
Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients

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Background: Hereditary angioedema (HAE) due to C1 inhibitor deficiency is clinically characterized by relapsing skin swellings, abdominal pain attacks, and life-threatening upper airway obstruction. Treatment with androgens prevents attacks for those with this condition.

Objective: To examine the benefits and risks of long-term treatment with danazol.

Methods: Data were generated retrospectively from 118 German and Danish patients who had HAE due to C1 inhibitor deficiency and were treated with danazol from 2 months to 30 years. The frequency and severity of acute attacks were registered before and during danazol treatment, and adverse effects to the treatment were noted. Data were collected by using standardized questionnaires.

Results: In all, 111 of 118 patients responded to danazol. During treatment, 54 of the 118 patients (45.8%) became symptom free or had 1 attack or less per year. In the other patients, hereditary angioedema ran a mild course. The frequency of acute attacks during danazol treatment was reduced to 16.2%, and the attacks were considerably milder than before treatment. Laryngeal edema was reduced to 4.8%. Adverse effects (weight gain, virilization, menstrual irregularities, headache, depression, and/or liver adenomas) occurred in 93 of the 118 patients and led to discontinuation of danazol therapy in 30 patients.

Conclusions: Danazol is highly beneficial in patients with frequent and severe attacks of HAE. Because the risk of adverse effects is high, close monitoring of patients is mandatory. However, many patients accept the adverse effects of prophylactic treatment to avoid the distressing and sometimes life-threatening attacks of this condition.

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INTRODUCTION

Hereditary angioedema (HAE) was first described clinically by Quincke¹ and Osler.² Classic HAE types I and II (Mendelian Inheritance in Man 106100) are associated with functional deficiency of C1 inhibitor (C1-INH) in plasma due to mutations of the C1-INH gene.^{3,4} The pathogenesis of the acute edema attacks of HAE is not completely known. The low plasma concentration of functionally active C1-INH permits the activation of the kallikrein-kinin system, the early steps of the classic complement pathway, and even the fibrinolytic system, causing the release of vasoactive peptides. Recent data suggest that bradykinin (BK) is the most important mediator of HAE attacks: (1) BK increased in plasma during acute attacks of HAE,^{5,6} (2) BK levels were higher in blood drawn from an angioedema site vs levels in the systemic circulation,⁷ (3) a mouse deficient in the *C1inh* and the *Bkb2r* (bradykinin B2 receptor) gene revealed diminished vascular permeability (this finding suggests that the BK/BKB2R pathway mediates angioedema formation),⁸ and (4) the BKB2R antagonist Icatibant is effective in skin swellings and abdominal pain attacks of HAE due to C1-INH deficiency.⁹

Clinically, HAE is characterized by relapsing episodes of edema at various body sites followed by disease-free intervals of variable duration. Skin swelling is disfiguring and in the case of facial edema bears the risk of being followed by laryngeal edema.¹⁰ Abdominal attacks are characterized by severe crampy pain, with or without vomiting, diarrhea, and ascites (termed *abdominal attacks*).¹¹ Episodes of upper airway obstruction (usually laryngeal edema) are potentially life threatening, and many cases of death by asphyxiation have been reported.¹²

Acute attacks can be treated successfully with C1-INH concentrate administered intravenously. In patients with many attacks, however, it is preferred to avoid attacks by a long-term prophylactic treatment instead of treating acute attacks. Long-term prophylaxis in those with HAE is performed with attenuated androgens (mainly danazol and stanozolol), tranexamic acid, or C1-INH concentrate substitution. After the benefit of methyltestosterone was found in 1960, danazol, an attenuated androgen, was introduced in 1976 in the prophylactic treatment of HAE.^{13,14} Later, stanozolol and oxandrolone were used in the long-term treatment of HAE; however, these drugs are not available in many countries.^{15,16} Since 1976, it has been reported that many patients can benefit from danazol.^{17–19} Because danazol may cause a number of mild to severe adverse effects, a high degree of attention to the benefit-risk ratio is required. Tranexamic acid can be moderately effective, at best. The experience of researchers and clinicians with C1-INH concentrate for long-term prophylaxis has been limited.^{20,21} It is likely that atten-

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uated androgens, with their advantages (effective, orally administered, and inexpensive) and disadvantages (high rate of adverse effects and sometimes severe adverse effects), will be used in the future in many patients who have frequent HAE attacks. Therefore, information about what patients can expect from this kind of long-term treatment in regard to benefits and adverse effects is extremely important for patients with severe HAE; such patients are disabled by their attacks and often cannot live a normal life because of the social and professional effects of the disease.

It is, therefore, important to ask the following questions concerning the benefits. (1) What is the response rate? (2) How effective is the treatment? How many patients become completely or nearly completely symptom free during this treatment? Concerning the risks, the following questions should be asked: (1) How many patients tolerate danazol without any adverse effects? (2) How many patients prefer to take danazol despite minor adverse effects, and what kinds of adverse effects occur and are tolerated? (3) How many patients discontinue danazol because of adverse effects, and what kinds of adverse effects cause discontinuation?

The aim of the present study is to answer these questions (ie, to quantify the benefits of danazol treatment and its adverse effects to determine the risk-benefit ratio in the treatment of HAE). We present data from a large series of patients with HAE before, during, and after long-term treatment with danazol.

METHODS

Study Design

Our retrospective analysis was based on data from clinical case record files. Criteria evaluated were the frequency and severity of episodes of HAE and affected organs before, during, and after treatment with danazol. Concerning potential adverse effects, subjective and objective data were registered. Documentation was accomplished by using standardized questionnaires.

Patients

A total of 356 patients with HAE due to C1-INH deficiency were surveyed in the angioedema outpatient service at the Department of Dermatology, University of Mainz, Mainz, Germany ($n = 277$), and at the Department of Dermatology, University of Odense, Odense, Denmark ($n = 79$). The diagnosis of HAE was made based on patient history, clinical examination, and laboratory results, including deficiency of functional C1-INH and C4 in plasma. In all, 118 of the 356 patients received danazol for long-term prophylaxis and constituted the sample of the present investigation. Basic information is summarized in Table 1.

Data Collection and Presentation and Laboratory Methods

When the patients were seen for the first time, they were asked about the affected organs in all episodes they had experienced until that time. Then, for each individual organ, they were asked about the onset of the first episode and the

Table 1. Basic Data Regarding 118 Patients With HAE Who Received Long-term Treatment With Danazol^a

Variable	Value ^b
Age, mean $\pm$ SD (range), y	
At the end of the study	50.0 $\pm$ 14.7 (17–85)
At the start of danazol treatment	33.3 $\pm$ 13.6 (15–74)
Male-female ratio	60:58
C1-INH protein level, mean $\pm$ SD, g/L ^c	
Those with HAE type I	0.05 $\pm$ 0.03
Those with HAE type II	0.29 $\pm$ 0.16
C1-INH activity (all patients), mean $\pm$ SD, % ^d	16.90 $\pm$ 9.60
C4 level (all patients), mean $\pm$ SD, g/L ^e	0.09 $\pm$ 0.05
Length of treatment, y	
≤ 1	16
2–5	21
6–10	21
11–15	27
16–20	19
21–25	6
26–30	8
Dosage, mg/d	
100	49
101–200	48
201–300	12
301–400	5
401–500	0
501–600	2
>600	2

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

^a There were 115 patients (88 families) with type I HAE and 3 patients (3 families) with type II HAE.

^b Data are given as number of patients unless otherwise indicated.

^c The normal range for C1-INH protein level was 0.15 to 0.35 g/L.

^d The normal range for C1-INH activity was 70% to 130%.

^e The normal range for C4 level was 0.20 to 0.50 g/L.

frequency of edema episodes per year. The visit included a physical examination and laboratory confirmation of the diagnosis of HAE. Later, the patients were seen for follow-up every 4 to 6 months during the first year and yearly thereafter. At each contact, the frequency of episodes and affected body sites of the symptoms were evaluated by questioning the patients and by analyzing a swelling calendar that the patients completed at home, noting time, duration, and severity of their angioedema episodes and the organs involved. In cases of missing data, patients were contacted by telephone.

One aim of the study was to quantify the reduction of swelling during danazol treatment. Therefore, for every patient, we recorded the number of edema attacks during the 3 years that preceded the onset of danazol treatment and, thus, calculated the average number of attacks per year. We compared this number with the average number of attacks per year that occurred during the years of prophylactic danazol treatment. Concerning adverse effects of long-term treatment with danazol, we obtained information about adverse effects that led to discontinuation of danazol therapy and adverse effects that were tolerated.

Protein levels of C1-INH antigen, C4, and C1q were assayed by radial immunodiffusion, and C1-INH activity was determined using the chromogenic substrate C₂H₅CO-Lys(e-Cbo)-Gly-Arg-pNA (Immunochrom C1-INH; Technoclone, Vienna, Austria).

RESULTS

A total of 118 of the 356 patients received danazol for 11.0 years on average (SD, ± 7.9 years; range, 2 months–30 years) (Table 1). Of the 118 patients, a subtotal of 58 received danazol for 2 months to 10 years, 46 for 11 to 20 years, and 14 for 21 to 30 years. The dosage at the beginning of treatment varied from 100 to 200 mg/d of danazol (our regimen) up to 600 mg/d (according to a regimen recommended previously in the literature).^{14,17,22} Gradually, the daily dose was reduced until the minimal effective dose was reached. The mean dosage of the 118 patients was 171.2 mg/d of danazol (range, 40–1,000 mg) (Table 1). Only 21 of the 118 patients received more than 200 mg/d of danazol on average.

In 58 of the 118 patients, use of the drug was discontinued. The reasons for discontinuation of the drug were as follows: (1) adverse effects ($n = 30$), (2) fear of adverse effects ($n = 11$), (3) no longer necessary ($n = 8$), and (4) ineffective ($n = 7$). Two patients discontinued use of the drug because of other reasons.

Benefits

The benefits of danazol treatment were great in most patients. Figure 1 shows the reduction rate of attacks during danazol treatment compared with the pretreatment period. In 7 of the 118 patients (5.9%), danazol was ineffective. In the 118 patients, the mean number of attacks per patient before treatment was 33.3 per year (SD, ± 26.0 per year) for 3 years. The mean number of attacks during danazol treatment per year per patient was 5.4 (SD, ± 9.7 per year) (ie, the reduction rate was 83.8%). Thus, the frequency of attacks per year during prophylactic treatment with danazol was greatly reduced in most of the patients compared with the pretreatment period (Fig 2A). This result was true for skin swelling, abdominal attacks, and laryngeal edema (Fig 2B–D). Laryngeal edema

occurred before treatment with danazol at a frequency of 0.271 per year per patient, and during danazol treatment at a frequency of 0.013 per year per patient (ie, the frequency of laryngeal edema was reduced from 100% to 4.8%).

During the period of taking danazol, 28 of the 118 patients (23.7%) were completely symptom free. Twenty-six patients (22.0%) had 1 attack or fewer per year, 32 (27.1%) had greater than 1 to 5 attacks per year, and 15 (12.7%) had greater than 5 to 10 attacks per year. Despite the treatment, 17 of the 118 patients (14.4%) had 11 attacks or more per year. (Percentages do not total 100 because of rounding.)

For some of the 5,026 attacks that occurred during danazol intake in the 118 patients, the following reasons for breakthrough attacks were reported: intentional dose reduction in an attempt to lower the minimal effective dose (418 attacks in 81 patients), sore throat and other provoking infections (17 attacks, including 9 attacks of laryngeal edema, in 4 patients), trauma (11 attacks in 2 patients), and interruption of danazol intake (171 attacks in 41 patients). Figure 3A and B shows the percentage of mild, moderate, and severe skin swellings and abdominal pain attacks, respectively, before, during, and after treatment with danazol.

In all, 58 of the 118 patients discontinued use of danazol medication for various reasons. In 56 of the 58 patients, the attacks recurred (Fig 2A–D). Because in 8 of the 58 patients the disease improved and danazol treatment, therefore, was discontinued, the mean number of attacks per patient per year was lower than before treatment. The mean latency until the first attacks was 2.9 weeks (SD, ± 1.8 weeks). In 12 patients, the first attacks after discontinuing danazol treatment were more frequent and more severe within the first 3 months than before treatment. A 28-year-old man who participated in a meeting of the Danish Patient Society for HAE heard about the possible adverse effects of danazol. He immediately discontinued danazol treatment and 2 weeks later experienced his first, and until then only, laryngeal edema.

In 2 male patients, tolerance to danazol was observed. The treatment initially worked sufficiently well, but after 4 and 6 years of treatment, respectively, more attacks occurred. Apparently, secondary resistance to danazol developed in these patients.

Adverse Effects and Laboratory Changes

Of the 118 patients, 25 (21.2%) had no adverse effects because of danazol treatment (18 men and 7 women). In 93 of the 118 patients (78.8%) (42 men and 51 women), 1 or more clinical adverse effects occurred (Table 2). The most frequent clinical adverse effects were weight gain (1 patient gained 45 kg within the first year of treatment with 800 mg/d of danazol); menstrual irregularities, including amenorrhea (in 16 of 38 premenopausal women); virilization in women; headache; myalgia; depression; and acne. One patient had a myocardial infarction at the age of 34 years after an average 200 mg/d of danazol for 16 years, followed by a second myocardial infarction 18 months later. He was a smoker but had no other risk factors for thromboembolic disease. A 58-year-old pa-

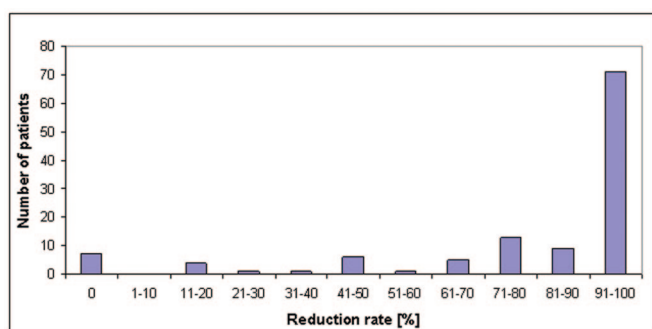


Figure 1. Reduction rate of attacks during long-term treatment with danazol in 118 patients with hereditary angioedema.

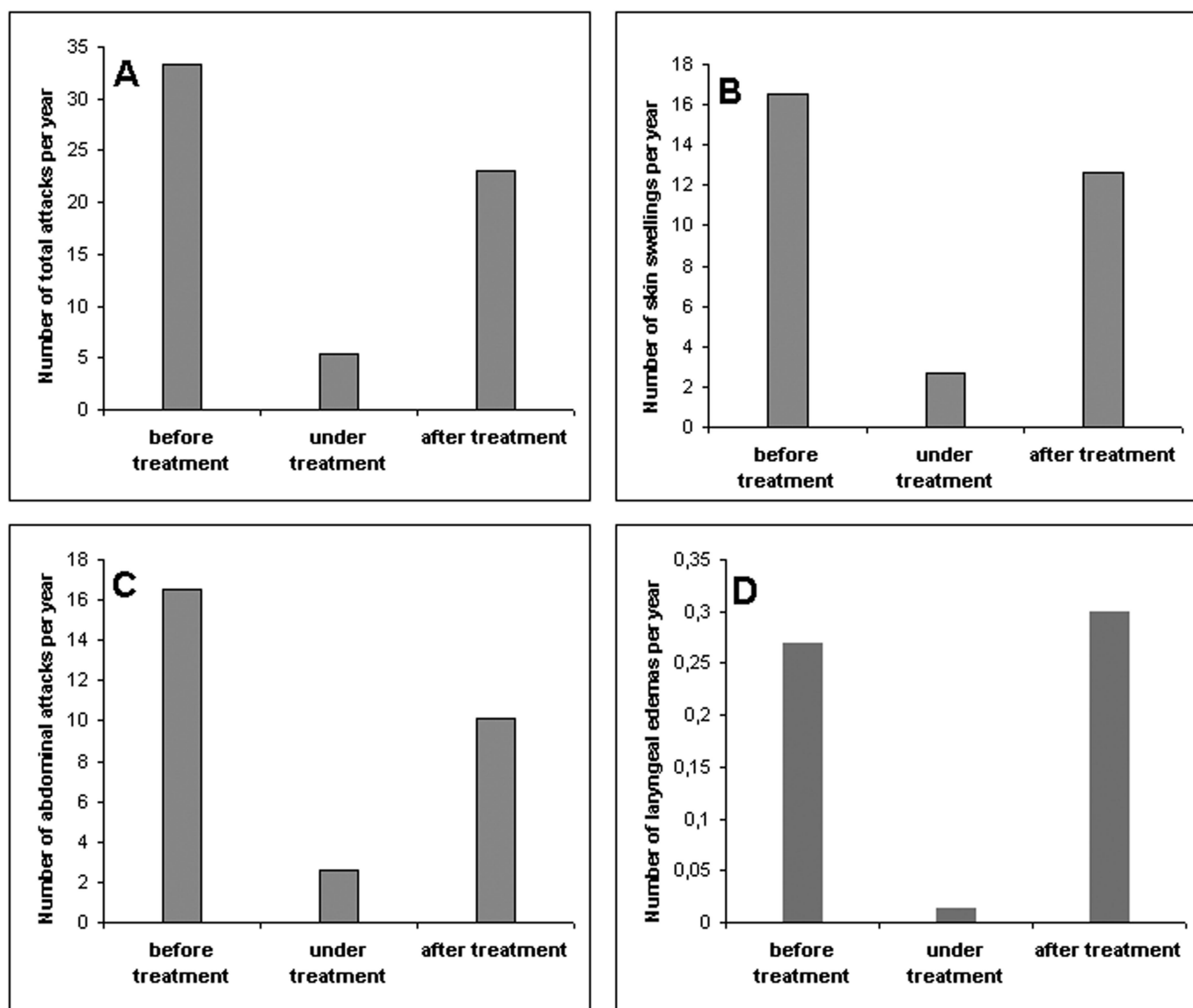


Figure 2. Mean number of attacks per patient in 118 patients before and during long-term treatment with danazol and after treatment in those 58 patients who discontinued danazol treatment for various reasons: all attacks (A), skin swellings (B), abdominal attacks (C), and laryngeal edemas (D).

tient without known hypertension had a stroke after a 3-year treatment with 400 mg/d of danazol. A third patient had a deep venous thrombosis in her lower leg when she was aged 63 years, complicated by lung embolus, after 11 months of treatment with danazol, 200 mg/d. A female patient had received an average dose of 300 mg/d of danazol for 12 years when, at the age of 61 years, she developed acute pancreatitis. A 38-year-old male patient underwent liver ultrasonography and a computed tomographic scan after more than 20 years of treatment with danazol (average dose, 200 mg/d). The scans showed multiple tumors and cysts, and a biopsy specimen showed benign biliary hamartomas. In 3 patients, liver cell adenoma was observed.

Of the 118 patients, 30 (25.4%) discontinued use of the drug because of adverse effects. The cause of their cessation of danazol was either clinical adverse effects ($n = 25$) or pathological laboratory findings ($n = 5$) (Table 2 and Table 3). One patient discontinued danazol treatment for both reasons. Figure 4 shows that 15 of the 30 patients discontinued danazol treatment within the first 2 years of treatment. In the other 15 patients, the adverse effects leading to discontinuation occurred between the 3rd and 17th year of intake. The mean dosage of danazol in those 30 patients who discontinued danazol treatment was 254 mg/d.

Of the 118 patients, 63 (53.4%) had adverse effects but tolerated the symptoms without discontinuation of use of the

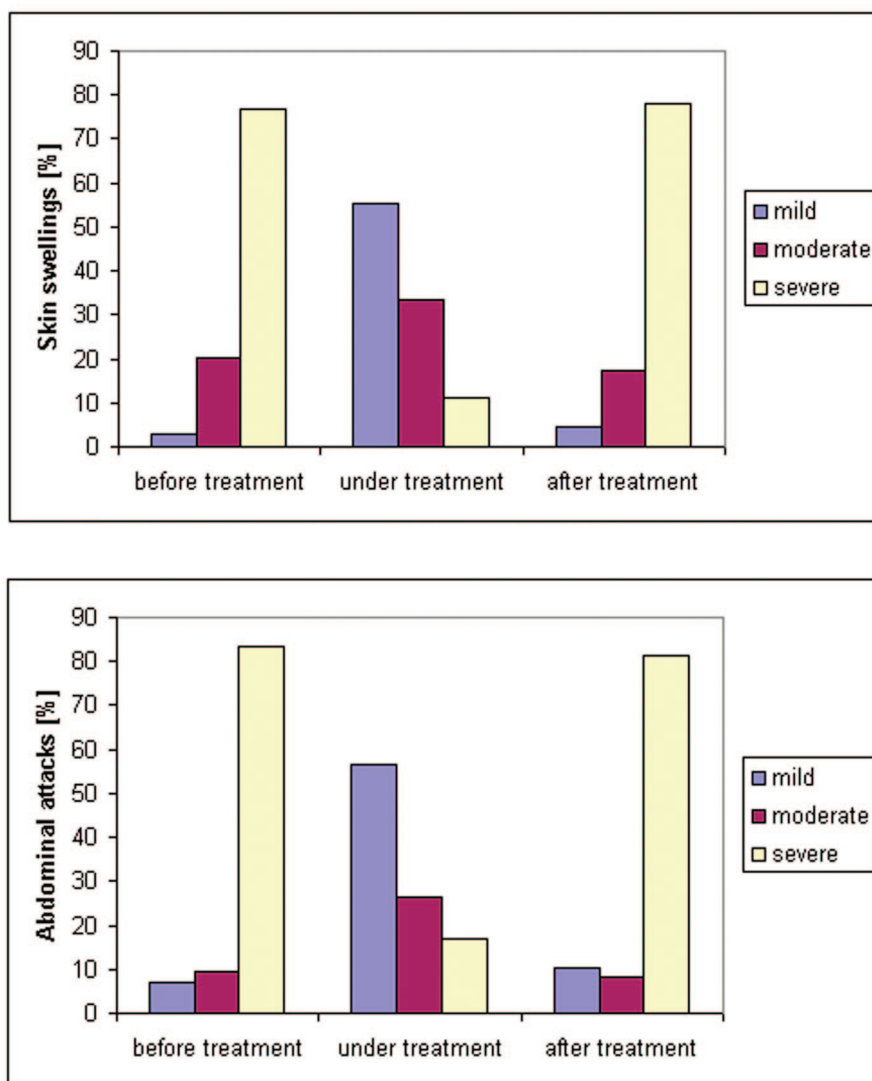


Figure 3. Percentage of mild, moderate, and severe skin swellings (A) and abdominal attacks (B) before, during, and after long-term treatment with danazol.

drug (Table 2). In these patients, the mean dose of danazol was 154.4 mg/d.

In 93 of the 118 patients with adverse effects, the total number of clinical symptoms secondary to long-term treatment with danazol was 224. To determine the eventual dose dependency of adverse effects, we related the number of adverse effects to the initial dose, the average daily dose, and the minimal effective dose per day (Table 4). The number of adverse effects increased with the daily dosage of danazol. Patients who received 200 mg/d of danazol or less had 2.6 adverse effects on average, whereas patients who received more than 200 mg/d of danazol had 3.3 clinical adverse effects on average. Because of the frequent signs of menstrual irregularities and virilization, the mean number of adverse effects was higher in women than in men: 51 of the 93

patients with adverse effects (54.8%) were women and had 150 of 224 adverse effects (67.0%), whereas 42 of the 93 patients (45.2%) were men and had 74 of the 224 adverse effects (33.0%).

Of 51 women, 39 showed signs of menstrual irregularities (irregular menses and amenorrhea) and virilization. Eight women discontinued danazol treatment because of these effects and 31 continued danazol treatment. In all 8 women who discontinued danazol treatment, menstrual irregularities and virilization symptoms led to discontinuation of danazol treatment within the first 2 years after the onset of danazol treatment. All 31 women who tolerated their symptoms of virilization were treated for more than 2 years (mean, 14.4 years).

Table 2. Clinical Adverse Effects Under Long-term Treatment With Danazol in 118 Patients^a

Clinical symptoms	Total No. of patients	No. of patients who discontinued danazol treatment because of this clinical symptom	No. of patients who tolerated this clinical symptom
Weight gain	50	4	46
Acne	11	1	10
Altered libido	3	0	3
Virilization			
Voice changes	17	2	15
Hair changes (more hair)	22	3	19
Decrease of breast size	6	0	6
Clitoris enlargement	6	0	6
More muscles (athletic type)	3	1	2
Laryngeal prominence	1	0	1
Myalgia (muscle cramps)	15	0	15
Menstrual irregularities and amenorrhea	17	4	13
Hypertension	2	0	2
Headache	16	1	15
Liver cell adenoma	3	3	0
Benign biliary hamartoma	1	0	1
Hemorrhagic cystitis	1	0	1
Nausea	2	1	1
Vertigo	1	0	1
Stroke during treatment	1	1	0
Myocardial infarction during treatment	1	1	0
Osteoporosis	1	0	1
Lower back pain	1	1	0
Increased sweating or outbreaks of sweating	9	0	9
Susceptibility to infection	1	0	1
Thromboembolic disease	1	1	0
Stomatitis	1	1	0
Pancreatitis	1	1	0
Retinitis	1	1	0
Cerebral dysfunction			
Paraphasia	2	1	1
Forgetfulness	2	1	1
Psychological abnormalities			
Depression	13	2	11
Aggressiveness	4	1	3
Tiredness	2	1	1
Panic attacks	1	0	1
Mood changes	1	1	0
Tachycardia	1	0	1
Arthralgia	1	0	1
Generalized itching	1	0	1
Early puberty	1	0	1
Total	224	34	190

^a Patients could have more than 1 adverse effect.

In 26 of the 118 patients, laboratory changes occurred as listed in Table 3. The most frequent pathological results were increased liver enzyme levels and increased cholesterol level. Six patients discontinued their danazol treatment because of laboratory changes.

DISCUSSION

In the present investigation, we tried to determine the benefits and risks of long-term prophylactic treatment with danazol in

those with HAE. Our results revealed that most patients benefited from danazol treatment in terms of frequency and severity of attacks. Almost 50% of patients became completely or practically symptom free (ie, they had ≤ 1 attack per year). In additional patients, the disease ran a mild course during danazol treatment. The patients had only a few attacks per year. So, the percentage of patients who benefited from this kind of treatment in terms of frequency and severity of attacks is high. Patients and their families often had lived

Table 3. Pathological Laboratory Changes in 26 Patients With HAE Undergoing Long-term Treatment With Danazol^a

Variable	Total No. of patients	Patients who continued danazol treatment despite laboratory changes	Patients who discontinued danazol treatment because of pathological laboratory findings
Liver enzymes ^b	17	12	5
Cholesterol	12	11	1
Increased number of erythrocytes	2	2	0
Lipase and amylase	1	0	1
Creatine kinase	1	1	0

^a Data are given as number of patients with the finding. Some patients had more than 1 laboratory change.

^b Aspartate aminotransferase, alanine aminotransferase, γ -glutamyltransferase, and alkaline phosphatase.

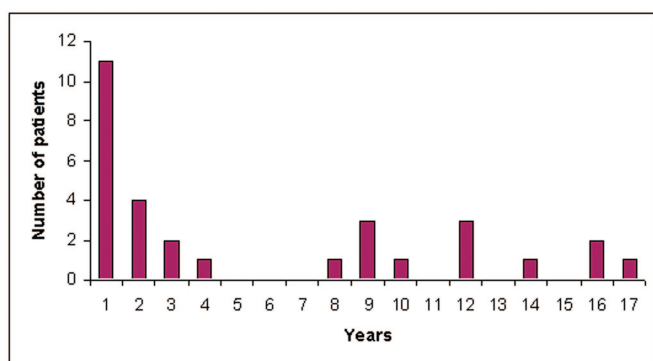


Figure 4. Period of danazol treatment, after which 30 patients discontinued use of the drug because of severe adverse effects.

with the fear of life-threatening or painful HAE attacks. The shift from “very often severely ill” to a “normal or practically normal life” was impressive.

During danazol treatment, the number of laryngeal edemas was reduced by 95.2%. On the other hand, some cases of laryngeal edema still occurred; therefore, we must conclude that long-term treatment with danazol is not a complete guarantee against laryngeal edema. Furthermore, our results show that the breakthrough attacks during danazol treatment were considerably milder than the attacks before treatment.

Seven of our patients did not respond to danazol. Cicardi et al¹⁹ mentioned 2 patients with HAE in whom attenuated androgens partly failed.

Although 21.2% of our patients had no adverse effects at all because of danazol treatment, the remaining 78.8% had 1 or more adverse effects. In 30 patients, mainly women, the adverse effects were so severe that the treatment had to be discontinued, often after a relatively short treatment period. In the other 63 patients, however, the adverse effects were mild or patients tolerated them because they did not want to return to their former state.

Most of our patients’ adverse effects have been observed in other patient series and have already been extensively reviewed.^{22,23} Weight gain is the most frequent problem; minimizing it requires a high degree of discipline concerning nutrition and sufficient physical exercise on the part of the patient. Many women showed signs of virilization; however,

only 6 of 55 patients discontinued danazol treatment for this reason.

Psychological and behavioral abnormalities were observed in a considerable proportion of patients (21 of the 118 patients in our series). Because such abnormalities may start slowly and sometimes do not seem noteworthy to the patients, this issue should be addressed during surveillance.

Liver cell adenoma is a major issue in treatment with danazol, and ultrasonographic examination of the liver at least once a year is mandatory.^{24,25} Recently, a case of hepatocellular focal nodular hyperplasia after 16 years of intake of danazol was described in a 32-year-old woman.²⁶ We believe that the benign biliary hamartomas observed in 1 of our patients were secondary to danazol treatment, because this outcome already has been reported in the literature.²⁷

Two of our patients developed hypertension during treatment with danazol. This represents a lower rate than has been reported^{22,23} and might be explained by the lower daily dose of danazol given to our patients. The myocardial infarction and stroke observed in relatively young patients might be adverse effects of danazol treatment, although cholesterol levels were not elevated in these patients. Another patient with myocardial infarction during danazol treatment was mentioned in the literature.²³ There is not sufficient documentation to relate myocardial infarction or stroke to danazol treatment. However, this issue requires attention in the future. Recently, it was reported that long-term use of danazol is associated with an altered lipid profile, including lowering of high-density lipoprotein levels and elevation of low-density lipoprotein concentrations.²⁸ Single cases of pancreatitis after treatment with danazol have been reported.^{29,30}

The mode of action of danazol in those with HAE due to C1-INH deficiency is not entirely clear. Concentrations of C1-INH and C4 in plasma increase after the start of danazol treatment.¹⁴ In patients treated with androgens, C1-INH protein and function and C4 concentration in plasma are higher than in untreated patients.¹⁹ Thus, an increased synthesis of C1-INH in the liver by androgens could be responsible for the androgens’ therapeutic effectiveness in those with HAE due to C1-INH deficiency. However, some patients with the recently described HAE with normal C1-INH (HAE type III), including HAE due to mutations in the coagulation factor XII gene, have been observed; in these patients, danazol was

Table 4. Dose Dependency of Adverse Effects in 93 Patients With HAE Treated With Danazol From 1 to 30 Years

Danazol dosage, mg/d	Initial dosage			Mean daily dosage			Minimal effective dosage ^a		
	No. of patients	No. of adverse effects	Adverse effects per patient	No. of patients	No. of adverse effects	Adverse effects per patient	No. of patients	No. of adverse effects	Adverse effects per patient
<100	34	76	2.2	35	81	2.3	47	98	2.1
101–200	20	56	2.8	40	112	2.8	27	69	2.6
201–300	5	15	3.0	10	30	3.0	4	12	3.0
301–400	14	42	3.0	4	13	3.2	3	9	3.0
401–500	0	0	0	0	0	0	0	0	0
501–600	14	43	3.1	2	7	3.5	0	0	0
601–700	0	0	0	1	5	5.0	0	0	0
701–800	5	23	4.6	0	0	0	0	0	0
801–900	1	1	1.0	0	0	0	0	0	0
901–1,000	0	0	0	1	8	8.0	0	0	0

Abbreviation: HAE, hereditary angioedema.

^a The number of patients in this group is only 81, because 6 patients did not respond to danazol and 6 patients could not taper off to the minimal effective dosage because danazol treatment was discontinued because of adverse effects.

clearly effective.^{31–35} Therefore, the effectiveness of androgens also could be related to a mechanism that is different from increased C1-INH production.

In the literature, we have not found a systematic approach in a patient series of this size and treatment length (≤ 30 years) that is comparable to the one presented herein. The reasons why we chose a retrospective case report study were the following: (1) HAE is a rare disease; (2) a considerable number of patients have only a few attacks per year and do not need long-term treatment; (3) in a prospective study, the observation period would be too short to obtain sufficient information about adverse effects; (4) patients need months or years of treatment to gradually reduce the dosage of danazol to determine the lowest effective daily dose; and (5) a placebo arm of a double-blind study would not be ethically justified.

In conclusion, during long-term prophylaxis with danazol, 94.1% of patients experienced a considerable treatment effect; that group included 45.7% of patients who became totally or nearly symptom free. The severity of attacks during danazol treatment was milder, on average, compared with attacks before treatment was instituted. Of patients, 5.9% did not respond to danazol. Our results show that many kinds of adverse effects may occur during long-term treatment with danazol. Some of these adverse effects are harmless and tolerable, whereas others are severe. The percentage of patients who had to discontinue danazol treatment because of severe adverse effects was high (25.4% in our series). For patients receiving danazol treatment, close clinical follow-up visits that focus on potential adverse effects are mandatory. In addition to clinical examinations and questioning of the patients, the following measurements should be obligatory at least once a year: blood pressure, liver enzyme levels, blood lipid levels, hematocrit, and creatine kinase level. Also, liver ultrasonography should be performed once a year.

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