ABSTRACT: McArdle's disease causes limitation in exercise capacity as well as disability, the severity of which has been associated with the angiotensin-converting enzyme (ACE) insertion (I)/deletion (D) haplotype—patients with the genotype associated with higher ACE activity show the most severe phenotype. Modulation of ACE activity through the use of inhibitors may thus positively affect disease expression. In a double-blind, randomized, placebo-controlled trial, we assessed the efficacy of an ACE inhibitor (2.5 mg ramipril) in 8 patients with McArdle's disease. End-points were changes in parameters of exercise physiology (cycloergometer and muscle ^{31}P-magnetic resonance spectroscopy), quality of life (QoL) according to the Short Form 36 (SF-36), and disability according to the World Health Organization–Disability Assessment Scale II (WHO-DAS II). Patients had lower QoL and higher disability than controls. Measures of exercise physiology were not changed by ramipril in the whole group, but treatment induced higher peak VO_2 ($P = 0.017$) in ACE D/D patients, yet not in I/D patients. Treatment significantly improved disability ($P < 0.05$). McArdle's disease is a disabling condition affecting patients' QoL. Treatment with ramipril improves disability and modifies exercise physiology only in D/D patients, raising the possibility of a differential haplotype-linked sensitivity to the treatment.

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RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND PILOT TRIAL OF RAMIPRIL IN McARDLE'S DISEASE

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McArdle's disease manifests in young adults with exercise intolerance, myalgias, and recurrent myoglobinuria.[6] Although most patients develop distinctive adaptive behaviors and are thus able to live normal, productive lives, the real burden of disease on the global functional profile of each patient may vary considerably. In spite of the care that most patients take in avoiding or preparing for acute, intense effort (e.g., by ingesting sucrose[26]), unexpected efforts often catch them off guard, and may cause massive muscle damage. In 20%–30% of cases, the disease evolves in a severe phenotype with fixed myopathy and severe limitation in daily-life activities.[15] The disease is associated with an array of mutations in the *PYGM* gene, and no phenotype/genotype correlation has been demonstrated.[15]

Despite increased understanding of the complex physiopathology and genetics of McArdle's disease, only limited advances have been made in effective therapy, mostly based on pre-effort sucrose ingestion and supervised exercise training.[4,11,14,17] Treatments directed toward increasing substrate availability to the exercising muscle have shown limited efficacy.[22]

Abbreviations: ACE, angiotensin-converting enzyme; ADP, adenosine diphosphate; ATP, adenosine triphosphate; D, deletion; I, insertion; PCr, phosphocreatine; Pi, inorganic phosphate; ^{31}P-MRS, 31-phosphorus magnetic resonance spectroscopy; QoL, quality of life; SF-36, Short Form 36; TC, time constant; WHO-DAS II, World Health Organization–Disability Assessment Scale II

Key words: ACE inhibitor; McArdle's disease; muscle glycogenosis; ramipril; therapeutic trial

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In a recent study[16] we demonstrated that a common insertion/deletion (I/D) polymorphism in the gene for angiotensin-converting enzyme (ACE) is associated with disease severity. McArdle's disease patients carrying one or two D alleles are overrepresented among the most severely affected patients. The D allele correlates with slightly higher serum and tissue ACE activity, and is associated with lower performance in endurance athletes and normal individuals.[30] Similar results obtained recently in a large cohort of Spanish patients[23] confirmed that an ACE genotype is an important factor modulating severity of McArdle's disease. The correlation between D/D ACE genotype and lower exercise capacity in healthy subjects has been questioned,[19] but was recently confirmed in women with McArdle's disease.[9]

The mechanism by which ACE activity variation may influence muscle function and exercise performance is complex.[12] ACE is a key element of the circulating renin–angiotensin system, and even its subtle variations influence general and local circulatory homeostasis. ACE activity is also important as part of the muscle local renin–angiotensin system,[7] and as such it has been shown to modulate endurance in single muscle groups.[30,31] The local muscle renin–angiotensin system influences substrate utilization,[5,8] and angiotensin receptor 1–mediated angiotensin II action is involved in overload-induced muscle hypertrophy.[10]

Because the most obvious difference associated with the ACE I/D polymorphism is the higher enzyme activity observed in carriers of the D allele, and because the allele with lower activity is associated with better exercise capacity, it is possible that ACE pharmacological inhibition may induce an improvement in exercise capacity. This effect, not observed when healthy subjects are treated with ACE inhibitors,[21] is present when the treatment involves subjects with reduced exercise capacity (e.g., elderly women).[18] ACE inhibition would attenuate angiotensin II production and bradykinin degradation, and also lead to increased availability of angiotensin 1–7, favoring vasodilation and substrate delivery through both systemic and local effects. Moreover, treatment with ACE inhibitors may influence muscle myosin heavy-chain composition, favoring the slow, aerobic, fatigue-resistant isoforms.[25] The effect may be more evident in one ACE genotype than the other, as it has been observed for the response to ACE inhibition in kidney and endothelium.[20,28]

ACE activity modulation may thus be a convenient means by which to influence the McArdle's disease phenotype. Ramipril, a well-established ACE inhibitor used to treat patients with cardiovascular disease, was shown to improve exercise performance and muscle strength in those with cardiopathy and in mildly hypertensive women.[18]

We tested in a double-blind, randomized, controlled trial the safety and efficacy of 12 weeks of low-dose ramipril treatment in 8 patients with McArdle's disease. Primary end-points were objective measures of exercise performance recorded during exercise testing and muscle metabolic parameters assessed by calf muscle 31-phosphorus magnetic resonance spectroscopy (^{31}P-MRS). Secondary end-points were subjective measures of disability and quality of life (QoL).

METHODS

The study design is schematized in Figure 1. All enrolled patients completed (T0) an incremental cycloergometer exercise test, a specially designed leg exercise protocol for ^{31}P-MRS, the Short Form 36 (SF-36),[27] and the World Health Organization–Disability Assessment Scale II (WHO-DAS II) interview.[29] The patients were then randomly assigned to daily treatment A (placebo) or B (2.5 mg ramipril) for 12 weeks. Every patient reported after 1 month for a scheduled visit that included a medical check-up and blood tests (complete blood count, blood glucose, creatinine, urea, uric acid, liver enzymes, sodium, chloride, potassium, and creatine kinase) to capture possible undesired effects such as cough, hypotension, and changes in blood count or kidney function. After 12 weeks of treatment, the patients repeated the assessments performed at T0 (T1). After a 4-week wash-out period, each patient was crossed over to the treatment opposite the one assigned between T0 and T1. The medical and laboratory studies were repeated 1 month after the beginning of the second treatment period, which lasted for 12 weeks. At the end of the second treatment period the tests performed at T0 and T1 were repeated (T2). The protocol was approved by our institutional ethical boards, and all patients gave their informed consent to participate.

Patients and Controls. Ten adults, 7 men and 3 women, with biochemically and molecularly proven McArdle's disease were assessed for eligibility between June 2004 and July 2005. Exclusion criteria were: hypertension; heart, kidney, or pulmonary disease; diabetes; use of any ACE inhibitor; ongoing long-term therapy with any drug; and pregnancy or lactation. One pregnant woman and one hypertensive man under treatment were excluded. All enrolled patients were asked not to modify their nutrition and exercise patterns during the period of the study. Demographic, clinical, and molecular details

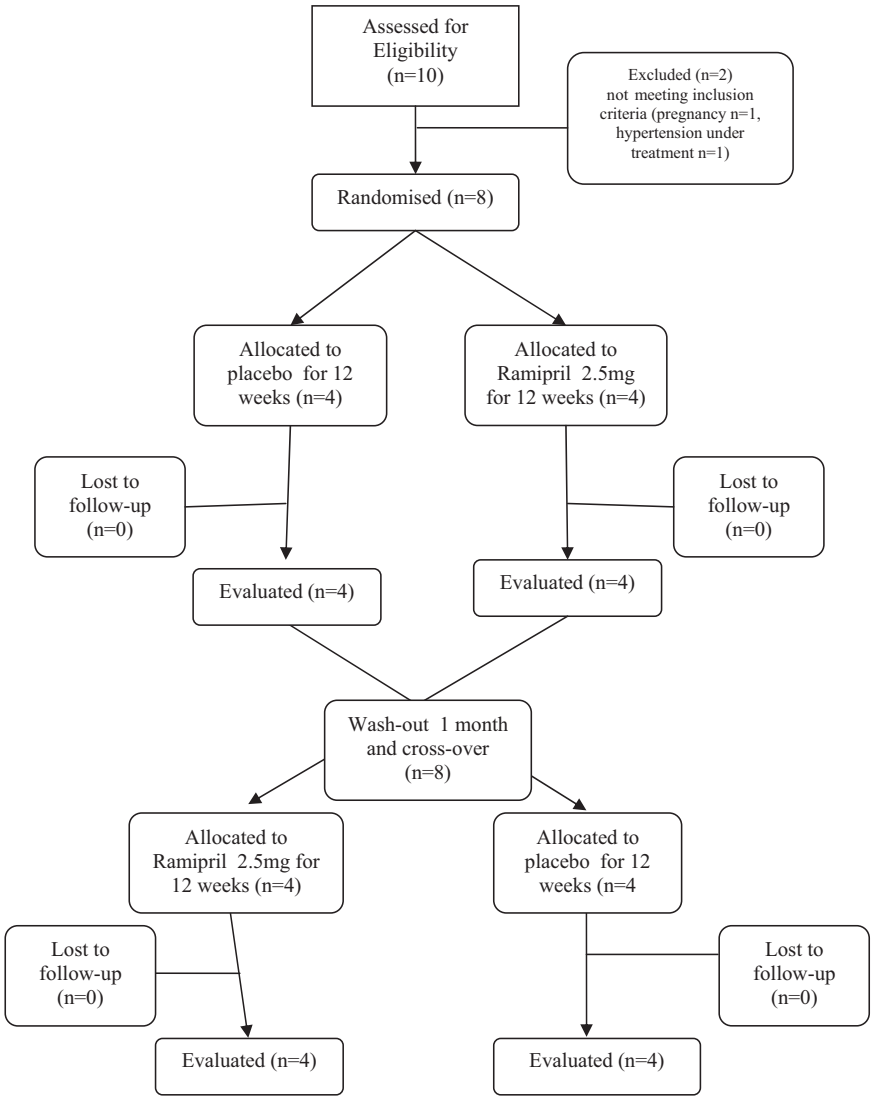

FIGURE 1. Flow chart of the study.

of participants are provided in Table 1. Mean age of the patients was 33 ± 10 years; the mean age of the control subjects was 33 ± 7 years (n = 12, 4 women and 8 men), all of whom underwent ^{31}P-MRS.

Interventions. Ramipril tablets (5 mg) and identical-looking placebo tablets were kindly donated by Aventis Pharma, and were provided to patients with the instruction to take one-half of a tablet every morning for 12 weeks.

Cycloergometer Exercise Testing. All patients entering the trial underwent an incremental exercise test on a cycloergometer (Seca Cardiotest 100; Vogel & Halke, Hamburg, Germany). All tests were completed by mid-afternoon, a minimum of 3 hours after a light, balanced meal. Patients were asked to maintain the pedaling rate (50–70/min) with a workload increase of 5 watts (W)/min until exhaustion. Heart rate, VO_2, VCO_2, VO_2/kg, and ventilation were recorded continuously with a portable telemetric system (Cosmed K4, Rome, Italy).

Skeletal Muscle MRS. ^{31}P-MRS investigations were performed with a 1.5-T scanner. As previously described,[13] subjects lay supine with a surface coil centered on the maximal circumference of the right calf muscle. Spectra were acquired at rest, during an aerobic incremental exercise of plantarflexion, and following recovery. Spectra were post-processed by a specially designed software procedure, and metabolite ratios/concentrations, including the apparent lactate production during exercise, were calculated.[2] The time con-

Table 1. Demographic, clinical, and genetic data of recruited patients.

Patient	Gender	Age	BMI	Clinical severity	*PYGM* mutations	ACE I/D genotype
1*	M	41	24.2	1	R429C/L397P	I/D
2*	M	32	25.4	2	R429C/L397P	D/D
3†	M	45	23.7	1	R50X/L397P	I/D
4†	F	44	31.2	2	R50X/L397P	D/D
5	M	41	26.7	2	R50X/V456M	D/D
6	F	19	28.8	1	R50X/R429C	I/D
7	M	34	26.2	1	V25/V25	I/D
8	M	19	21.5	1	R50X/?	I/D

*Clinical severity was graded as reported elsewhere.[9] BMI, body mass index. *and †identify sibling pairs.*

stant (TC) of phosphocreatine (PCr) recovery was established by mono-exponential fit, and reported as a function of the minimum cytosolic pH reached during recovery normalized to pH at 7.00.[13] Adenosine diphosphate (ADP) concentration was calculated from the creatine kinase equilibrium and the maximum rate of mitochondrial ATP synthesis (V_{max}) was calculated from the initial rate of PCr post-exercise re-synthesis (V) and the end-exercise [ADP] ([ADP]end): $V_{max} = V\{1 + (K_m / [ADP]end)\}$.[13]

QoL and Disability Measures. The SF-36 is a well-established tool to record perceived QoL in adults with various disabling conditions and has been translated and validated in Italian.[1] It provides a total score and scores in domains covering various aspects of life.

WHO-DAS II is a tool established and validated worldwide to record disability within the conceptual framework of the International Classification of Functioning, Health and Disability. The WHO-DAS provides a normalized score (% of normal national control) on activities in six major life areas (understanding and communication, getting around, self-care, getting along with people, life activities, participating in society) performed in the previous 30 days.[3,29]

Statistical Analysis. ^{31}P-MRS and exercise test data in McArdle's disease patients were compared with controls using Student's unpaired t-test. Wilcoxon's matched-pairs signed-rank test was used to compare placebo and ramipril results in McArdle's disease. Significance was set at $P > 0.05$.

RESULTS

Compliance and Safety. The study was closed in March 2006. All patients completed the study. There was only one report of mild, occasional cough, which did not prevent continuation of the treatment in the patient (subject 5) while on active treatment. We did not observe any change in hematological and biochemical screening tests and urine tests performed at 1 month of treatment to check for undesired effects. Blood pressure and heart rate were also stable.

Exercise Test. All patients performed at a significantly lower level compared with controls and to theoretical targets considering their age, gender, and body mass index. Maximal workload was 76.9 ± 7.9 W, 39 ± 14% of expected. Time to exhaustion was 11.2 ± 1.6 min. The incremental nature of the effort precluded the observation of a typical second-wind phenomenon. Maximal heart rate was 165 ± 14.3 bpm. Peak VO_2 was 19.6 ± 3.75 ml/min/kg. There was no significant difference in any exercise-test parameter between tests performed after treatment with placebo and after treatment with ramipril (Fig. 2a). Comparing the two ACE genotypes, DD patients showed an increase in peak VO_2 (from 15.8 ± 2.7 to 17.4 ± 3.5 ml/min/kg) after treatment with the active drug, which was not observed in patients with the I/D genotype (Fig. 2b). This change was, however, not paralleled by a concomitant increase in maximal workload or a significant change in heart rate (data not shown).

^{31}P-MRS. At baseline, patients with McArdle's disease showed typical skeletal muscle abnormalities (Table 2). At rest, cytosolic pH was increased, and a reduced muscle ATP concentration is the most likely cause of high PCr/adenosine triphosphate (PCr/ATP) and inorganic phosphate (Pi)/ATP (Pi/ATP), given the reduced ATP/(PCr + Pi) and normal PCr/Pi ratio. Exercise duration was reduced in McArdle's disease and, during exercise, cytosolic pH rose steadily to above normal due to the lack of lactate production; in fact, the apparent lactate concentration at the end of exercise was not significantly different from zero (Table 2). Because of the pH rise, ADP concentration at the end of exercise was increased in McArdle's disease despite the similar relative PCr consumption. Post-exercise recovery showed profound impairment of the indices of mitochondrial ATP production rate such as TC of PCr and V_{max}. There were no significant differences in any of the ^{31}P-MRS measurements between treatment with active drug or placebo (Table 2), or between I/D and D/D patients at baseline and when placebo and drug treatment effects were evaluated in I/D and D/D patients.

Disability and QoL Measures. Figure 3a shows the QoL profile reported by patients and normal con-

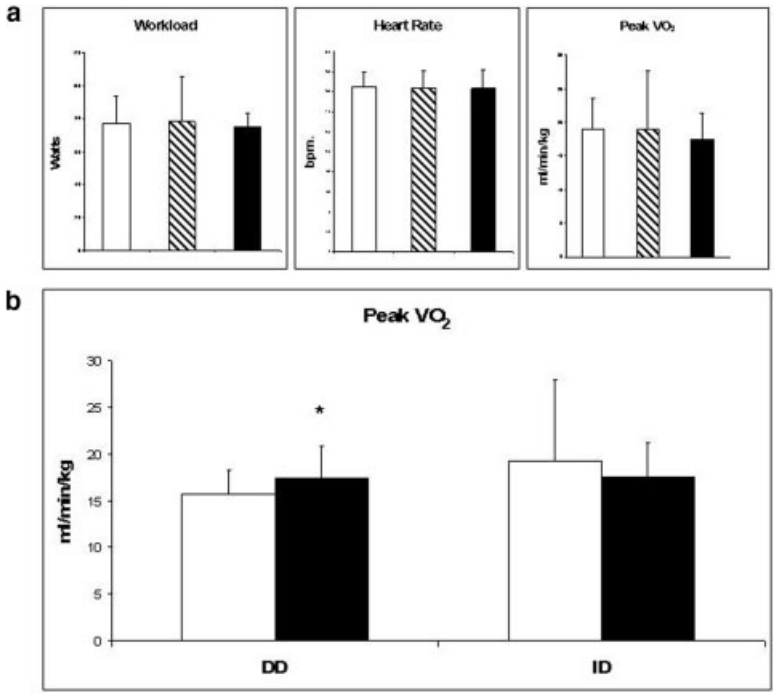

FIGURE 2. Exercise parameters in patients with McArdle's disease who were treated with ramipril or placebo. **(a)** Maximal workload (watts), maximal heart rate (beats per minute, bpm), and peak VO_2 (ml/min/kg). White columns: baseline; hatched columns: placebo; black columns: ramipril. **(b)** Peak VO_2 in ACE D/D or I/D patients treated with ramipril (black columns) or placebo (white columns). $^*P < 0.05$.

trols. In most domains, patients with McArdle's disease showed lower scores, although the differences were significant only for the domains of physical activity ($P < 0.02$), pain ($P < 0.03$), general health ($P < 0.05$), and vitality ($P < 0.05$). There was improvement ($P < 0.05$) in the emotional status and social role domains compared with baseline in both treatments (58.3 ± 49.6 at T0 compared to 74.9 ± 34.5 with placebo, and 87.5 ± 24.8 with ramipril), but there was no difference between placebo and ramipril. None of the other domains showed any significant difference between the two treatments (Fig. 3b). There were no differences in QoL between D/D and I/D patients.

The WHO-DAS II score in our patients was significantly lower ($P < 0.02$) than in controls, with a normalized score of 83.8 ± 10.3. The scores reporting disability were mostly concentrated in the "getting around" and "life activities" domains.

Comparing the treatment arms, there was a significant difference in favor of ramipril (normalized score after placebo was 79.9 ± 15.5, and after ramipril was 89.2 ± 10.5, $P < 0.05$) (Fig. 4). The increase was more pronounced in the ACE D/D subgroup, but was not statistically significant, and it was absent in the ACE I/D group (Fig. 4).

DISCUSSION

Long-term treatment with low-dose ramipril in adult patients with McArdle's disease is safe and well tolerated. We failed to show any treatment effect in the objective measures of exercise performance and muscle metabolism chosen as primary end-points, but we did find a significant change in disability score with ramipril treatment.

The present study confirms that exercise testing and ^{31}P-MRS are excellent tools to characterize the functional metabolic profile of patients with McArdle's disease, detecting a number of severe abnormalities secondary to impaired glycolytic and oxidative ATP production. Although the objective measures selected as primary end-points were specific for McArdle's disease, none showed significant changes with ramipril. The slight improvement of peak VO_2 after ramipril treatment in DD patients in the absence of a concomitant change in maximal workload is difficult to explain, and its significance, considering the small number of subjects ($n = 3$), is questionable. However, it should be noted that, for patients performing at such a low level of efficiency, even small increases in VO_2 (10%) may translate into significant functional improvements.

Table 2. Summary of ^{31}P-MRS results.

Variable	Controls	McArdle's (T0)	McArdle's (placebo)	McArdle's (ramipril)	*t*-test: Controls vs. patients at T0: *P*-value (unpaired)	*t*-test: Placebo vs ramipril: *P*-value (paired)
Age (years)	33 (7)	33 (10)	34 (10)	34 (10)	0.86	
Rest						
pH	7.03 (0.02)	7.07 (0.03)	7.06 (0.01)	7.05 (0.03)	0.0004	0.46
PCr/ATP	3.79 (0.28)	4.43 (0.66)	4.20 (0.58)	4.24 (0.40)	0.0078	0.82
Pi/ATP	0.52 (0.07)	0.65 (0.14)	0.69 (0.13)	0.72 (0.19)	0.0108	0.64
PCr/Pi	7.39 (0.92)	6.87 (0.84)	6.19 (0.95)	6.32 (1.93)	0.22	0.74
ATP/PCr + Pi	0.23 (0.02)	0.20 (0.04)	0.21 (0.03)	0.20 (0.02)	0.018	0.66
First minute of exercise						
pH	7.11 (0.02)	7.16 (0.05)	7.15 (0.06)	7.12 (0.05)	0.0057	0.48
PCr/(PCr + Pi)	0.71 (0.07)	0.76 (0.04)	0.77 (0.11)	0.72 (0.04)	0.09	0.32
[ADP] μM	44 (11)	51 (37)	43 (14)	55 (54)	0.55	0.52
End-exercise						
end pH	6.88 (0.09)	7.24 (0.05)	7.25 (0.07)	7.23 (0.05)	<0.00001	0.66
exercise duration (min)	5.4 (1.2)	3.0 (0.8)	3.0 (0.8)	3.0 (0.8)	0.00015	0.45
PCr/(PCr + Pi)	0.25 (0.08)	0.30 (0.05)	0.30 (0.07)	0.32 (0.09)	0.17	0.64
[ADP] μM	129 (6)	207 (7)	217 (122)	191 (102)	0.017	0.68
End-exercise apparent [lactate] (mM)	6.37 (2.90)	−0.38 (0.85)	−0.46 (1.13)	0.73 (1.16)	0.00001	0.72
PCr (% of rest)	35 (11)	37 (7)	39 (9)	41 (10)	0.77	0.74
Recovery						
V_{max} (mM/min)	48 (7)	23 (5)	21 (4)	18 (3)	<0.00001	0.09
TC PCr (s)	36 (9)	73 (9)	72 (13)	80 (16)	<0.00001	0.26
pH_{min}	6.68 (0.13)	7.06 (0.02)	7.07 (0.02)	7.07 (0.02)	<0.00001	0.86
TC PCr normalized (s)	21 (6)	76 (9)	75 (13)	83 (16)	<0.00001	0.26

Data presented as mean (SD).

The SF-36 showed significant improvement in the domain of emotional status–role in both treatment arms, but no difference in any domain when comparing placebo vs. active treatment. The observed improvement in emotional perception may be a measure of the placebo effect. The WHO-DAS II profile of patients was significantly lower than that of the normative population, and showed a significant improvement after treatment with ramipril compared with placebo, the difference being mainly driven by scores in domains 2 (moving around) and 5 (life activities).

The observed improvement in disability scores after ramipril treatment is relevant, because it reflects actual changes in activities that were not performed or performed with difficulty without treatment (e.g., walking for long distance or climbing a flight of stairs, getting work done), and were done more easily during ramipril treatment. The discrepancy observed between the results of the WHO-DAS II and the SF-36 may be explained by considering the nature of these tools: the former reports limitations in activities or restrictions in participation in life areas, whereas the latter asks the patient to report his or her perception of the problems. Subjective perceptions may show a slower dynamic of change, which may require longer treatment periods.

Physiological parameters measured during exercise testing and MRS have been used as outcome measures in most studies exploring treatments for patients with McArdle's disease,[4] but a search for a correlation between these objective indicators and actual burden of disease has never been attempted.

We checked whether patients with a different ACE genotype responded differently to treatment. In spite of the very small number of subjects, which limits statistical analysis, the results of peak VO_2 and the WHO-DAS II may suggest a better treatment response in patients with the D/D genotype compared with those with the I/D genotype, but this trend will need to be confirmed with a larger cohort of subjects. The rationale of the trial postulated that in patients with the D/D genotype, in whom one may expect a more severe phenotype, a slightly higher ACE activity associated with this genotype may benefit from pharmacological inhibition. However, a comparison of the physiological and MRS profile among our patients did not confirm such a difference, which was instead reflected in the WHO-DAS II score.

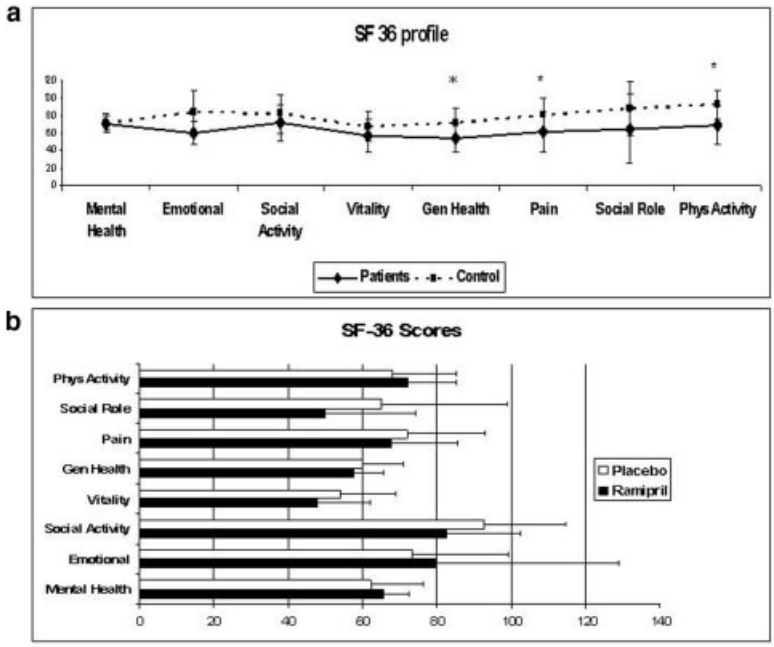

FIGURE 3. SF-36 scores. **(a)** SF-36 profile of patients at T0 compared with normal age- and gender-matched Italian controls (±SD). *$P <$ 0.05. **(b)** Scores (±SD) of SF-36 domains in patients after ramipril or placebo treatment.

The original observation of association between the ACE genotype and clinical severity[16] was based on clinical grading, which in this work may be operationalized by the disability score, and not on exercise testing. However, most of the patients were mildly affected, having a clinical severity score of 1 (5 subjects) or 2 (3 subjects). The absence of more severely affected patients may have produced a ceiling effect on the parameters of exercise testing. Another possibility is that the observed correlation has different strength levels in various patient groups. Recent work has shown a significant gender effect on severity of McArdle's disease severity in a large group of patients from Spain.[23]

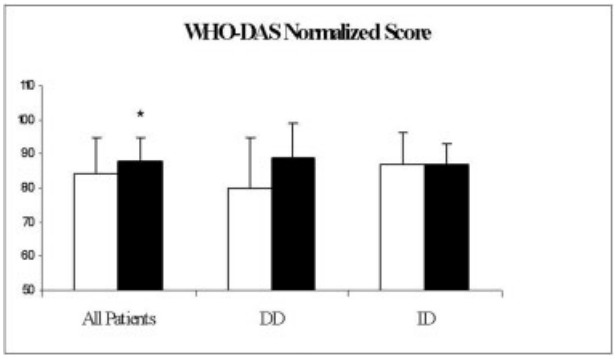

FIGURE 4. WHO-DAS II–normalized scores of patients with McArdle's disease. Results are shown as ± SD for the whole group of patients and separately according to ACE genotype. White columns: placebo; black columns: ramipril. *$P < 0.05$.

Treatment strategies in patients with McArdle's disease can target programmed exercise, such as with sucrose ingestion,[26] or focus on a more general and long-lasting improved exercise tolerance. A program of moderate aerobic training was shown to improve exercise capacity and tolerance through an increase in oxidative capacity.[11,14,17] Although such an approach is both safe and efficacious, its general application needs long-term commitment. All patients with McArdle's disease should be advised to engage in regular monitored exercise, but it may be of interest to explore whether an ACE inhibitor such as ramipril offers additional benefit.

In conclusion, our study has failed to demonstrate a significant effect of long-term treatment with 2.5 mg ramipril on objective functional outcomes measures in patients with McArdle's disease. A subjective appreciation of diminished disability was reported by the ramipril-treated patients. Given the tolerability shown by patients to much higher ramipril dosages (10–15 mg) in a recently published study,[24] higher doses may need to be tested also in McArdle's disease. Finally, the possibility of a differential haplotype-linked sensibility to the treatment is suggested by the separate analysis of I/D and D/D patients. Our results, albeit on a small number of patients, may encourage imple-

mentation of a larger trial on patients with McArdle's disease.

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REFERENCES

1. Apolone G, Mosconi P. The Italian SF-36 survey: translation, validation and norming. J Clin Epidemiol 1998;51:1025–1036.
2. Bendahan D, Kemp G, Roussel M, Fur YL, Cozzone PJ. ATP synthesis and proton handling in short periods of exercise and subsequent recovery. J Appl Physiol 2003;94:2391–2397.
3. Chwastiack LA, Von Korff M. Disability in depression and back pain evaluation of the World Health Organization Disability Assessment Schedule (WHO DAS II) in a primary care setting. J Clin Epidemiol 2003;56:507–524.
4. Day SH, Gohlke P, Dhamrait SS, Williams AG. No correlation between circulating ACE activity and VO_2max or mechanical efficiency in women. Eur J Appl Physiol 2007;99:11–18.
5. Dietze GJ, Wicklmayr M, Rett K, Jacob S, Henriksen EJ. Potential role of bradykinin in forearm muscle metabolism in humans. Diabetes 1996;45(suppl):S110–S114.
6. Di Mauro S, Tsujino S. Non-lysosomal glycogenoses. In: Engel AG, Franzini-Armstrong C (eds): Myology, 2nd edition. New York: McGraw-Hill; 1994, p 1554–1576.
7. Dragovich T, Minhall R, Jackman HL, Wang LX, Erdos EG. Kininase II-type enzymes. Their putative role in muscle energy metabolism. Diabetes 1996;1(suppl):S34–S37.
8. Frossard M, Joukhadar C, Steffen G, Schmid R, Eichler HG, Muller M. Paracrine effects of angiotensin-converting-enzyme and angiotensin-II-receptor inhibition on transcapillary glucose transport in humans. Life Sci 2000;66:PL147–PL154.
9. Gomez-Gallego F, Santiago C, Moran M, Perez M, Matè-Muñoz JL, Fernandez del Valle M, et al. The I allele of the ACE gene is associated with improved exercise capacity in women with McArdle disease. Br J Sports Med, July 6, 2007 [Epub ahead of print].
10. Gordon S, Davis BS, Carlson CJ, Booth FW. Ang II is required for optimal overload-induced skeletal muscle hypertrophy. Am J Physiol 2001;280:E150–E159.
11. Haller RG, Wyrick P, Taivassalo T, Vissing J. Aerobic conditioning: an effective therapy in McArdle's disease. Ann Neurol 2006;59:922–928.
12. Jones A, Woods DR. Skeletal muscle RAS and exercise performance. Int J Biochem Cell Biol 2003;35:855–866.
13. Lodi R, Tonon C, Valentino ML, Iotti S, Clementi V, Malucelli E, et al. Deficit of in vivo mitochondrial ATP production in OPA1-related dominant optic atrophy due to the common c.2708–2711delTTAG deletion. Ann Neurol 2004;56:719–723.
14. Lucia A, Matè-Muñoz JL, Pérez M, Foster C, Gutierrez-Rivas E, Arenas J. Double trouble (McArdle's disease and myasthenia gravis): how can exercise help? Muscle Nerve 2007;35:125–128.
15. Martin MA, Rubio JC, Buchbinder J, Fernandez-Hojas R, del Hoyo P, Teijeira S, et al. Molecular heterogeneity of myophosphorylase deficiency (McArdle's disease): a genotype–phenotype correlation study. Ann Neurol 2001;50:574–581.
16. Martinuzzi A, Sartori E, Fanin M, Nascimbeni A, Valente L, Angelini C, et al. Phenotype modulators in myophosphorylase deficiency. Ann Neurol 2003;53:497–502.
17. Mat`-Muñoz JL, Moran M, Pérez M, Chamorro-Viña C, Gomez-Gallego F, Santiago C, et al. Favorable responses to acute and chronic exercise in McArdle's patients. Clin J Sports Med 2007;17:297–303.
18. Onder G, Penninx BWJH, Balkrishnan R, Fried LP, Chaves PH, Williamson J, et al. Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. Lancet 2002;359:926–930.
19. Paradas C, Fernandez-Cadenas I, Gallardo E, Lligè D, Arenas J, Illa I, et al. Variable presentation of the clinical phenotype of McArdle's disease in a kindred harbouring a novel compound genotype in the muscle glycogen phosphorylase gene. Neurosci Lett 2005;391:28–31.
20. Prasad A, Narayanan S, Husain S, Padder F, Waclawiw M, Epstein N, et al. Insertion–deletion polymorphism of the ACE gene modulates reversibility of endothelial dysfunction with ACE inhibition. Circulation 2000;102:35–41.
21. Predel HG, Rohden C, Heine O, Prinz U, Rost RE. ACE inhibition and physical exercise: studies on physical work capacity, energy metabolism, and maximal oxygen uptake in well trained, healthy subjects. J Cardiovasc Pharmacol 1994; 23(suppl):S25–S28.
22. Quinlivan R, Beynon RJ. Pharmacological and nutritional treatment for McArdle's disease (glycogen storage type V). Cochrane Systematic Rev 2006;CD003458.
23. Rubio JC, Gomez-Gallego F, Santiago C, Garcia-Consuegra I, Perz M, Bariopedro MI, et al. Genotype modulators of clinical severity in McArdle disease. Neurosci Lett 2007;422:217–222.
24. The DREAM Trial Investigators. Effect of Ramipril on the incidence of diabetes. N Engl J Med 2006;355:1–12.
25. Vescovo G, Dalla Libera L, Serafini F, Leprotti C, Facchin L, Volterrani M, et al. Improved exercise tolerance after losartan and enalapril in heart failure: correlation with changes in skeletal muscle myosin heavy chain composition. Circulation 1998;98:1742–1749.
26. Vissing J, Haller RG. The effect of oral sucrose on exercise tolerance in patients with McArdle's disease. N Engl J Med 2003;349:2503–2509.
27. Ware JE, Sherbourne CD. The MOS 36-item short form health survey (SF-36): I. Conceptual framework and item selection. Med Care 1992;30:473–483.
28. Weakers L, Bouhanick B, Hadjadj S, Gallois Y, Roussel R, Pean F, et al. Modulation of the renal response to ACE inhibition by ACE insertion/deletion polymorphism during hyperglycemia in normotensive, normoalbuminuric type 1 diabetic patients. Diabetes 2005;54:2961–2967.
29. WHO Mental Health Bulletin. A newsletter on noncommunicable diseases and mental health. WHO Mental Health Bulletin 2000;78:6–30.
30. Williams AG, Rayson MP, Jubb M, World M, Woods DR, et al. The ACE gene and muscle performance. Nature 2000;403:614.
31. Woods D, Onambele G, Woledge R, Skelton D, Bruce S, Humphries S, et al. Angiotensin-I converting enzyme genotype-dependent benefit from hormone replacement therapy in isometric muscle strength and bone mineral density. J Clin Endocrinol Metab 2001;86:2200–2204.