no indications that patients with acquired C1-inhibitor deficiency required more frequent injections or higher doses over time (although the number of patients with acquired angioedema was small).

Safety

No serious adverse events occurred with self-administration of C1-inhibitor during the follow-up period. Recorded adverse events included skin irritation at the site of injection (2.1% of injections), minor hematomas at the puncture site (1.6% of injections), dizziness at the time of injection (0.3% of injections), mild pain in the extremities after the injection (0.3% of injections), and a subfebrile increase in temperature (0.1% of injections). All adverse events were self-limiting and did not result in the need to seek medical assistance.

DISCUSSION

Hereditary or acquired C1-inhibitor deficiency results in angioedema attacks with important clinical consequences, depending on their localization and severity.¹ Apart from the morbidity caused by these attacks and

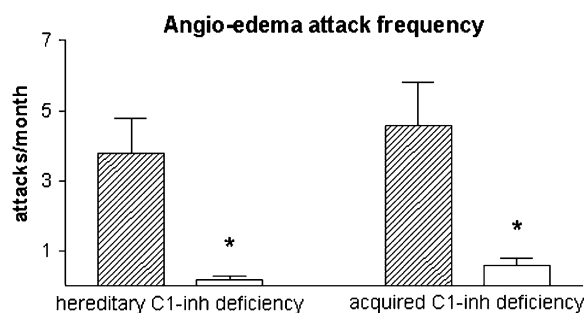


FIG 3. Frequency of angioedema attacks per month after initiation of prophylaxis with C1-inhibitor (*C1-inh*) concentrate (striped bars) compared with the situation before the start of prophylaxis in patients (open bars) with hereditary and acquired C1-inhibitor deficiency. Mean values and SDs are given. * $P < .001$.

the risk that a life-threatening situation will occur, patients suffer from the unpredictable nature of the disease and the dependence of medical facilities when they need intravenous treatment with C1-inhibitor. This might lead to unnecessary delays before appropriate treatment is instituted. Here we show that after a short education and training program, on-demand self-administration of C1-inhibitor concentrate is a feasible option in patients who have frequent, serious angioedema attacks. Patients are shown to be capable of self-administering the intravenous medication without technical problems or medical complications. The observation that patients are capable of self-administration of intravenous medication is reminiscent of the experience in other conditions, such as intravenous self-administration of clotting factor concentrates in patients with hemophilia.¹⁶

In patients with on-demand treatment, self-administration resulted in a decreased time between the onset of the attack and the administration of C1-inhibitor concentrate. Consequently, the time between the onset of the attack and the initial relief of symptoms was proportionally decreased. Unexpectedly, however, the time to complete disappearance of symptoms was much more reduced than could be expected on the basis of the earlier treatment of the patients, suggesting that early C1-inhibitor treatment during an angioedema attack more efficiently shortens the duration and reduces the severity of the attack.

Self-administration of C1-inhibitor concentrate also facilitates the use of this treatment as prophylaxis in patients with very frequent angioedema attacks despite full treatment with first-line drugs to prevent angioedema attacks (eg, the administration of danazol and tranexamic acid) or in patients who do not tolerate full first-line prophylaxis. These patients self-administered C1-inhibitor concentrate about once every week, resulting in a virtual elimination of angioedema attacks. In view of the half-life of C1-inhibitor of about 48 hours, the observation that approximately once-weekly prophylactic administration appears to be effective in almost completely preventing angioedema attacks in these patients confirms the notion that for prevention of attacks, subphysiologic levels of C1-inhibitor (as low as 40% of normal levels) are

sufficient. The virtual lack of any angioedema attacks with the dosing schedule of once per 5 to 7 days might indicate that larger dosing intervals, with consequently less consumption of C1-inhibitor concentrate, might be possible, although this remains to be studied.

We did not formally assess sequential quality-of-life issues in our cohorts of patients. However, from previous studies, it is clear that the unpredictability of the disease and the dependence on physicians and others to receive timely and adequate treatment is a serious concern for patients with C1-inhibitor deficiency.¹⁷ In addition, social issues, such as absence from work or school, might become seriously distressing as well. We speculate that self-administration of C1-inhibitor concentrate might be helpful in diminishing these worries and issues that might affect the quality of life in patients with C1-inhibitor deficiency.

Obviously, there are also some limitations associated with the use of C1-inhibitor concentrate in general and potential hazards of self-administration by patients. C1-inhibitor concentrate is a plasma-derived product and therefore carries the risk of transmission of blood-borne infections.¹⁸ Although proper microorganism-reducing steps, such as careful donor selection and screening, heat treatment and, more recently, nanofiltration of the product, in addition to other measures, at present minimize the risk of transmission of infectious agents, the use of blood-derived products should in general be restricted as much as possible. This requirement was part of our education for patients, who, as a rule, actually did not need much encouragement to use as little as possible of this blood product. Our initial theoretic fear that self-administration of C1-inhibitor could result in overconsumption of the concentrate (eg, being used also for less severe but still annoying attacks) was not justified in our study. From the documentation of the patients receiving self-administration (discussed every 3-6 months during their visit at the outpatient clinic), it was clear that patients strictly adhered to the predefined indications for use of C1-inhibitor concentrate.

In conclusion, intravenous self-administration of C1-inhibitor concentrate is a feasible option for patients who frequently need this treatment and results in more rapid and potentially therefore more effective treatment of severe angioedema attacks in patients with C1-inhibitor deficiency. In addition, self-administration might facilitate prophylactic treatment schemes in patients with very frequent angioedema attacks if other options are insufficiently effective.

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