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# The effect of long-term danazol prophylaxis on liver function in hereditary angioedema—a longitudinal study

Henriette Farkas · Ibolya Czaller · Dorottya Csuka · Anikó Vas · Szilvia Valentin · Lillian Varga · Gábor Széplaki · László Jakab · George Füst · Zoltán Prohászka · George Harmat · Beata Visy · István Karádi

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## Abstract

**Background** Danazol is a drug most widely used for the prophylaxis of hereditary angioedema resulting from the deficiency of the C1-inhibitor. Potential hepatotoxic or liver tumor-inducing side effects of long-term danazol prophylaxis have been investigated during the follow-up of hereditary angioedema patients.

**Methods** Characteristic parameters of liver function (including bilirubin, GOT, GPT,  $\gamma$ GT, total protein, ALP, LDH), as well as findings of viral serology screens and abdominal ultrasonography—determined during years 0 and 5 of follow-up of patient groups taking/not taking danazol—have been reviewed and analyzed comparatively. **Results** From a population of 126 hereditary angioedema patients, 46 subjects taking danazol and another 46 not taking danazol fulfilled the inclusion criteria. Longitudinal follow-up did not reveal any clinically relevant difference between the liver function parameters determined in years 0

and 5 in the two groups. Abdominal ultrasound did not detect neoplastic or other potentially treatment-related alterations of the liver parenchyma. There were no discontinuations of treatment during the study.

**Conclusions** Our results clearly suggest that, administered at the lowest effective dose, danazol does not induce liver injury in hereditary angioedema patients.

**Keywords** C1-inhibitor deficiency · Treatment · Ultrasound · Safety · Side effect · Danazol · Liver function

## Abbreviations

GOT	Glutamate-oxaloacetate transaminase
GPT	Glutamate-pyruvate transaminase
$\gamma$ GT	Gamma-glutamyltransferase
ALP	Alkaline phosphatase
LDH	Lactate dehydrogenase
HAE	Hereditary angioedema
C1-INH	C1-inhibitor
pdhC1-INH	Plasma-derived human C1-inhibitor concentrate
AAS	Anabolic androgen steroid
LDL	Low-density lipoprotein

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## Introduction

Hereditary angioedema (HAE)—a disorder of autosomal dominant inheritance—results from the deficiency of the C1-inhibitor (C1-INH) gene. It is characterized by paroxysms of edema formation in the subcutis and/or the submucosa of the upper airways and the gastrointestinal tract [1–3]. Edema formation is attributed largely to bradykinin released during the activation of various plasma

cascade (e.g., fibrinolytic, coagulation, complement, and contact) systems.

The management of HAE comprises two essential stages: the therapy of overt attacks and prevention of their recurrence. Currently, plasma-derived human C1-INH (pdhC1-INH) concentrate or bradykinin-receptor antagonist is the remedy of choice to relieve acute attacks [1, 4–6]. Agents appropriate for short- or long-term prophylaxis in clinical practice include antifibrinolytic agents and attenuated anabolic steroids (danazol, stanozolol, oxandrolone), as well as pdhC1-INH concentrate in certain cases [1, 4, 7, 8]. In 1955, Spaulding published the first paper about the beneficial effect of methyltestosterone in HAE [9]. Anabolic steroids were introduced into the clinical management of HAE in 1976, and an abundance of reports have confirmed their effectiveness since then [10–15]. Nowadays, a 17- $\alpha$ -alkylated anabolic androgen steroid (AAS) known as danazol is the most commonly used prophylactic drug, the exact mode of action of which has not yet been elucidated [16–18].

Danazol can prevent the occurrence of attacks in the majority of patients and can reduce attack frequency and severity. The following side effects can be expected during its administration: virilization, masculinization, deepening of the voice, hair loss, clitoral/penile enlargement, amenorrhea, hirsutism, libido changes, androgen-induced premature closure of epiphyses in children, psychiatric and behavioral effects, depression, aggressive behavior, flushing, diaphoresis, vaginal dryness, irritation, diminution of breasts, glucose intolerance, insulin resistance, hypogonadism, testicular atrophy, reduction of HDL cholesterol and elevation of LDL cholesterol levels, and hepatotoxicity [19]. A substantial proportion of studies appraising the side effects of treatment with danazol were conducted in patients with endometriosis, although large patient populations with idiopathic thrombocytopenic purpura (ITP) were also studied [20–22]. Unfortunately, experience from these studies is not fully suitable for extrapolation to HAE patients, owing to differences in treatment duration and danazol dosage [22].

Adverse reactions observed in HAE patients receiving danazol have been reported in review articles and clinical summaries [4, 14, 23]. Major side effects of danazol in HAE patients include proatherogenic changes in lipid profile [24], hepatotoxicity, elevated liver enzyme activity, cholestatic jaundice, peliosis hepatis, and various neoplastic lesions. The hepatotoxic effect of danazol has been discussed in a limited number of predominantly cross-sectional studies and case reports; no longitudinal studies have been undertaken yet [13, 25–30]. Since patients are concerned about side effects—especially liver injury—and often decline treatment with this effective agent (which is almost the sole remedy available in many countries), the

objective of our study was to clarify the effects of long-term danazol treatment on liver function.

## Methods

### Study design

Retrospective analysis of data accumulated in the Hungarian HAE Registry since 1995 was performed. Laboratory parameters informative of liver function (serum bilirubin, GOT, GPT,  $\gamma$ GT, total protein, ALP, LDH), results of viral serology tests, and findings of abdominal ultrasonography—all obtained once a year at least—were reviewed. In addition to positive family history and presence of clinical manifestations, inclusion criteria also comprised known HAE, confirmed by complement studies and followed-up for 4 years at least.

Patients who had been taking danazol without interruption for at least 4 years were eligible for enrollment in *the danazol group*. Subjects who had been followed up for a minimum of 4 years and underwent laboratory testing at least annually, but had not received danazol until the end of the study period were eligible for inclusion in *the control group*.

Initial data from ‘year 0’ were defined as baseline parameters (obtained during a 1-year period at maximum) before the initiation of danazol treatment. Only data recorded later than 1995 were taken into account, in order to ensure the use of standard methodology and reference ranges in all patients, as this was considered a prerequisite for making meaningful comparisons. Danazol treatment of six patients had started before 1995 and accordingly, their year 0 data were chosen from the period after 1995. ‘year 5’ data were defined as the follow-up information recorded at a time closest to 5 years after obtaining the corresponding year 0 data.

The reference ranges of serum bilirubin, GOT, GPT,  $\gamma$ GT, and total protein remained essentially unchanged during the 5-year study period. In the case of ALP and LDH, however, reference ranges had changed and therefore, test results obtained after 1 February 2001 were considered year 0 values in patients receiving danazol. Thus, post-baseline values (recorded after the start of danazol treatment) were taken into account for 26 subjects.

The *longitudinal study* was implemented by comparing year 0 and year 5 laboratory values within the individual study groups. The *abdominal ultrasonography* study compared the latest follow-up abdominal/liver ultrasonography findings obtained in the two groups with each other.

Occasionally, danazol dose was adjusted as required by attack frequency and therefore, the potential influence of danazol dose on laboratory parameters was assessed in view of the cumulative dose taken by individual subjects. In

patients who had been taking danazol longer than 5 years, the latest parameters were adjusted according to the actual duration of danazol treatment. The parameters of patients receiving danazol for more than 10 years were analyzed separately.

### Study subjects

All 126 HAE patients registered with and managed at the Hungarian HAE Center as of July 2008 were included in this study and treated according to the Budapest protocol [4].

#### *Patients taking danazol*

Fifty-eight of the 126 patients underwent danazol prophylaxis (according to registry records as of July 2008). The daily dose ranged from 33 to 200 mg; however, occasionally it was escalated to 300–400 mg/day temporarily. Seven patients did not fulfill the requirement of 4 years of danazol treatment and four of these patients were excluded. The remaining three patients had been followed up extensively during the period before danazol was introduced, and therefore, this earlier period made them eligible for inclusion into the control group. An additional three patients were withdrawn from the study after all of them had been ascertained to suffer from severe alcohol dependence. Finally, two other patients who received danazol only briefly were also excluded from the 5-year study.

Thus, the danazol group comprised 46 patients (22 males and 24 females). These subjects did not receive other prophylactic agents or any other drug with known potential for causing liver damage.

#### *Patients not taking danazol*

Sixty-eight patients had never received danazol; the duration of follow-up was shorter than 4 years in 24 of these. An additional subject was excluded for alcoholism. On the other hand, the three patients referred to above (with sufficiently long follow-up before the initiation of danazol treatment) were included in the control group. Thus, the control group consisted of 46 HAE patients (15 males and 31 females), none of whom received prophylactic drugs or were treated with tranexamic acid for long-term prophylaxis. The study was approved by the institutional review board and all subjects gave informed consent. Table 1 summarizes the descriptive statistics of the two patient groups.

### Laboratory procedures

Laboratory measurement of liver function parameters was performed using computerized laboratory analyzers. Cobas

Integra 400/800 (Roche, Basel, Switzerland) was used for measuring serum bilirubin, GOT, GPT,  $\gamma$ GT, ALP, LDH, and total protein levels. Virus serology (screening for HBsAg, anti-HCV) was performed upon enrollment and at every subsequent control visit.

### Ultrasonography of the abdomen and liver

Screening of liver status comprised appraising the size (relative to the lower pole of the kidney), structure, and (increased/reduced) echogenicity (in comparison to that of the renal parenchyma) of the liver, as well as evaluation of intrahepatic biliary passages and the condition of the gall bladder.

The liver parenchyma was reviewed for the presence of circumscribed, focal lesions, and abnormalities of the portal and hepatic veins were actively sought. Detected lesions were grouped according to diagnosis as well as the above considerations (Table 6). Comparisons were made between the groups taking vs. not-taking danazol. The proportion of young patients was greater in the group not receiving danazol.

### Statistical analysis

Calculations were performed with SPSS for Windows v13.0 (SPSS, Chicago, IL, USA) and Prism v4.00 (Graph-Pad Software, San Diego, CA, USA). Since many variables had non-Gaussian distributions, we used Wilcoxon's non-parametric test for year 0 and year 5 comparisons, whereas Spearman's rho-coefficient was used to calculate correlations. Fisher's exact test was also performed. Values presented in the text are medians (with minimum-maximum range).

The level of two-tailed significance was set at  $P < 0.05$  ( $2\alpha = 0.05$ , 95% confidence).

## Results

### Longitudinal study

Within the group not treated with danazol, no significant differences could be demonstrated between the group of children and adolescents (<18 years old, young group) and adults ( $\geq 18$  years old, adult group). In the adult group, no significant changes occurred during the follow-up period in any of the laboratory parameters tested (Table 2).

In the young group a significant decrease in GOT and LDH, as well as a significant increase in  $\gamma$ GT and total protein levels was ascertained.

Changes in the laboratory parameters in patients treated with danazol during the 5-year follow-up period are

**Table 1** Descriptive statistics of the two patient groups

		Treated with danazol	Not treated with danazol
Subjects	Number	46	46
Age at the start of the study (years)	Median (min-max)	32.5 (9–62)	16 (2–73)
Sex	Male/female	22/24	15/31
	Percentage	47.83/52.17	32.61/67.39
HAE type	I:II	41/5	43/3
	Percentage	89.13/10.87	93.48/6.52
Duration of follow-up (year)	Median (25;75)	5.03 (4.76; 5.37)	5.05 (4.58; 5.41)
	Mean	5.009	5.003
Daily dose (mg)	Median (25;75)	98.44 (55.21; 146.3)	–
	Mean	108	–
Cumulative dose over 5 years (g)	Median (25;75)	184.1 (102.4; 274.8)	–
	Mean	198.8	–

summarized in Table 3. No significant changes occurred in bilirubin or GOT levels. The most marked changes occurred in the LDH levels; in both groups they dropped, and the decrease was more marked in the adult group. GPT and  $\gamma$ GT levels were weakly or marginally significantly higher in year 5 than in year 0. In spite of this, however, 92.4% of these values were within the reference range in year 5. There were differences between the two age groups in some parameters: total protein levels increased only in the adult group, while ALP levels diminished only in the young group.

By the end of the fifth year, values of 14 subjects (30.4% of the group) exceeded the reference range, including two patients with simultaneous elevation of two ( $\gamma$ GT and total protein) out of the seven studied parameters. In these 14

subjects, the elevation of values exceeded the upper limit of the reference range by 14.1% on average. In the group not taking danazol, the values of 16 parameters were above the reference range in 12 patients (21.6% of the group). A decrease below the lower limit of the reference range was seen with LDH level only.

There was no difference in the liver function parameters between male and female patients in either treatment group.

In the danazol-treated group, two formerly seropositive patients (one each) were infected by the hepatitis B and hepatitis C virus, respectively. One patient in the control group was HBV positive. Although the source of infection could not be identified in any of these cases, its relation to either HAE or to treatment with C1-INH can be ruled out with certainty. All three patients are in remission currently

**Table 2** Year 0 and year 5 laboratory parameters for patients not treated with danazol

	Number	Group	Year 0 Median (min-max)	Year 5 Median (min-max)	Wilcoxon <i>P</i> -value
Bilirubin	19	≥18 years	9.5 (5–23.1)	9.3 (4.5–24.2)	0.968
	27	<18 years	8.6 (4.1–24)	10.9 (4.3–29.8)	0.249
GOT	19	≥18 years	20 (8–50)	17 (11–41)	0.369
	27	<18 years	27 (15–58)	18 (11–32)	<0.0001
GPT	19	≥18 years	16 (8–111)	15 (9–70)	0.663
	27	<18 years	15 (9–28)	15 (10–30)	0.518
$\gamma$ GT	19	≥18 years	15 (10–161)	20 (9–116)	0.093
	27	<18 years	12 (9–21)	14 (9–33)	0.006
Total protein	19	≥18 years	73 (67–86)	73 (67–83)	0.537
	27	<18 years	72 (62–81)	76 (64–84)	<0.0001
ALP	21	≥18 years	76 (41–129)	77 (49–132)	0.237
	25	<18 years	160 (54–363)	92 (41–413)	0.069
LDH	21	≥18 years	165 (135–227)	146 (124–241)	0.126
	25	<18 years	220 (144–427)	155 (114–281)	<0.0001

**Table 3** Year 0 and year 5 laboratory parameters for patients treated with danazol

Danzol-treated subjects	Number	Group	Year 0 Median (min–max)	Year 5 Median (min–max)	Wilcoxon <i>P</i> value
Bilirubin	39	≥18 years	12.2 (5.5–40.4)	10.8 (5.4–44.5)	0.295
	7	<18 years	9.8 (5.5–11.8)	11.1 (7.7–14.6)	0.204
GOT	39	≥18 years	20 (13–55)	20 (13–34)	0.200
	7	<18 years	23 (19–35)	22 (16–31)	0.350
GPT	39	≥18 years	18 (8–85)	22 (10–47)	0.021
	7	<18 years	18 (9–24)	26 (9–30)	0.058
γGT	39	≥18 years	18 (5–59)	23 (9–48)	0.031
	7	<18 years	14 (9–18)	19 (9–38)	0.046
Total protein	39	≥18 years	72 (63–79)	74 (63–82)	0.003
	7	<18 years	72 (69–79)	73 (71–82)	0.292
ALP	38	≥18 years	69.5 (38–201)	67 (40–122)	0.159
	8	<18 years	197 (61–366)	73.5 (60–138)	0.025
LDH	38	≥18 years	170 (107–251)	150 (108–216)	<0.0001
	8	<18 years	165.5 (124–202)	151.5 (107–180)	0.012

and exhibit no differences compared to the normal population as regards liver enzyme activity, laboratory parameters, and findings of hepatic ultrasonography.

There was no correlation between the cumulative dose of danazol during the follow-up period and the 5-year laboratory parameters (Table 4).

In patients who had been taking danazol for more than 5 years (*n*=36), no correlation could be ascertained between the duration of drug treatment and the latest determined values of liver function parameters (from 2007 and 2008). Mean duration of danazol treatment was 8.58 years in this subset.

All follow-up data from patients who had been treated with danazol for more than 10 years without interruption were aggregated for the descriptive analysis presented in Table 5. As evidenced by these data—occasional outliers notwithstanding—all monitored parameters have persisted heretofore in the reference range.

**Abdominal and hepatic ultrasonography**

Pre-existing liver disease was not identified in the medical and family history of patients at enrollment. All three

above-mentioned patients with hepatitis are in remission currently, and their condition is checked regularly by a hepatologist. Abdominal ultrasound (US) findings were available for all 46 patients taking danazol, but only for 38 subjects in the control group. Comparison of the US findings of these two groups revealed a circumscribed, focal lesion or other abnormality in a single case only. This, however, is unrelated to danazol treatment, as the lesion had been detected before treatment was initiated. At that time, diagnostic work-up was supplemented by native and contrast-enhanced abdominal CT, which identified the 7-mm lesion found in the right lobe of the liver as a benign hemangioma. Biopsy was not performed. Monitoring of the lesion regularly for 4 years has not detected any change in its size. Abnormalities of hepatic status, diagnoses, and number of cases in the two groups are set out in Table 6. Analysis of these data with Fisher’s exact tests did not reveal any significant difference between the two groups (Table 6). Mean duration of the time that elapsed before the occurrence of the lesions identified was 5.97 years.

In view of these results, no differences were found by abdominal ultrasonography in comparison to controls.

**Table 4** Correlation between the cumulative dose of danazol during the follow-up period and the 5-year laboratory parameters

Spearman's rho	Year 5 values	Bilirubin <sub>5</sub>	GOT <sub>5</sub>	GPT <sub>5</sub>	γGT <sub>5</sub>	Total protein <sub>5</sub>	ALP <sub>5</sub>	LDH <sub>5</sub>
Cumulative dose over 5 years (g)	Correlation coefficient	−0.251	−0.108	−0.083	−0.034	−0.162	−0.149	−0.037
	<i>P</i> (two-tailed)	0.092	0.474	0.585	0.824	0.283	0.325	0.806
	Number	46	46	46	46	46	46	46

**Table 5** Descriptive analysis of patients treated with danazol continuously for more than 10 years

Patient no.	Sex	Bilirubin (μmol/l)	GOT (U/l)	GPT U/l	γGT U/l	Total protein (g/l)	Mean daily dose (mg)	Duration of treatment (years)
7	M	7.7 (5–10.3)	21 (18–31)	25 (13–38)	14 (12–29)	75 (70–76)	81	10
10	F	19.1(10.5–28.2)	20 (18.51)	19 (12–66)	18 (10–50)	73 (66–86)	91	10.7
12	F	10.3 (8–14.2)	20 (16–32)	22 (15–41)	12 (10–16)	72.5 (70–76)	170	10.72
15	M	7.8 (3–13.3)	20.5 (11–48)	26 (9–107)	25 (16.78)	69 (56–75)	200	21.9
17	M	8.4 (4.7–11.6)	19 (12–33)	15 (8–30)	15 (10–23)	69 (66.79)	136	11.81
18	M	10.9 (6.4–26.1)	23.5 (14–43)	22.5(13–47)	13 (10–19)	76 (72–82)	51	10.99
20	F	8 (5.5–12.5)	28 (21–32)	36 (24–45)	38 (24–71)	74 (68–78)	59	10.37
24	F	10 (5–17)	25.5 (14–41)	17 (9–41)	29 (13.81)	68.5 (62–74)	196	20.18
31	F	11 (8.5–16.5)	20 (15–39)	14 (11–37)	16 (11–28)	70 (63–76)	164	12.87
35	M	13.5 (3.3–27.1)	26 (15–40)	34 (19–53)	40 (13–85)	72 (66–74)	100	16.68
36	M	8.5 (4.5–11.1)	29 (22–50)	31 (15–76)	33 (13–76)	74 (72–75)	123	16.68
37	F	11 (2.3–19)	36.5 (26–45)	35 (22–60)	34 (24–63)	76.5 (73–81)	141	16.68
40	F	11 (5–15.6)	24 (16–37)	22 (14–38)	38 (12–84)	73 (68–85)	190	12.13

## Discussion

As demonstrated by our findings, long-term prophylaxis with danazol is associated with only minor changes in hepatic function and does not induce ultrasound-detectable structural alterations in the liver.

The first half of the study compared liver function parameters from year 0 and year 5 of patients taking/not taking danazol and described the values of patients treated with danazol for more than 5 or 10 years. Minimal and

clinically unimportant elevation of any of the seven monitored parameters above the upper limit of the reference range was ascertained in 14 patients taking danazol. The significant elevation of γGT levels might be attributed to—among others causes—the known tendency of γGT activity to increase with age. Statistical calculations showed a clear correlation in this respect [31]. In the case of bilirubin, deviation from the reference range might have been influenced by Gilbert's disease, diagnosed in 4 subjects. Notwithstanding this, no clinically relevant difference in

**Table 6** Results of abdominal ultrasonography for group treated with danazol and group not treated with danazol

	Group not treated with danazol	Group treated with danazol	<i>P</i> value (Fischer's exact test)
By types of lesions			
Hepatomegaly	4 (10.5%)	7 (15.2%)	0.7469
Diffuse hepatic lesions	4 (10.5%)	5 (10.9%)	1.0000
Cholelithiasis	2 (5.3%)	2 (4.3%)	1.0000
Sludge	0 (0%)	1 (2.2%)	1.0000
Focal sparing	1 (2.6%)	1 (2.2%)	1.0000
Liver cyst	0 (0%)	2 (4.3%)	0.4986
Haemangioma	2 (5.3%)	4 (8.7%)	0.6850
All lesions	13 (34.2%)	22 (47.8%)	0.2676
All patients	38 (100%)	46 (100%)	
By observed abnormalities			
Hepatomegaly	4 (10.5%)	7 (15.2%)	0.7469
Parenchymal reflectivity ↓	1 (2.6%)	3 (6.5%)	0.6229
Parenchymal reflectivity ↑	6 (15.8%)	9 (19.6%)	0.7777
Lesion in gall bladder	2 (5.3%)	3 (6.5%)	1.0000
All lesions	13 (34.2%)	22 (47.8%)	0.2676
All patients	38 (100%)	46 (100%)	

GOT and total bilirubin levels emerged over 5 years. The increase in GPT level was significant, although all changes were confined within the reference range. During follow-up, ALP level decreased significantly in young patients taking danazol. This may be explained by the fact that the skeletal growth of subjects—who had been of pediatric age at the start of danazol treatment—concluded during the study period. ALP levels did not change significantly in the group not taking danazol; this is attributed to the large proportion of subjects still in the stage of skeletal growth within this group. A highly significant decrease in LDH level occurred in both groups, regardless of the type of treatment. This was an unexpected finding. No accurate explanation for this phenomenon is available yet. Total protein level followed an increasing trend, which is related to the anabolic effect of danazol; an opposite change would occur in hepatic impairment.

No correlation was found between the cumulative dose of danazol and the values of laboratory parameters measured at the end of the 5-year period, again indicating that there is no strong relationship between the danazol treatment and liver function. Liver function parameters were not related to the duration of drug treatment.

No clinically relevant changes were seen in the laboratory parameters of patients who have been taking danazol for more than 10 years. The occasional occurrence of outliers was a transitory phenomenon, as evidenced by their normalization despite ongoing danazol treatment, as well as the elimination of underlying causes transient in nature (infections, gallstones).

No substantial differences could be ascertained between the groups with regards to the parameters of male and of female patients. The results are in agreement with the findings from cross-sectional studies conducted by other researchers, that is, danazol does not cause clinically significant alteration of liver function parameters when administered at the lowest effective dose [12, 13, 32, 33].

Ultrasonographic appearance of the liver was not different between the groups taking/not taking danazol. No adenoma or cancer was found in the hepatic region. A circumscribed lesion was detected in one patient, but its etiology was unrelated to danazol treatment. Hepatic adenomas and cancer described during danazol therapy of other disorders might have been related to high—400 to 600 or occasionally 800 mg—daily doses administered over several years, as well as to insufficient patient monitoring [21, 26–28, 34–37]. Of note, Bork reported cases with benign liver tumors that developed during low-dose treatment for longer than 10 years. Therefore, treatment duration seems important, in addition to drug dose. Evidently, other individual factors may have their role, as no ultrasonographic abnormalities suggestive of a neoplas-

tic change could be detected in the liver in any of our patients who had taken danazol longer than 10 years.

Severe complications (hepatic rupture, hemorrhage, peliosis, malignant transformation) can be prevented by early recognition of liver tumors. Discontinuation of danazol may achieve regression or disappearance of small, benign neoplasms. In the case of larger and usually symptomatic tumors (causing abdominal pain) located beneath the capsule, surgical removal (partial or hemihepatectomy) is recommended along with discontinuation of danazol [28, 29, 37]. When necessary, C1-INH substitution should be considered.

Thus, it may be concluded that danazol—which has been in clinical use for more than three decades—did not induce any significant alterations of liver function parameters or the development of progressive hepatic lesions or tumors detectable by ultrasonography when administered according to the long-term treatment protocol adopted by our institution. No drug-related adverse reactions warranting treatment discontinuation were observed during this study. The importance of determining the lowest effective dose must be emphasized—along with the importance of repeating laboratory screening and abdominal ultrasonography at least annually. These check-ups afford early recognition of side effects and thereby create the opportunity for dosage adjustment or treatment discontinuation.

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