

# **Open trial to evaluate the efficacy and safety and the dose-escalation of idebenone in patients with Friedreich's ataxia**

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# **EARLY ONSET ATAXIAS WITH NON-KNOWN ETIOLOGY**

## **■ Ataxia of Friedreich**

### **– Investigations:**

#### **■ Cardiac evaluation:**

**– ECG: Right axis deviation of the QRS axis, T wave inversion, and deviations of the ST segment are present in 80% of the patients.**

#### **– Echocardiography:**

- Concentric left ventricular hypertrophy, and asymmetric septal hypertrophy that evolves with scarce frequency of malignant ventricular arrhythmias.**

**■ Left ventricular dilatation is unusual in the Friedreich's ataxia, and may associate auricular and ventricular arrhythmias.**

# Idebenone

- **Short-chain benzoquinone analogue of Co Q-10.**
- **Natural component of the mitochondria.**
- **It intervenes in the mitochondrial respiratory chain function.**
- **It acts as a potent free-radical scavenger.**
- **In Japan "Mnésis®" for the memory.**

# **Effect of idebenone on cardiomyopathy in Friedreich's ataxia: a preliminary study.**

**(Rustin *et al.* Lancet 1999; 354: 477-479)**

- **Three patients with FDRA were treated with idebenone (5 mg/kg/day) during 4-9 months.**
- **They were subjected to a ultrasonographic control of the heart activity.**
- **In the three patients a decrease of the mass of the VI was observed.**
- **CONCLUSION: The idebenone protects the heart muscle of the damage induced by the iron.**

# **Oxidative stress in patients with Freidreich ataxia**

*(Schulz et al, Neurology 2000; 55: 1719-1721)*

- **The authors measured the concentration of 8-OH-2'dG in urine (marker of oxidative damage of ADN)**
- **33 FRDA-20 controls (5 mg/kg/day of Idebenona during 8 weeks)**
- **CONCLUSION:**
  - **The idebenone diminishes the liberation of 8OH2'dG.**
  - **The 8OH2'dG can be useful to monitor the follow-up of these patients.**

# Idebenone

- Reduction of the size of the heart in children (Pandolfo, 2001).
- Reduction of the size of the heart (Rustin *et al*, 1999, 2002).
- Reduction of the size of the heart (Munnich A, Brice A, 2002).
- Reduction of the size of the heart (Hausse *et al*, 2002; Rustin *et al*, 2002; Rustin, 2003).
  - Age of patients: 4-22 years
  - Dose of Idebenona: 5-10 mg/Kg/día

## Idebenone

- **$^{31}\text{P}$ -MRS of skeletal muscle didn't show recovery of the mitochondrial activity, neither improvement of the cardiomyopathy (Schols *et al*, 2001, 2004) (crossover, placebo-controlled trial).**

## **Friedreich's ataxia: Idebenone treatment in early stage patients.**

*(Artuch et al, 2002).*

- **Nine Friedreich's ataxia patients (age range 11-19 years) were treated with Idebenone (5 mg/kg/day).**
- **Improvement of the cerebellar syndrome in patient with light affectation after 3 months of therapy with Idebenone ( $p = 0.017$ ).**
- **Significant correlation (+) between levels of Idebenone and percentages of the difference between ICARS scores before and 12 months after the start of the therapy ( $p = 0.002$ ).**
- **Nonsignificant reduction of the heart hypertrophy were observed in echocardiographic measurements.**

## **Idebenone treatment in Friedreich patients: One-year-long randomized placebo-controlled trial.**

*(Marotti et al. Neurology 2003; 60: 1676-1679)*

- **Twenty-nine patients were randomized to either Idebenone (14 patients) or placebo (15 patients).**
- **They found significant reductions of interventricular septal thickness and left ventricular mass in the idebenone (5 mg/kg/day) group vs placebo group.**
- **The absolute cardiac changes were modest.**
- **Analysis of the ICARS total scores and subscores didn't reveal significant differences between the two patient groups.**

## **Idebenone treatment in Friedreich's ataxia: Neurological, cardiac, and biochemical monitoring.**

*(Buyse et al. Neurology 2003; 60: 1679-1681)*

- **Eight patients with FRDA with hypertrophic cardiomyopathy, aged between 8.6 and 27.1 (mean 15 years).**
- **They found significant reduction of cardiac hypertrophy in six of eight patients.**
- **Cardiac strain and strain rate imaging showed that the reduction of hypertrophy is preceded by an early and linear improvement in cardiac function.**
- **Idebenone didn't halt the progression of ataxia.**

# Idebenone

- **Phase I: “Trial of Idebenone to Treat Patients with Friedreich's Ataxia”, to establish the maximum tolerated dose of Idebenone in children, adolescents, and adults with Friedreich's ataxia (no longer recruiting patients).**
  - **Safety Study of Idebenone (60 mg/kg/day) to Treat FRDA.**
  - **Secondary objective: pharmacokinetics.**
  - **Total enrollment: 16**
  - **Outcomes in this phase I trial are types and frequency of adverse events, if any, and compliance with the dosing regimen. Our secondary endpoint is pharmacokinetics of this dosing regimen.**
- **A multicenter, double-blinded, placebo-controlled phase III trial using an ataxia scale developed for FRDA as the primary endpoint.**

# Idebenone

- **Phase I trial: Safety Study of Idebenone to Treat Friedreich's Ataxia (no longer recruiting patients).**
  - **Toxicity and tolerability of the Idebenone given as a multiple-dose regimen.**
  - **Total enrollment: 100**
  - **→ Phase II to further evaluate safety and to estimate the efficacy of idebenone using cardiac parameters as our primary endpoints. In addition, they are currently in the process of validating a clinical evaluation scale for FRDA that they hope to employ in measuring neurological parameters as a secondary endpoint in the phase II trial.**

# Idebenone

- **Phase II trial: A Six Month Double-Blind, Placebo-Controlled Phase 2 Clinical Trial to Determine the Safety and Efficacy of Idebenone Administered to Patients with Friedreich's Ataxia (no longer recruiting patients).**
  - Patients with genetically confirmed Friedreich's ataxia who are between 9 and 18 years of age, weigh between 65 and 175 pounds and can walk 25 feet with or without an assistive device may be eligible for this study.
  - They aim to enroll 48 subjects composed of children (ages 9-11) and adolescents (ages 12-17) with FA divided evenly among 4 treatment arms (placebo, low, intermediate, and high dose idebenone).

# Idebenone

- **Phase I/II trial: Effect of Iron-Chelating Therapy in Friedreich Ataxia. Study Phase I/II (currently recruiting patients).**
  - **Primary Outcomes: Assessment of iron overload at T0 and month 2.**
  - **Secondary Outcomes: Clinical (monthly) and biological parameter follow-up (weekly blood count,; plasma iron, ferritin, transferrin and liver enzymes)**
  - **Expected Total Enrollment: 26**
  - **The current clinical trial is a monocentric open phase1-2 trial**

# **EARLY ONSET ATAXIAS WITH NON-KNOWN ETIOLOGY**

- **Friedreich's ataxia (FDRA):**
- **Idebenone → Neurological improvement?:**
  - **Fatigue, dysarthria, fine movements of the hands, walk, lower limbs... (controversial).**

# EARLY ONSET ATAXIAS WITH NON-KNOWN ETIOLOGY

## ■ Friedreich's ataxia (FDRA)

### – Treatment (IV):

#### ■ Medication (III):

– **Idebenone: 5 → 10 → 20 mg/kg/day**

– **Mitoquinone**

# **Present series**

**Group of patients with Idebenone therapy**

# Patients and methods

- We studied 16 patients with Friedreich's ataxia (FDRA). The study protocol was approved by the Ethic Committee, and written informed consent was obtained.
- Inclusion criteria included diagnosis of FRDA confirmed by molecular investigations, interventricular septal (IVS) thickness or left ventricular posterior wall (LVPW) thickness of at least 12 mm observed by echocardiography.

# Baseline characteristics of FRDA patients

<i>Patients</i>	<i>Gender</i>	<i>Age at enrollment (years)</i>	<i>Disease duration</i>	<i>Total score at neurologic rating scale (ICARS)</i>
1 ♀	M	24	15	48
2 ♀	F	18	17	28
3 ♀	M	40	22	33
4 ♀	F	30	18	63
5 ♀	M	34	21	54
6 ♀	M	21	9	34
7 ♀	F	22	19	60
8 ♀	F	18	12	48
9 ♀	M	22	12	45
10 ♀	F	34	16	39
11 ♀	F	15	5	41
12 ♀	F	35	18	58
13 ♀	M	35	22	52
14 ♀	M	41	36	60
15 ♀	M	28	15	68
16 ♀	F	20	3	36
<i>Summary</i>	M/F = 8/8	27.31±8.36	16.25±7.68	47.93±12.02

# Baseline characteristics of FRDA patients and daily dose Idebenone

<i>Patients</i>	Daily dose of idebenone, first-year follow-up	Daily dose of idebenone, second-year follow-up	Daily dose of idebenone, third-year follow-up
1 †	5 mg/kg/day	10 mg/kg/day	20 mg/kg/day
2 †	5 mg/kg/day	10 mg/kg/day	20 mg/kg/day
3 †	5 mg/kg/day	10 mg/kg/day	20 mg/kg/day
4 †		10 mg/kg/day	20 mg/kg/day
5 †	5 mg/kg/day	10 mg/kg/day	20 mg/kg/day
6 †	5 mg/kg/day	10 mg/kg/day	20 mg/kg/day
7 †	5 mg/kg/day	10 mg/kg/day	20 mg/kg/day
8 †	5 mg/kg/day	10 mg/kg/day	20 mg/kg/day
9 †	5 mg/kg/day	10 mg/kg/day	20 mg/kg/day
10 †	20 mg/kg/day	20 mg/kg/day	30 mg/kg/day
11 †	5 mg/kg/day	5 mg/kg/day	20 mg/kg/day
12 †	5 mg/kg/day	0	0
13 †	5 mg/kg/day	10 mg/kg/day	0
14 †	10 mg/kg/day	10 mg/kg/day	0
15 †		10 mg/kg/day	20 mg/kg/day
16 †		10 mg/kg/day	20 mg/kg/day

# Patients and methods

	Mean	Sd	Range
Age at enrollment (years)	27.31	8.36	15-41
Disease duration (years)	16.25	7.68	5-2



# Patients and methods

## ■ Clinical evaluations:

- At each follow-up evaluation, all patients underwent clinical and neurological evaluation, neuro-otology, EMG and nerve conduction velocities, TMS, MMEP, neuroimaging, and heart ultrasound evaluation.
- Neurological assessment was performed using the International Cooperative Ataxia Rating Scale (ICARS), Graded neurological scale for use in acute hemispheric stroke treatment protocols (motor function, pathologic reflexes, and sensory function), Reflexes scale (Wartenberg), and Tonicity scale (Ashworth).
- Cardiac evaluation included electrocardiogram (ECG) and a complete M-mode, two dimensional Doppler echocardiography.
- Monitoring of Idebenone treatment was carried out in eight patients with FRDA by HPLC-procedure (Artuch et al, 2002).

# Patients and methods

## ■ **Statistical analyses:**

- **Continuous values are expressed as mean±Sd. Nonparametric tests (Wilcoxon signed ranks test for paired data, Mann-Whitney test for unpaired data) and linear regression (to compare changes in data studied over time) were used at  $p < 0.05$ .**
- **The relative change in ultrasound measurements was computed as the percentage difference between the pre-treatment (baseline) and post-treatment values.**

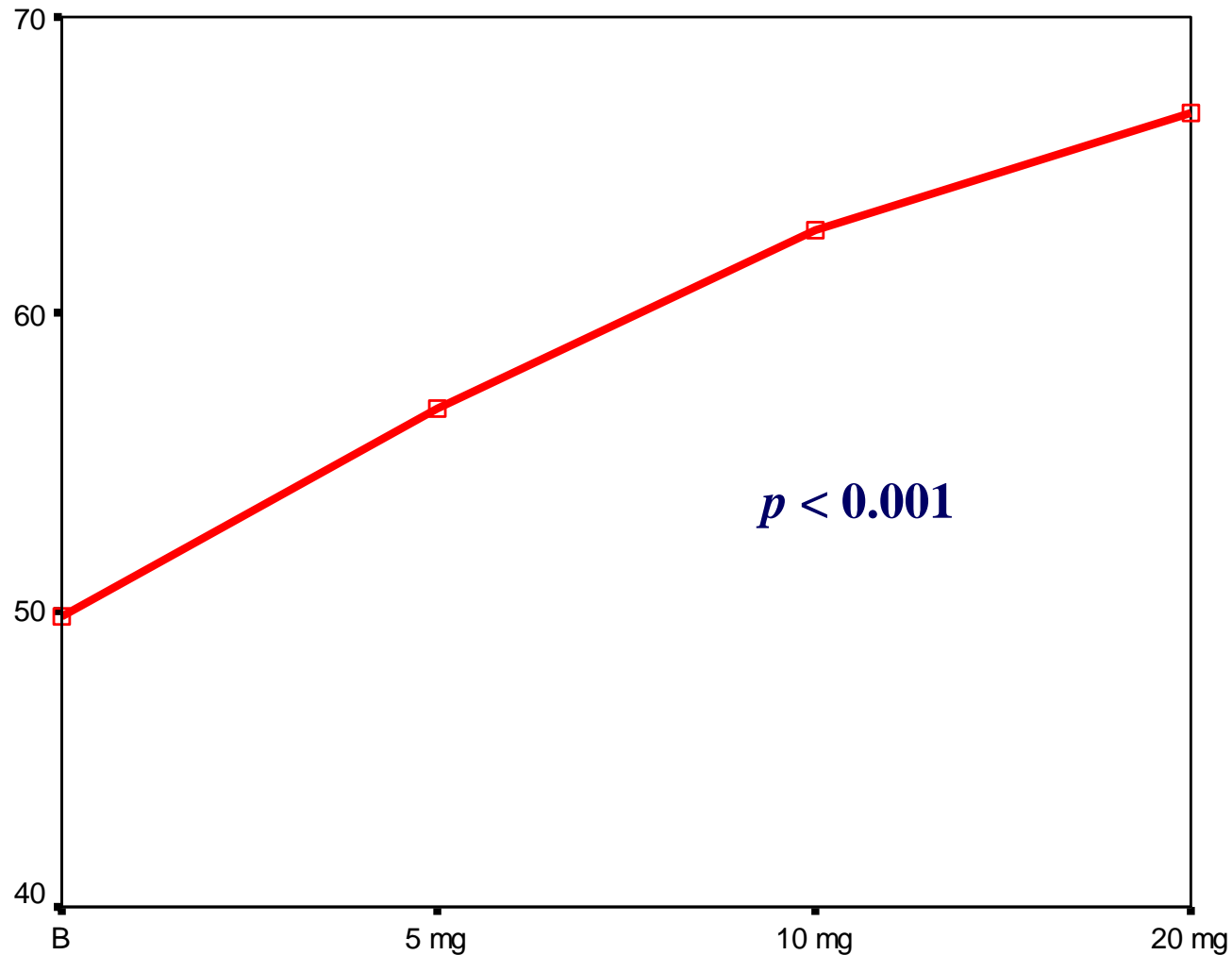
# Results

# Effect on the nervous system of the treatment with Idebenone

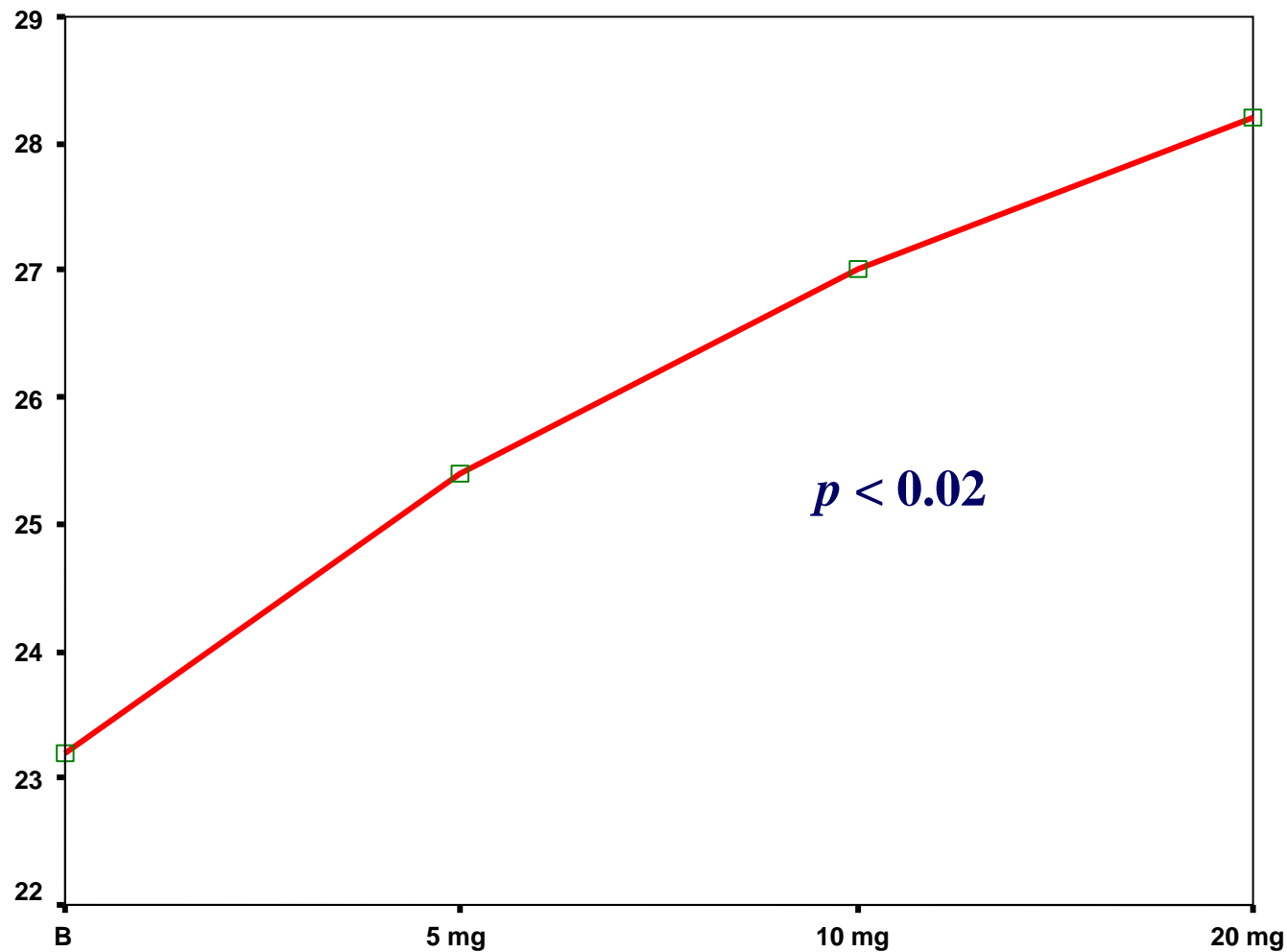
## *Wilcoxon signed ranks test: Impairment*

<i>Posture/gait</i>	<i><math>p &lt; 0.02</math></i>
<i>Kinetic function</i>	<i><math>p &lt; 0.001</math></i>
<i>Speech disorder</i>	<i><math>p &lt; 0.027</math></i>
<i>Oculomotor changes</i>	<i><math>p &lt; 0.005</math></i>
<i>Total ICARS</i>	<i><math>p &lt; 0.001</math></i>

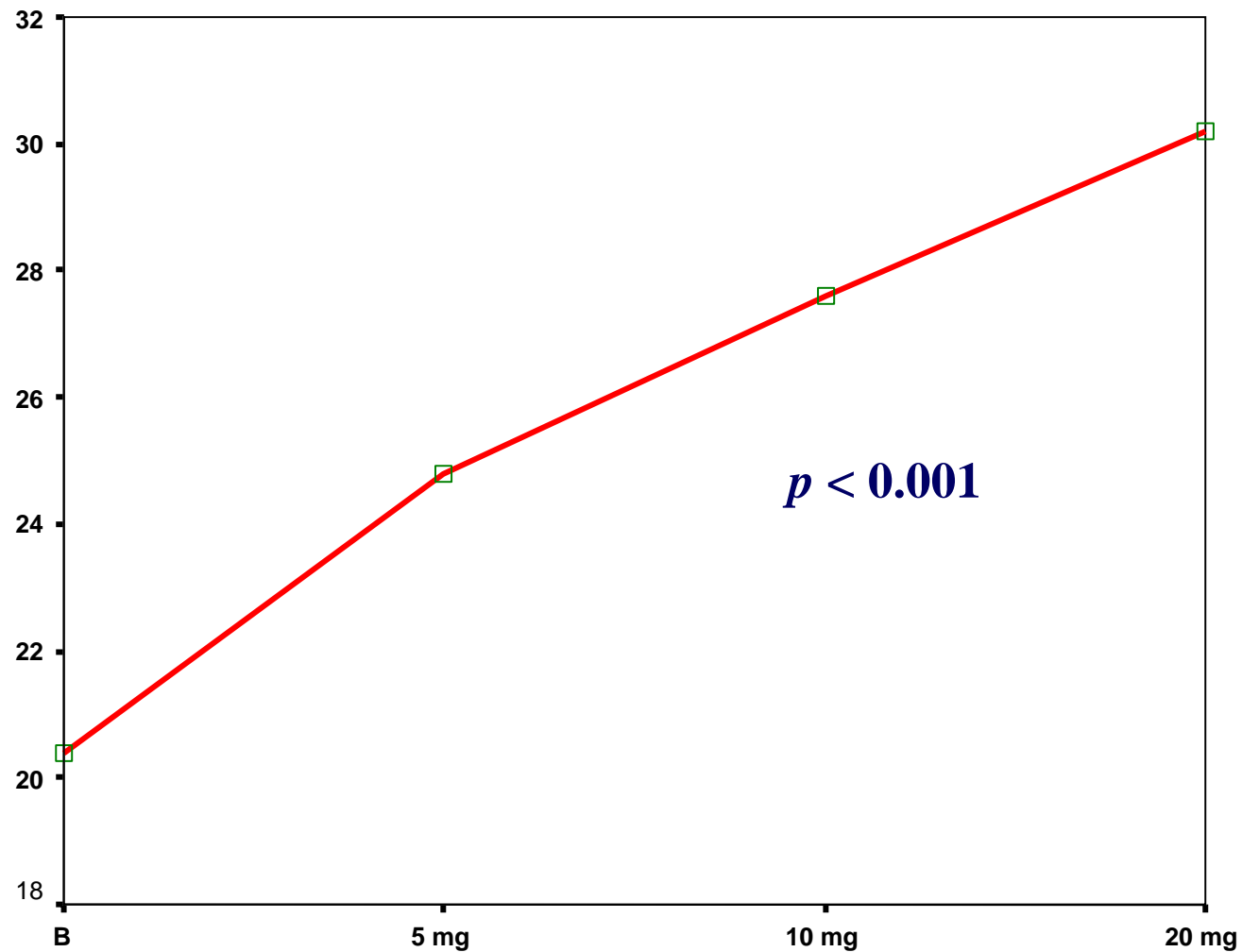
# Effect on the nervous system of the treatment with Idebenone. Total ICARS



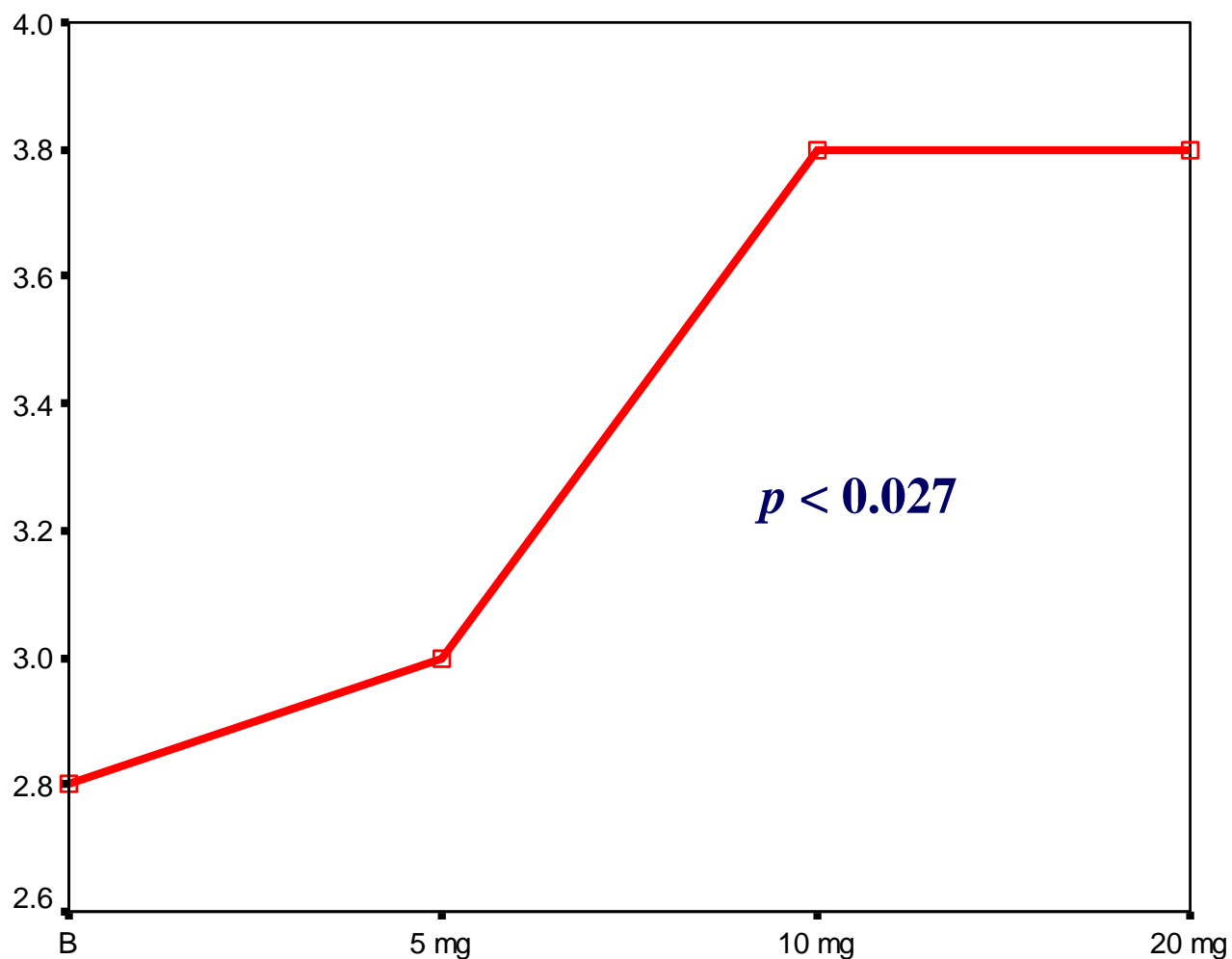
# Effect on the nervous system of the treatment with Idebenone. Posture/Gait



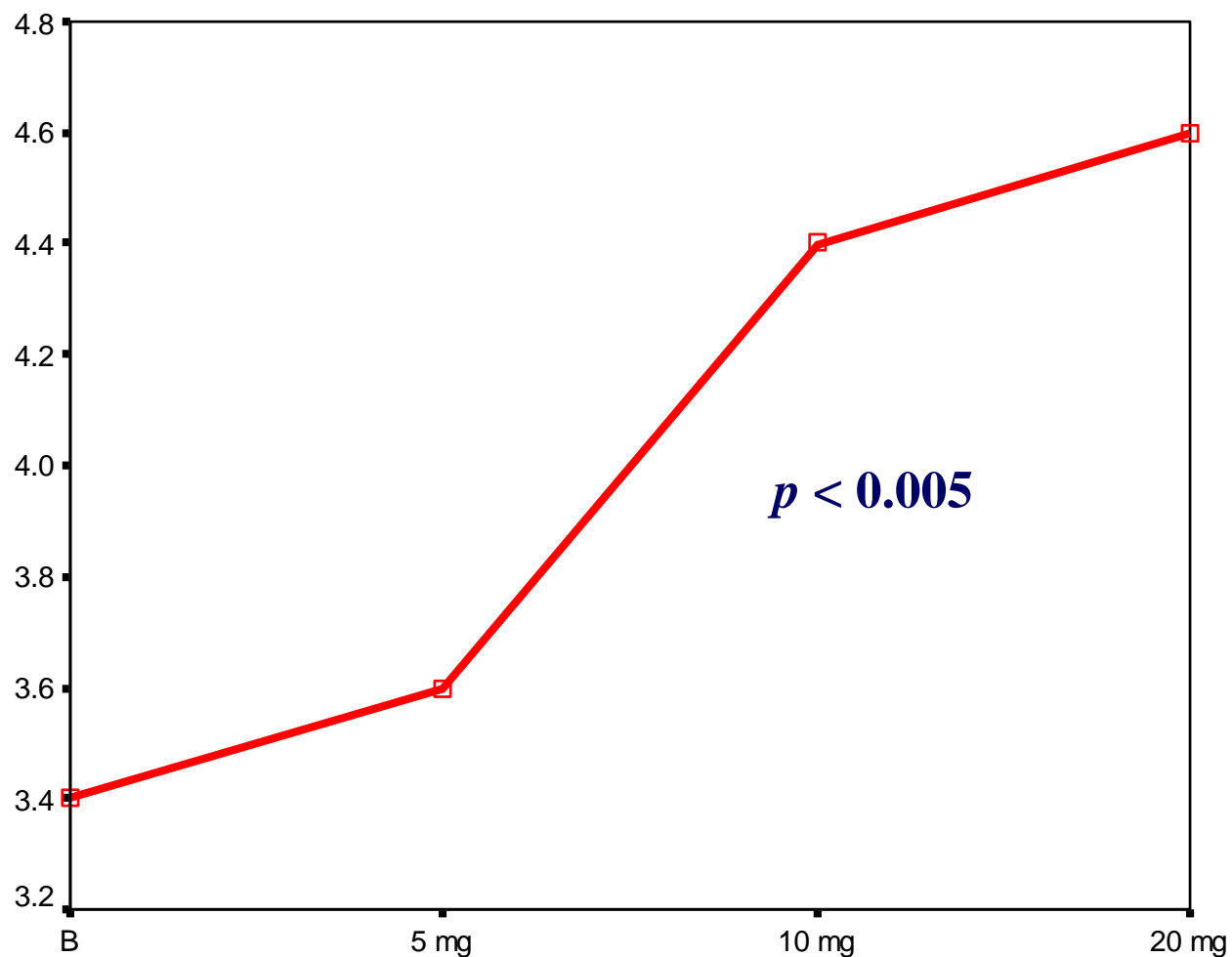
# Effect on the nervous system of the treatment with Idebenone. Kinetic Function



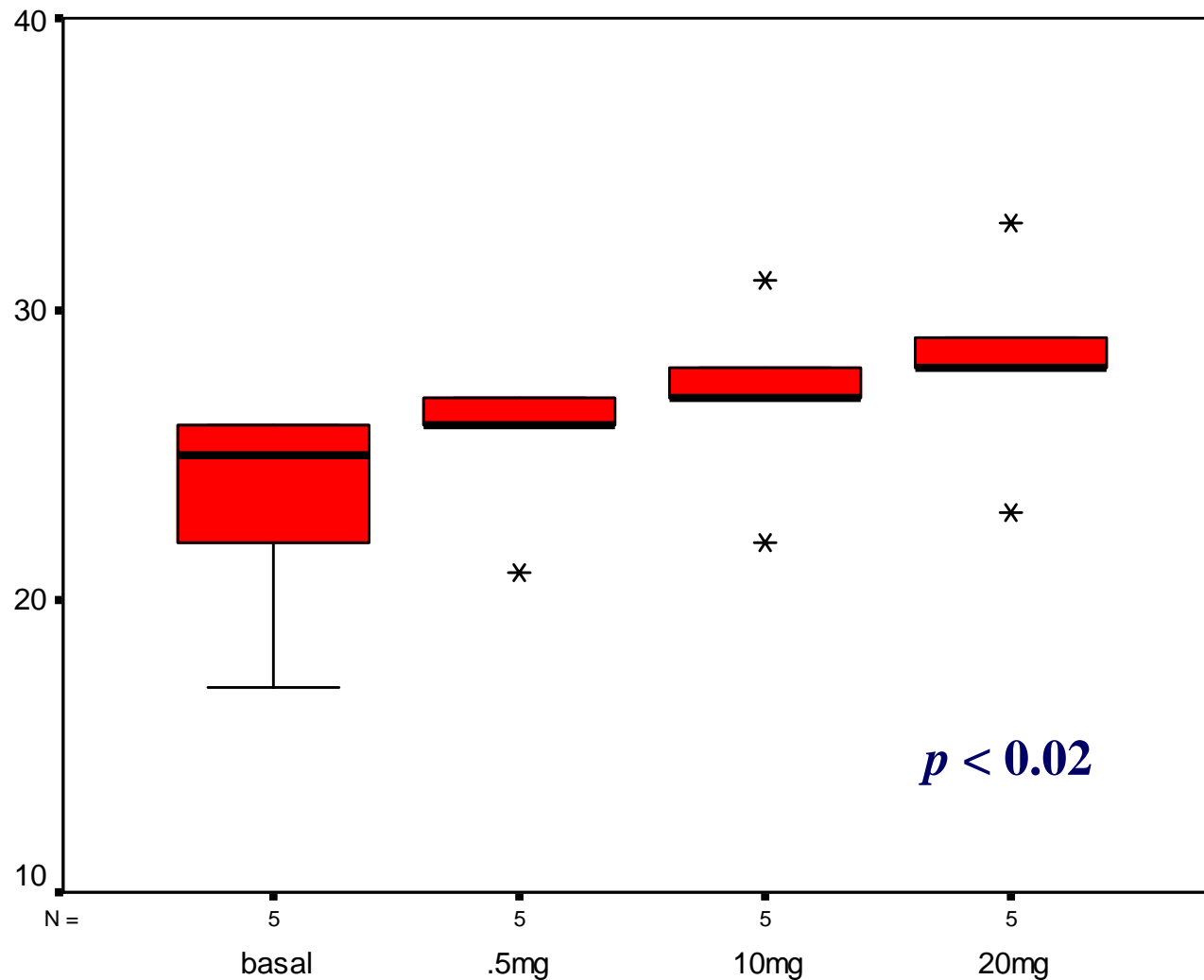
# Effect on the nervous system of the treatment with Idebenone. Speech disorder



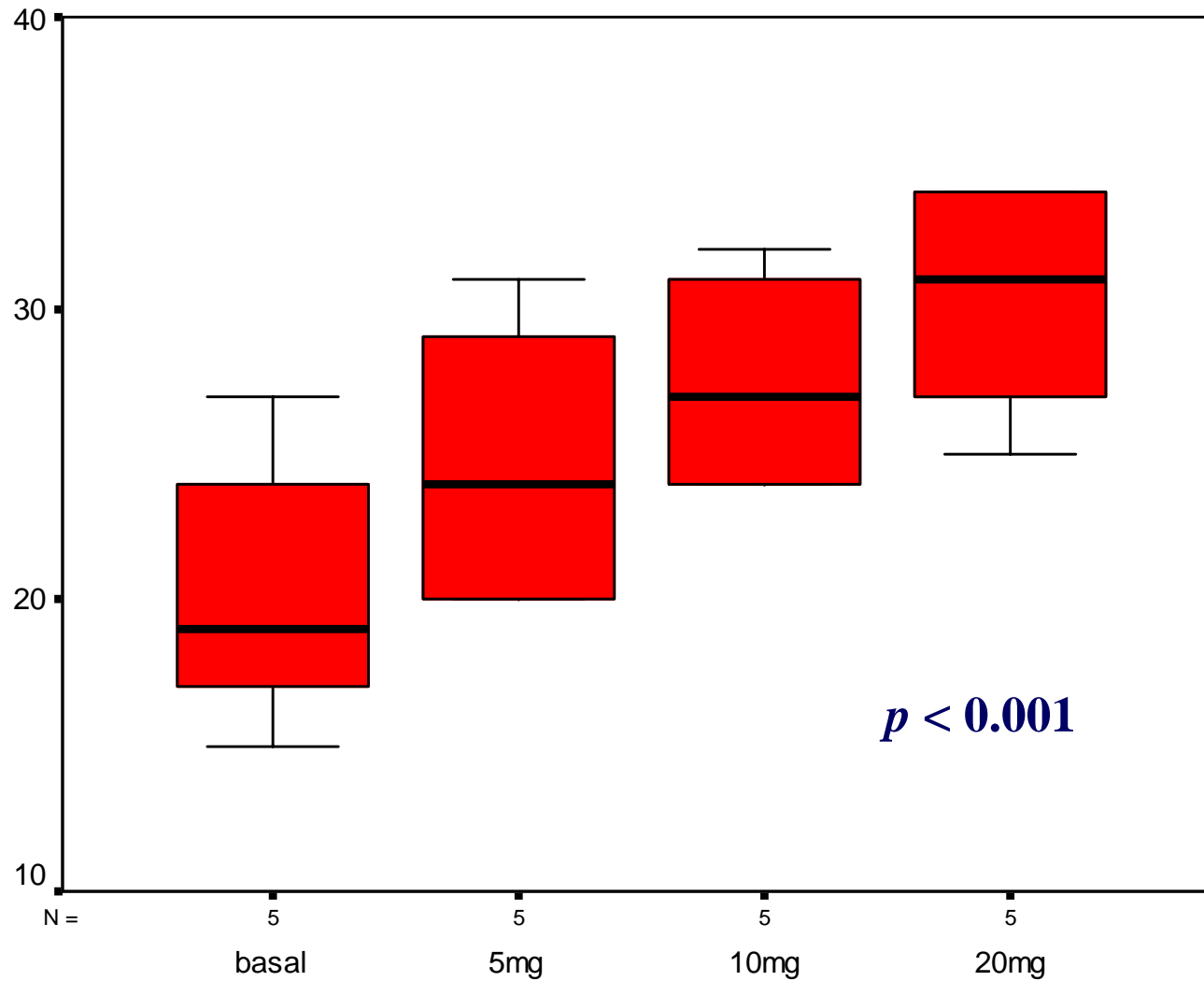
# Effect on the nervous system of the treatment with Idebenone. Oculomotor changes



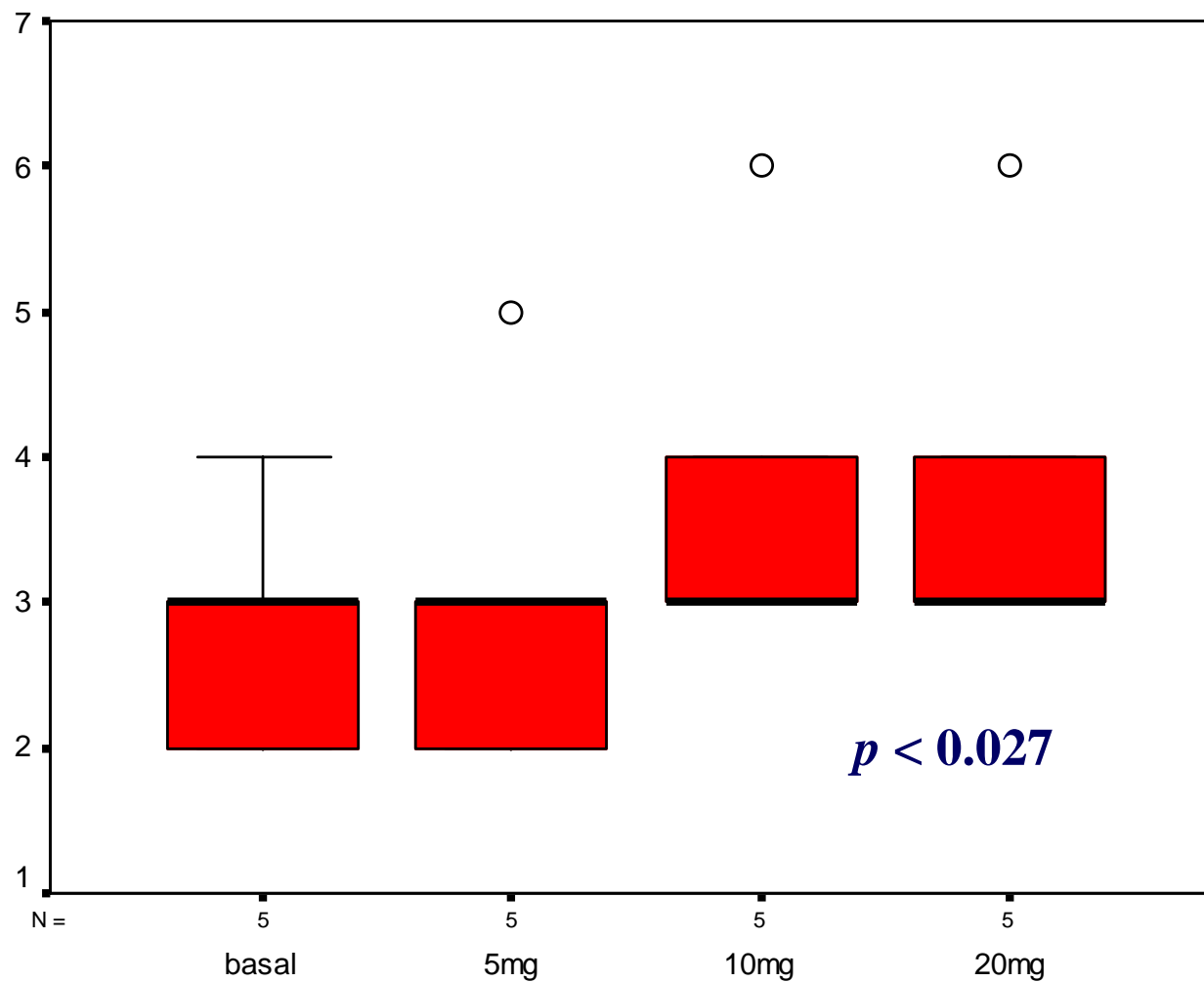
# Effect on the nervous system of the treatment with Idebenone. Posture/Gait



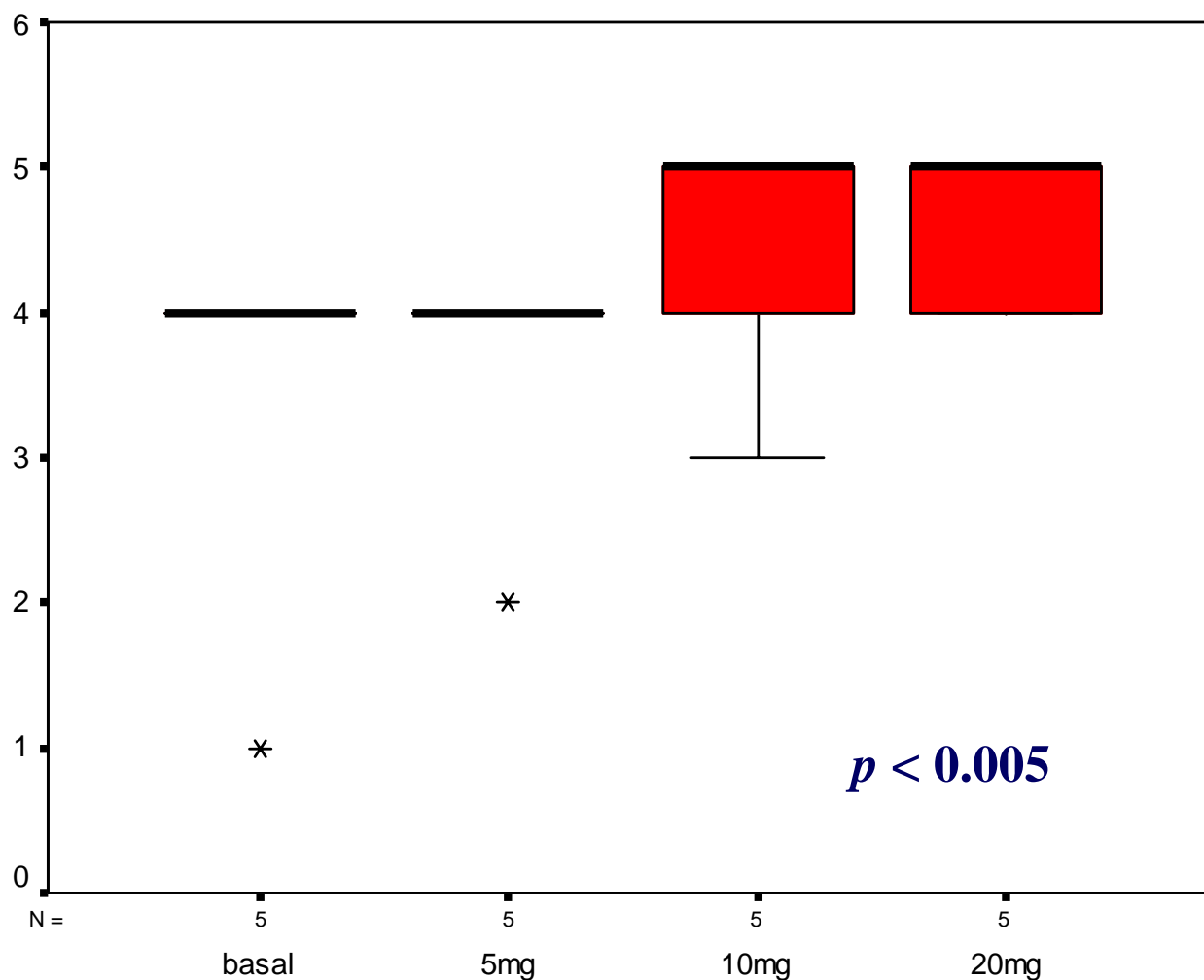
# Effect on the nervous system of the treatment with Idebenone. Kinetic Function



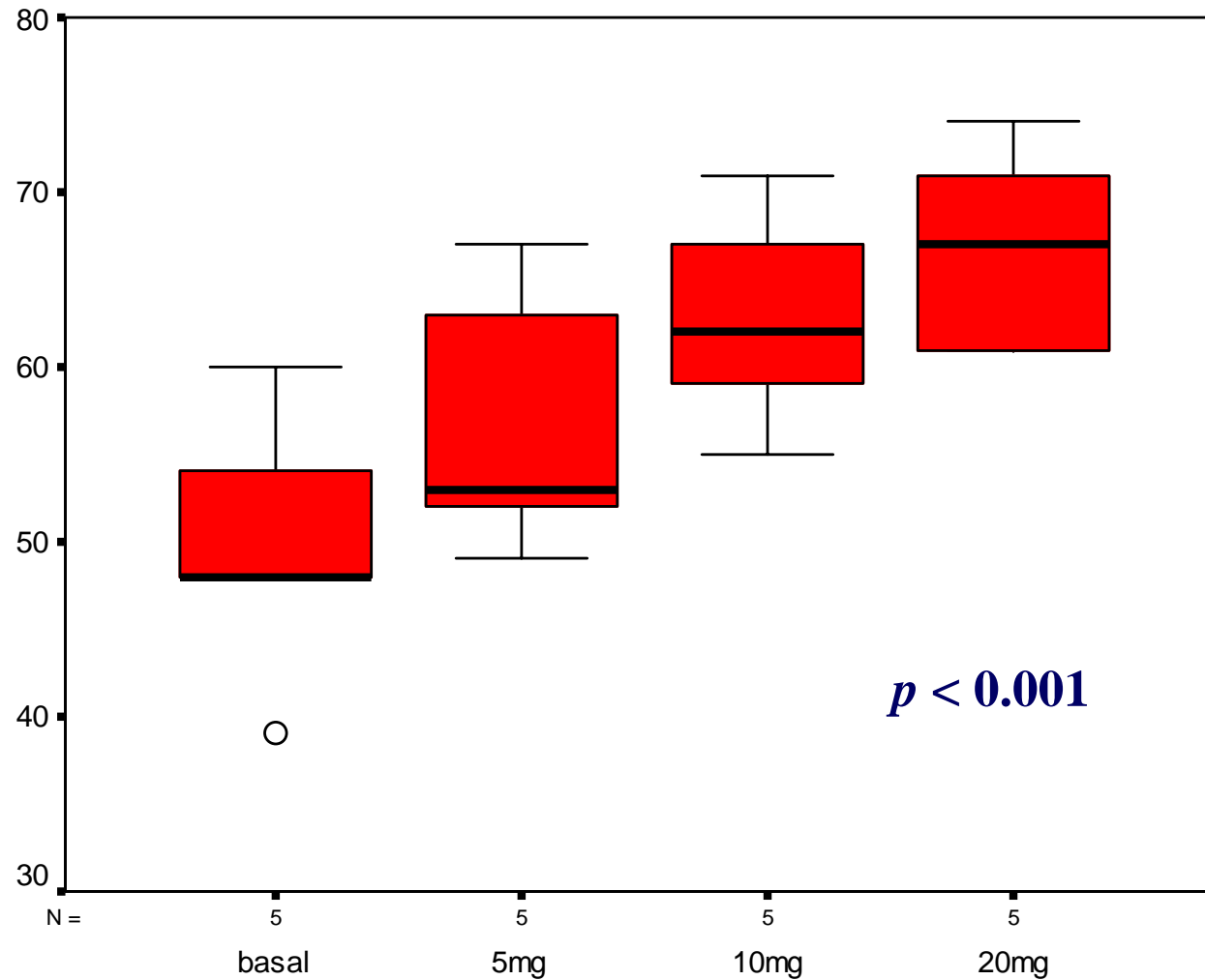
# Effect on the nervous system of the treatment with Idebenone. Speech disorder



# Effect on the nervous system of the treatment with Idebenone. Oculomotor changes



# Effect on the nervous system of the treatment with Idebenone. Total ICARS

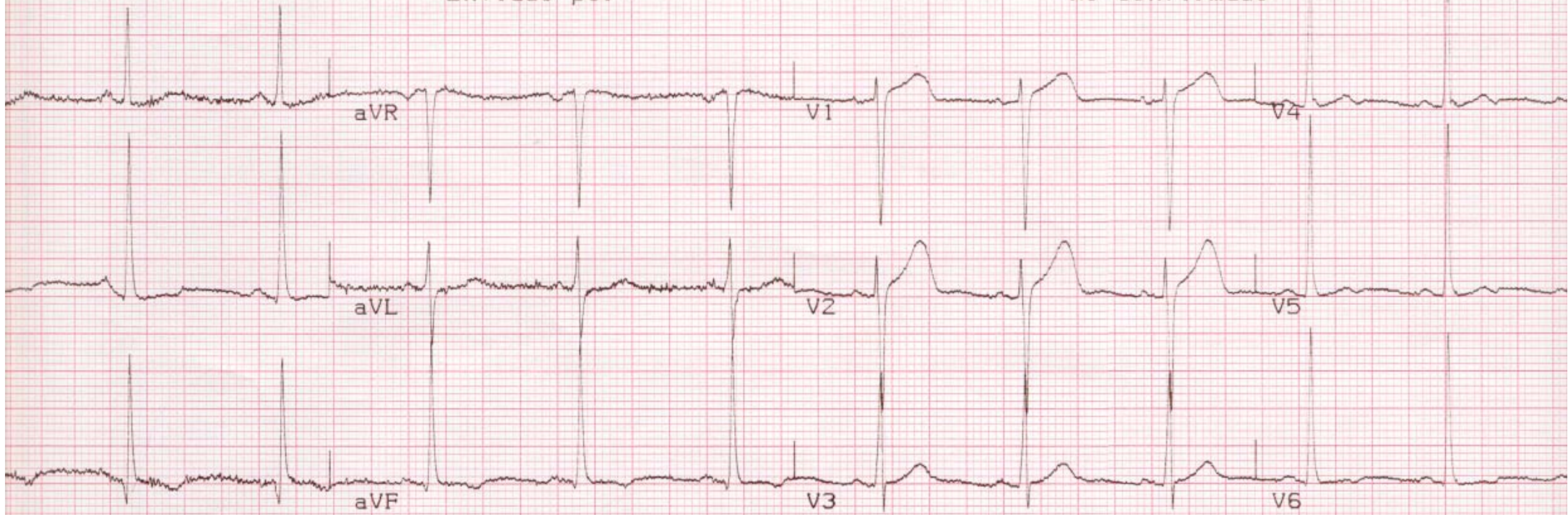


QT/QTc 372/415 ms

Ejes P-R-T 38 62 -9

Enviado por:

No confirmado

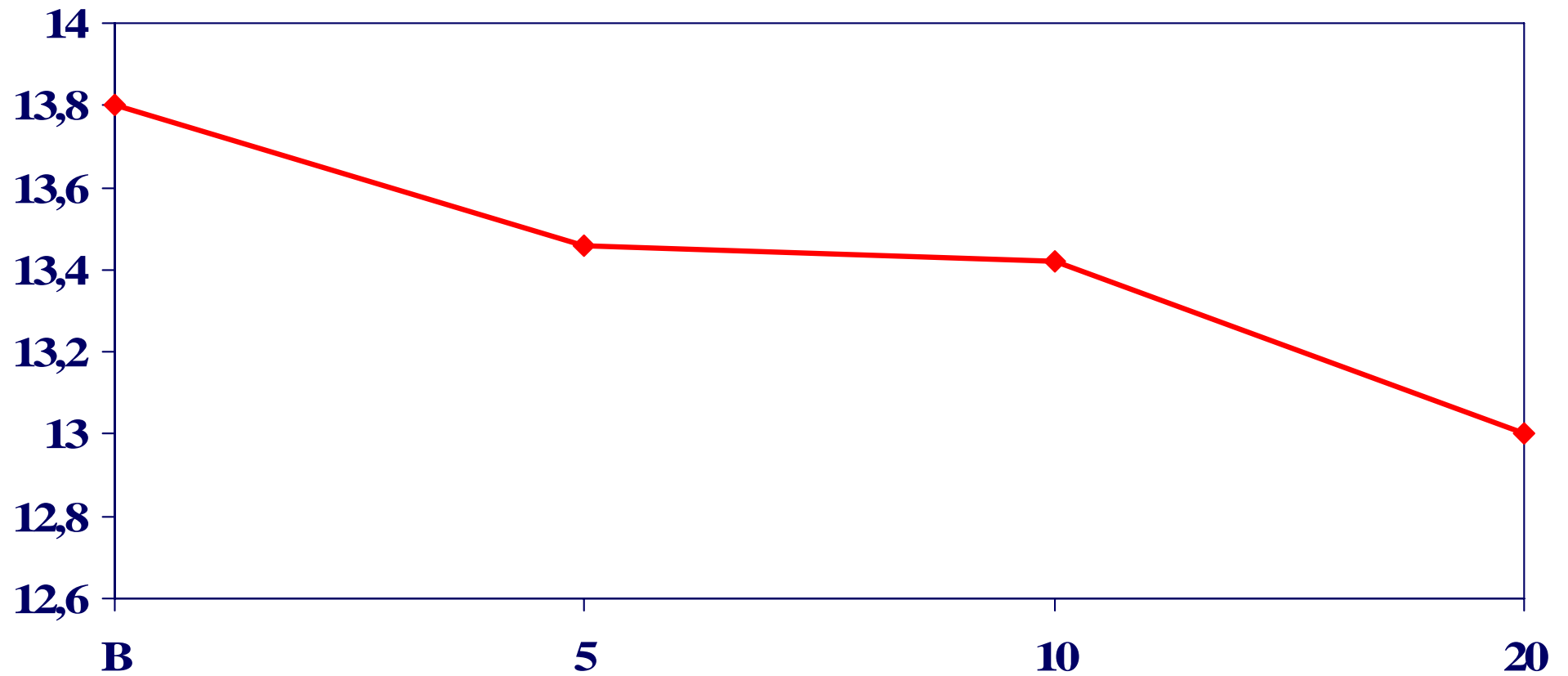


# Echocardiographic measures of interventricular septal thickness measured in diastole (IVSd), and changes at 3-year follow-up in Friedreich ataxia patients

<i>Patients</i>	IVSd thickness (mm), baseline	IVSd thickness (mm), 1-year follow-up	IVSd thickness (%), at 1-year follow-up	IVSd thickness (mm), 2-year follow-up	IVSd thickness (%), at 2-year follow-up	IVSd thickness (mm), 3-year follow-up	IVSd thickness (%), at 3-year follow-up
1 †	15	15	0	15	0	15	0
2 †	11	13	18	12	-7	—	—
3 †	13	14	8	13	-7	13	0
4 †	14			13	-7	13	0
5 †	13	12	-8	13	8	13	0
6 †	11	12	9	12	0	—	—
7 †	13	14	8	14	0	14	0
8 †	13	13	0	13	0	13	0
10 †	11	11	0	9 <sup>▲</sup>	-18	10	11
11 †	11	11	0	13 <sup>▼</sup>	18	13	0
9 †	17	19	12	19	0	19*	0
12 †	15	16	7	13*	-18	15*	15
13 †	16	16	0	15*	-6	14*	-7
14 †	10	9	-10	10*	11	DM*	DM
15 †	14			13	-7		
16 †	10			14	4	12	-14
	Normal Value: 6 - 11 mm		3,38±7.85 (NS)	Normal value: 6 - 11 mm	-1,81±9.49 (NS)	Normal value: 6 - 11 mm	0,41±7.31 (NS)

DM= Dilated cardiomyopathy; IVSd thickness= Interventricular septal thickness measured in diastole; <sup>▲</sup> dose: 20 mg/kg/day; <sup>▼</sup> dose: 5 mg/kg/day

# IVSd thickness (mm)

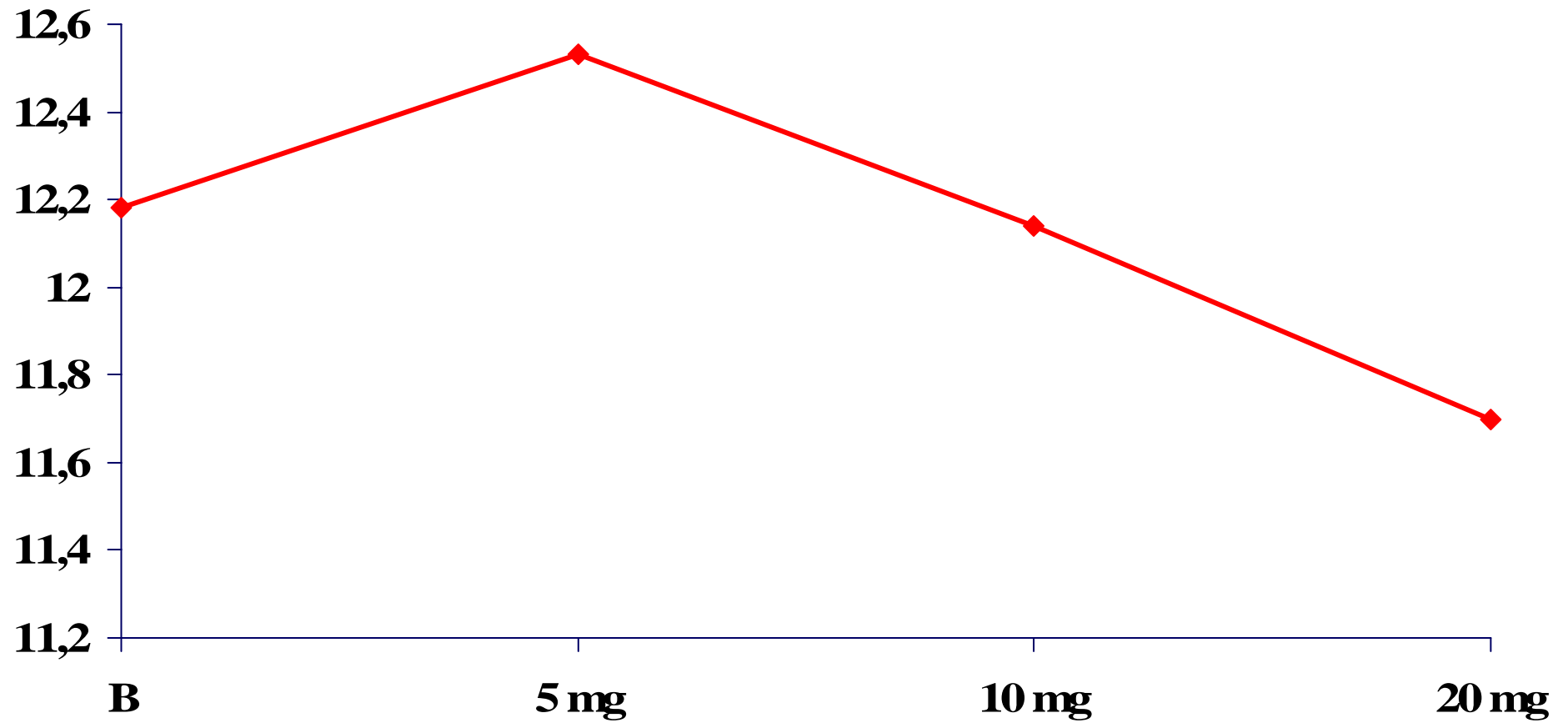


# Echocardiographic measures of posterior wall (PW) thickness, and changes at 3-year follow-up in Friedreich ataxia patients

<i>Patients</i>	PW thickness (mm), baseline	PW thickness (mm), 1-year follow-up	PW thickness changes (%)	PW thickness (mm), 2-year follow-up	PW thickness changes (%)	PW thickness (mm), 3-year follow-up	PW thickness changes (%)
1 †	15	18	20	15	-16	14	-7
2 †	10	10	0	11	10	—	—
3 †	10	11	10	11	0	11	0
4 †	13			12	-7	12	0
5 †	13	14	8	12	-14	12	0
6 †	11	14	27	12	-14	—	—
7 †	14	13	-7	13	0	11	-15
8 †	14	14	0	11	-21	10	-9
10 †	12	11	-8	9 <sup>▲</sup>	-18	10	11
11 †	11	9	-18	12 <sup>▼</sup>	33	12	0
9 †	12	12	0	13	8	11*	-15
12 †	13	14	8	13*	-7	13*	0
13 †	15	15	0	15*	0	12*	-20
14 †	12	8	-33	7*	-12	DM*	DM
15 †	9			10	9		
16 †	11			14	27	12	-14
	Normal value: 6 - 11 mm		0.53±15.48 (NS)	Normal value: 6 - 11 mm	-1.37±15.67 (NS)	Normal value: 6 - 11 mm	-5.75±9.04 (NS)

DM= Dilated cardiomyopathy; PW thickness= Posterior wall thickness; <sup>▲</sup> dose: 20 mg/kg/day; <sup>▼</sup> dose: 5 mg/kg/day

# LVPW thickness (mm)

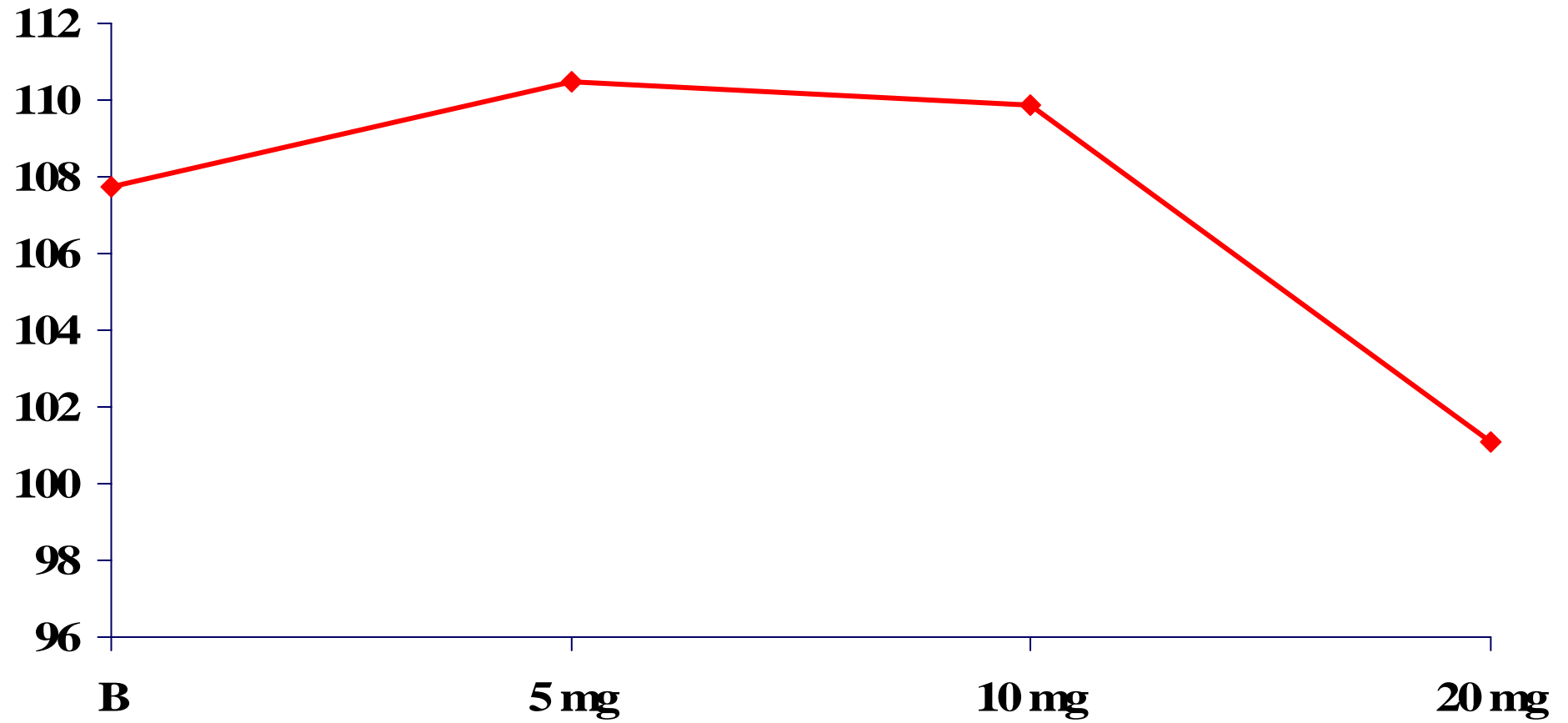


# Echocardiographic measures of left ventricular mass (LVM) index, and changes at 3-year follow-up in Friedreich ataxia patients

<i>Patients</i>	LVM index (g/m <sup>2</sup> ), baseline	LVM index (g/m <sup>2</sup> ), 1-year follow-up	LVM index change (%) at 1-year follow-up	LVM index (g/m <sup>2</sup> ), 2-year follow-up	LVM index change (%) at 2-year follow-up	LVM index (g/m <sup>2</sup> ), 3-year follow-up	LVM index change (%) at 3-year follow-up
1 †	133	129	-3	112	-13	112	0
2 †	93	103	11	89	-13	—	—
3 †	108	122	13	110	-10	99	-10
4 †	102			95	-6	89	-6
5 †	124	111	-10	105	-5	104	-1
6 †	98	101	3	103	2	—	—
7 †	107	112	5	114	2	108	-5
8 †	111	107	-4	117	9	92	-21
10 †	70	71	1	67 <sup>▲</sup>	-5	78	17
11 †	89	79	-11	94 <sup>▼</sup>	20	94	0
9 †	147	144	-2	156	9	120*	-23
12 †	119	122	3	104*	-14	123*	18
13 †	101	118	16	110*	-7	95*	-14
14 †	116	117	1	148*	26	DM*	DM
15 †	111			140	26		
16 †	95			126	32	112	-11
	Normal values: Male: 97±14 g/m <sup>2</sup> / Female: 82±13 g/m <sup>2</sup>		1.76±8.16 (NS)	Normal values: Male: 97±14 g/m <sup>2</sup> / Female: 82±13 g/m <sup>2</sup>	3.31±15.36 (NS)	Normal values: Male: 97±14 g/m <sup>2</sup> / Female: 82±13 g/m <sup>2</sup>	-4.66±12.79 (NS)

DM= dilated cardiomyopathy; LVM= Left ventricular mass; <sup>▲</sup> dose: 20 mg/kg/day; <sup>▼</sup> dose: 5 mg/kg/day; \*withdrawal.

# LVM index (g/m<sup>2</sup>)

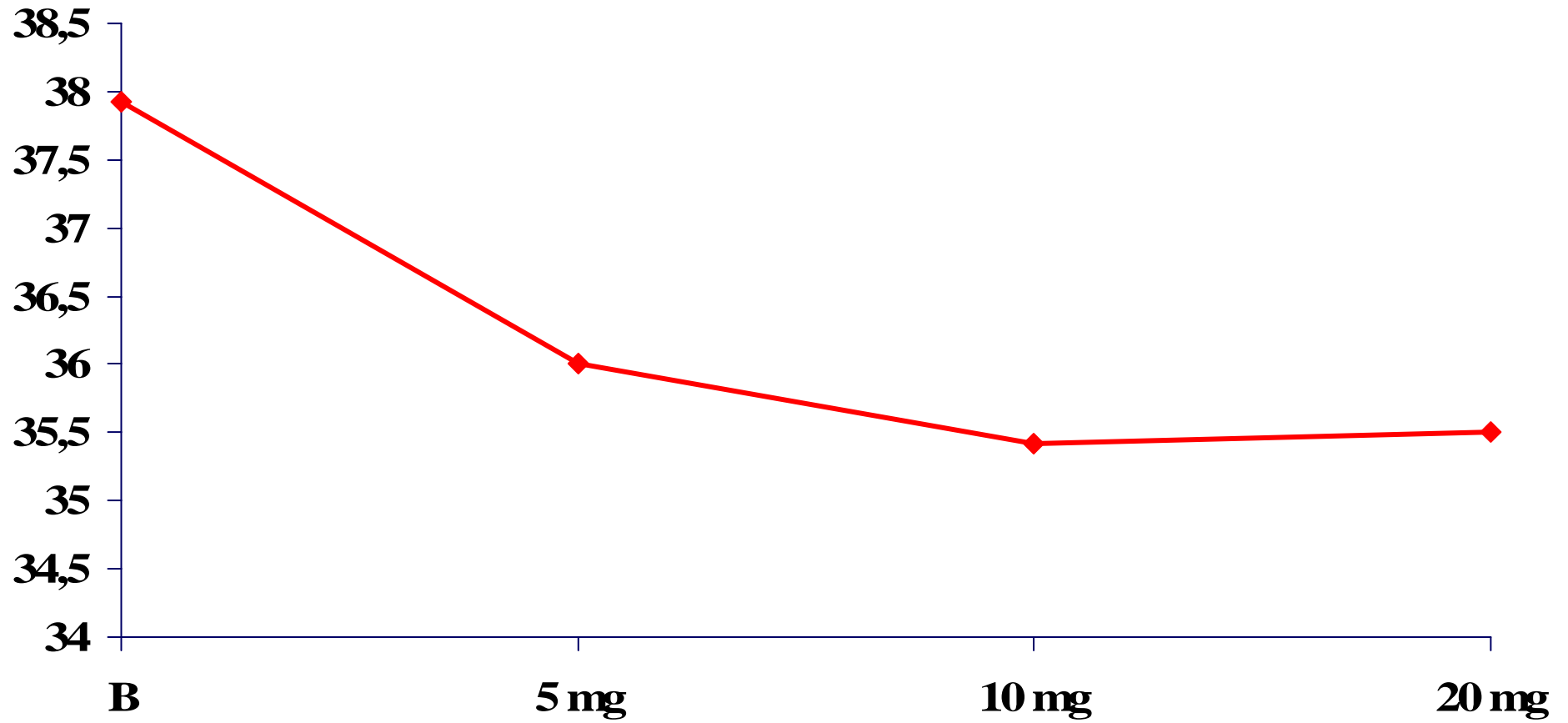


# Echocardiographic measures of shortening fraction (%), and changes at 3-year follow-up in Friedreich ataxia patients

<i>Patients</i>	Shortening fraction (%), baseline	Shortening fraction (%), 1-year follow-up	Shortening fraction changes (%)	Shortening fraction (%), 2-year follow-up	Shortening fraction changes (%)	Shortening fraction (%), 3-year follow-up	Shortening fraction changes (%)
1 †	35	44	26	36	-18	32	-11
2 †	32	35	9	30	-14	—	—
3 †	27	28	4	30	7	33	10
4 †	54			36	-33	33	-8
5 †	40	35	-13	31	-11	44	42
6 †	35	40	14	34	-15	—	—
7 †	41	44	7	37	-14	31	-6
8 †	41	41	0	35	-14	33	-6
10 †	47	43	-9	45 <sup>▲</sup>	4	40	-11
11 †	39	38	-3	34 <sup>▼</sup>	-10	35	3
9 †	50	33	-34	42	27	34*	-19
12 †	35	48	37	36*	-25	38*	5
13 †	38	27	-29	37*	37	36*	-3
14 †	29	12	-59	21*	75	DM*	DM
15 †	35			36	2		
16 †	29			33	13	37	12
	Normal value >25%		-3.84±25.70 (NS)	Normal value >25%	0.68±27.11 (NS)	Normal value >25%	0.66±15.91 (NS)

DM= Dilated cardiomyopathy; <sup>▲</sup> dose: 20 mg/kg/day; <sup>▼</sup> dose: 5 mg/kg/day; \*withdrawal

# Shortening fraction (%)

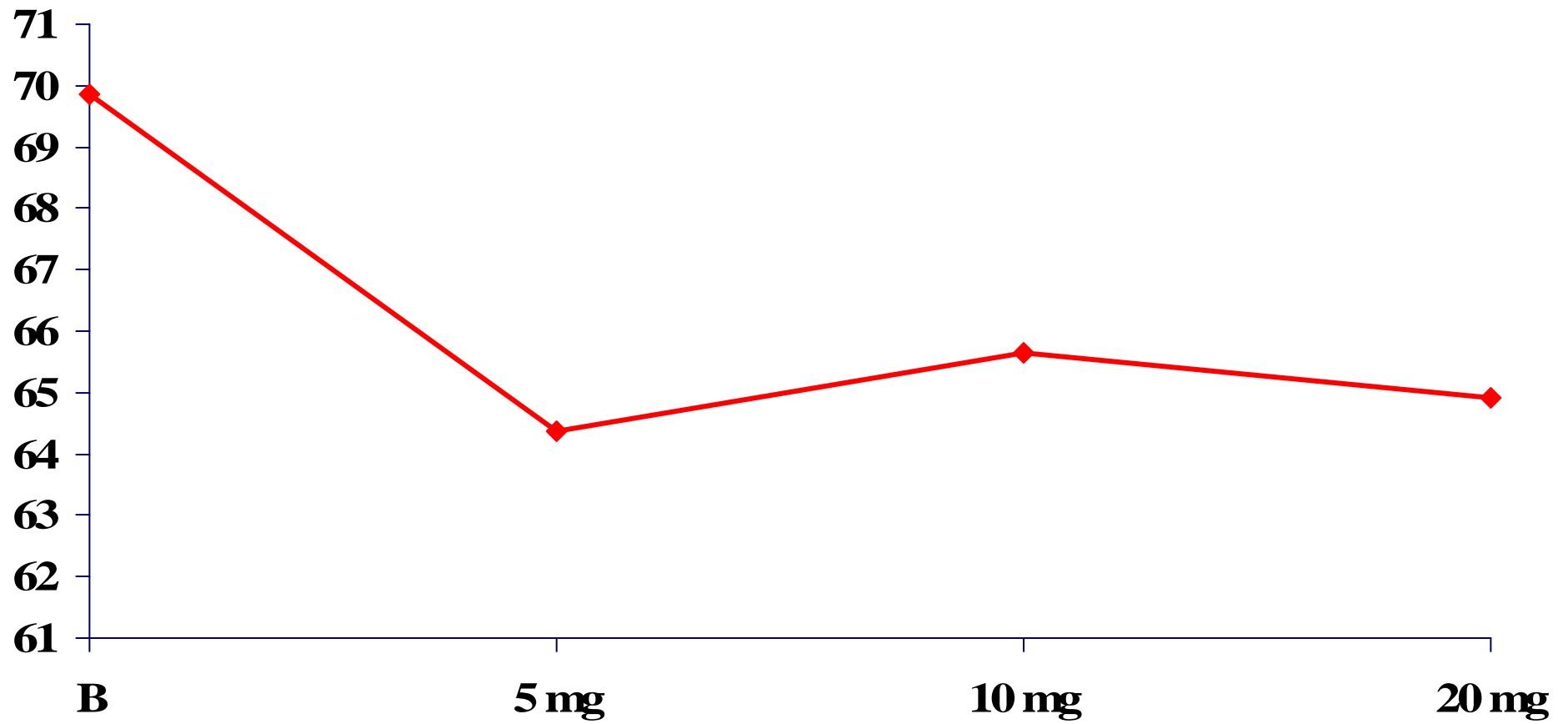


# Echocardiographic measures of ejection fraction (%), and changes at 3-year follow-up in Friedreich ataxia patients

<i>Patients</i>	Ejection fraction (%), baseline	Ejection fraction (%), 1-year follow-up	Ejection fraction changes (%)	Ejection fraction (%), 2-year follow-up	Ejection fraction changes (%)	Ejection fraction (%), 3-year follow-up	Ejection fraction changes (%)
1 †	65	77	18	66	-14	62	-6
2 †	61	65	7	59	-9	—	—
3 †	60	54	-10	57	5	61	7
4 †	85			66	-22	62	-6
5 †	72	65	-10	58	-10	75	29
6 †	65	71	9	63	-11	—	—
7 †	75	75	0	67	-10	59	-12
8 †	73	73	0	66	-9	63	-5
10 †	78	75	-4	77 <sup>▲</sup>	2	72	-7
11 †	70	69	-1	63 <sup>▼</sup>	-8	65	3
9 †	82	62	-24	73	17	64*	-12
12 †	77	71	-8	67*	-5	69*	3
13 †	70	54	-23	67*	24	67*	0
14 †	55	26	-53	40*	53	20*	-50
15 †	65			66	1		
16 †	65			71	9	63	-11
	Normal value >55%	Normal value >55%	-7.61±18.01 (NS)	Normal value >55%	0.81±18.30 (NS)	Normal value >55%	-5.15±17.36 (NS)

▲ dose: 20 mg/kg/day; ▼ dose: 5 mg/kg/day; \*withdrawal

# Ejection fraction (%)



# Conclusions (I)

- The left ventricular mass (LVM) index improved in 38,4% of the 13 patients with Idebenone therapy (5 mg/kg/day), but it worsened in 62,6% of them. Therefore, LVM index didn't significantly reduce in this series.
- The LVM index improved in 35,7% of the 14 patients with Idebenone therapy (10 mg/kg/day), but it worsened in 65,3% of them. Therefore, LVM index didn't significantly reduce in this series.
- The LVM index improved in 50,0% of the 10 patients with Idebenone therapy (20 mg/kg/day), but it worsened in 50,0% of them. Therefore, LVM index didn't significantly reduce in this series.

## Conclusions (II)

- The interventricular septum at end diastole (IVSd) measured  $12.9 \pm 2.1$  (range 10 to 17) and the posterior wall  $12.9 \pm 1.8$  (range 9 to 16) initially. After this therapy (20 mg/kg/day), there was a non-significant reduction in these dimensions ( $13.0 \pm 1.3$ , range 10 to 15;  $11.7 \pm 1.2$ , range 10 to 14 respectively).
- Four other patients retired of the study of one's own free-will, improving later both LVM index and IVSd in two of them, and in other two both shortening and ejection fractions increase.
- However, only one of them maintained the improvement partially up to two years after the withdrawal.

## Conclusions (III)

- **Our study demonstrate that long-term Idebenone therapy didn't improve or arrest the progression of neurological syndrome.**
- **Idebenone could prevent or slow the cardiac hypertrophy in FDRA, although dose  $\geq$  than 20 mg/kg/day seem to be necessary.**
- **Idebenone was well tolerated and without major adverse effects. However, myocardial dysfunction could be impaired in some patients with severe cardiac dysfunction.**

*¿Idebenone?*



*In due course...*

*¿Idebenone?*



*In due course...*

**Biology, Clinic and Therapy of the Cerebellar Ataxias. Study of the neurological and cardiological evolution, and of the antioxidant system state, and of the mitochondrial function in patient with Friedreich's ataxia after riboflavin supplement.**

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# Riboflavin supplement in FRDA.

**–Main objective: To carry out studies of clinical and biochemical control of patient with Friedreich's ataxia after riboflavin supplement therapy.**

**–Concrete objectives:**

*–1) To evaluate if riboflavin supplement modifies the neurological and cardiological evolution of this illness.*

*–2) To analyze biochemical markers related with the oxidative stress and to evaluate its state after riboflavin supplement therapy.*

*–3) To carry out studies of mitochondrial function, especially of the riboflavin dependent enzymes, and to compare the mitochondrial function before and after the riboflavin supplement therapy.*

*–4) To compare the evolution of patients after 4 years of single therapy with idebenone with the evolution after 1 year of single therapy with riboflavin supplement.*

# Riboflavin supplement in FRDA.

**–Methodology: Design.** Prospective, longitudinal study of 15 patients with Friedreich's ataxia. Complete clinical and biochemical study will be carried out before riboflavin supplement therapy and on months 3, 6, 9 and 12 after the beginning of treatment. Riboflavin is recommended to be administered in a minimal dose between 10-15 mg/kg/day (p.o., 3 times daily ).

*–Neurological studies: Complete examination, ICARS scale, and recorded it on video, in all the checkpoints.*

*–Cardiological studies: Baseline echocardiography 2-D and cardiological MR imaging and after one year riboflavin supplement therapy.*

*–Biochemical studies: They will be carried out in all the checkpoints. The antioxidant system and markers of oxidative stress will be studied by means of spectrometric procedures and of high-pressure liquid chromatography with ultraviolet and electrochemical detection. The mitochondrial function will be studied in mononuclear cells by enzymatic (enzymatic activity quantification) and polarographic (oxygen consumption) procedures. The therapies will be monitored by means of the quantification of both idebenona and riboflavin blood levels through high-pressure liquid chromatography with electrochemical detection and fluorescence methods, respectively.*

# Baseline characteristics of FRDA patines. Riboflavina

<i>Patients</i>	<i>Gender</i>	<i>Age at enrollment (years)</i>	<i>Disease duration</i>	<i>Total score at neurologic rating scale (ICARS)-1</i>	<i>Total score at neurologic rating scale (ICARS)-2</i>
1 †	M	31	19	59	
2 †	H	26	8	16	16
3 †	H	29	1	2	2
4 †	H	30	20	63	63
5 †	M	29	11	7	9
6 †	M	31	4	17	16
7 †	H	35	27	37	
8 †	H	37	29	43	
9 †	M	27	14	60	
10 †	M	34	21	51	
11 †	H	31	13	13	
12 †	M	21	11	60	
13 †	M	35	4	8	
14 †	H	38	25	50	50
15 †	H	49	39	64	64
16 †	M	38	21	66	
17 †	H	42	22	52	
<i>Summary</i>	M/F = 8/9	33.11±6.58	17.00±10.10	39.29±23.32	

## **Pilot, open study on effectiveness, tolerance and safety of treatment with trophic factor IGF-1 in degenerative cerebellar ataxia.**

**–Justification of study' design:** Experimental evidence exists on the therapeutic potential of IGF-1 to be taken subcutaneously in the cerebellar ataxias. The subcutaneous administration of IGF-1 to rodents with sporadic or hereditary ataxia cures the motor dyscoordination (Car *et al.* 2001, Fernandez *et al.* 1998). In at least 4 different animal models of cerebellar ataxia, the IGF-1 system is directly involved in the development of the illness.

*–Keeping in mind the data of preclinical effectiveness in the previous experimental models, the beginning of a pilot study phase IIA on the effectiveness, safety, and tolerance to IGF-1, to be taken subcutaneously, in patients of both sexes with degenerative cerebellar ataxia of slight to moderate grade, is justified.*

**–Patients and methods:** The study will include a maximum of 30 patients with degenerative cerebellar ataxia, between the ages of 14 and 85 years, inclusive, which present a score in the scale of Trouillas (ICARS) between 20 and 50. The patients will have to be affected indistinctly with:

- 1. "Pure" cerebellar Ataxia;*
- 2. OPCA phenotype;*
- 3. Spinopontin atrophies; and*
- 5. Ataxia of Friedreich.*

## **Pilot, open study on effectiveness, tolerance and safety of treatment with trophic factor IGF-1 in degenerative cerebellar ataxia.**

**–Main objectives: To determine the effectiveness of IGF-1 in patients with degenerative cerebellar ataxia of slight to moderate degree, assessed by means of Trouillas'scale (Trouillas *et al*, 1997); volumetric measures of brain MR; and neuro-otology study.**

**–All doses (50 µg/kg, twice a day) have to be taken subcutaneously, alternating the injection areas, for 2 years.**

**–Key variables: Main variables concern changes with regard to the basal levels in the following parameters:**

**–*ICARS***

**–*Brain Magnetic Resonance (MR)***

**–*Neuro-otology***

**–Main objectives: To determine the effectiveness of IGF-1 in patients with degenerative cerebellar ataxia of slight to moderate degree, assessed by means of Trouillas'scale; volumetric measures of brain MR; and neuro-otology study.**

# Translational medicine

