

Long-term use of carnitine in methylmalonic aciduria, propionic aciduria and isovaleric aciduria in Italy: a qualitative survey

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Abstract. – OBJECTIVE: Organic acidurias (OAs) are a group of rare metabolic disorders that disrupt the regular amino acid metabolism. OAs are characterized by recurrent episodes of acidemia, ketonuria and hyperammonemia which can result in brain/liver damage and renal failure, and despite the life-long protein-restricted diet, impaired growth and long-term complications can occur. Consequently, a long-term management of OAs patients is required, aimed principally at reducing the frequency and duration of metabolic decompensation/hyperammonemia episodes. Nevertheless, unlike the acute phase, evidence on the chronic management of OAs patients is less consolidated.

SUBJECTS AND METHODS: To expand the knowledge on this field, 13 Italian referral centers for the management of OAs were involved in a survey focused on the long-term use of carnitine (Carbaglu®, Recordati Rare Diseases).

RESULTS: Participating centers reported a reduction between 69% and 81% in the annual

number of metabolic decompensations with the chronic use of carnitine and an improvement in protein intake. Most centers reported no difficulty using carnitine as a long-term therapy, along with a great compliance.

CONCLUSIONS: Taken together, obtained data align with the available literature and support a positive clinical experience with the long-term carnitine administration. Additional studies aimed at better defining a proper dosage for the chronic administration of carnitine and the clinical and biochemical characteristics of patients treated chronically are needed. In addition, the potential impact of this treatment regimen on the neurological development and growth of patients should be elucidated.

Key Words:

Organic acidurias, Propionic acidemia, Methylmalonic acidemia, Isovaleric acidemia, Hyperammonemia, Carnitine.

Introduction

Organic acidurias (OAs) are a group of rare autosomal recessive inherited metabolic disorders (IMD) that disrupt the regular amino acid metabolism, particularly branched-chain amino acids, causing an abnormal build-up of acids. More than 65 organic acidurias have been described¹. Among them, methylmalonic aciduria (MMA), propionic aciduria (PA), maple syrup urine disease and isovaleric aciduria (IVA) are generally referred to as classical OAs^{2,3}.

OA incidence varies, according to the disease type, from 1 out of 10,000 to >1 out of 1000,000 live births². However, different sample sizes of the populations screened over different time periods and differences in case definitions make it difficult to ultimately define the actual incidence of OAs⁴⁻⁸. Newborn screening for OAs has been performed in Italy since 2016 (law n. 167/2016 on diagnostic tests for the prevention and treatment of hereditary metabolic diseases), showing an approximate incidence of 1/10,000 live births for OAs in the Italian population⁹.

In their classical form, OAs appear in the first days of life. However, late-onset forms are known, in which the disease can present at any age. OAs are usually characterized by recurrent episodes of acidemia, ketonuria and hyperammonemia, leading to coma and even death if not promptly treated^{1,10-12}.

A diet with protein restriction and high calories, carnitine and emergency treatment modalities represent life-saving therapies during (and beyond) acute decompensation episodes³. Ammonia-scavenger drugs, such as sodium benzoate, sodium phenylbutyrate, carglumic acid, arginine hydrochloride and recently glycerol phenylbutyrate, are also often used to manage acute hyperammonemia episodes^{5,10}. In patients with PA or MMA in whom the disease is difficult to manage with diet and pharmacological therapy and who experience repeated metabolic decompensation, liver transplantation (LT) can reduce the number of hospitalizations and improve the quality of life¹. Combined liver-kidney (LT/KT) and kidney transplantation in MMA have been performed in several patients to improve the disease outcome¹⁰. However, transplantation is still limited and although LT or LT/KT was associated with a reduction in the incidence of hyperammonemia and pancreatitis in most patients, the absence of significant reduction in other biochemical param-

eters, including C3, denotes that transplantation does not result in metabolic cure in individuals with PA and MMA.

Repeated and frequent episodes of metabolic decompensations (with or without hyperammonemia) can result in brain/liver damage and renal failure, and severity increases with a longer duration of hyperammonemia^{10,13}. Additionally, despite the life-long protein-restricted diet, impaired growth and long-term complications can still occur¹⁴.

Consequently, the approach to OAs patients should not be limited to treating acute symptoms, but long-term management is required, aimed principally at reducing the frequency and duration of metabolic decompensation/hyperammonemia episodes. Evidence on the chronic management of OA patients is increasing^{3,13,15-17}.

Chronic use can be defined as the use beyond the acute episode and for a period of >6 months. Among the few drugs approved for the treatment of OAs, carglumic acid represents a promising option for the long-term management of these conditions. Indeed, besides its consolidated effectiveness and favorable toxicity profile in the management of acute hyperammonemia episodes¹⁸⁻²¹, carglumic acid may also be helpful beyond metabolic decompensation by decreasing the number of hyperammonemia decompensations, favoring dietary protein intake and consequently promoting the patient's quality of life³.

The project entitled "*The long-term management of organic acidurias: comparing experiences*" was conducted among a group of Italian experts in the management of OAs to qualitatively assess the Italian experience with the long-term use of carglumic acid (Carbaglu[®], Recordati Rare Diseases; hereafter termed as carglumic acid). This paper presents the results of this project, with the aim to address some practical aspects of chronic OA management with carglumic acid that could be useful to improve clinical practice.

Subjects and Methods

Thirteen Italian referral centers for the management of OAs (90% of the total) were involved in the project; a long-term experience in the use of carglumic acid (>4 years) was considered as inclusion criterium. Referral centers were located throughout the national territory (Turin, Milan, Monza, Trento, Verona, Padua, Piacenza,

Bologna, Florence, Bari, Naples, Catania). All involved centers treat both pediatric and adult patients.

The project intended to qualitatively collect and describe the experiences of the participating centers with the long-term use of carglumic acid (Carbaglu®, Recordati Rare Diseases).

Italian experts first met in December 2020 at an online meeting to define the structure of a survey helpful in collecting information about OA patient management and about the chronic use of carglumic acid. The online survey was sent in February 2021 to all participants, and subsequently, the data were processed. A second advisory board was held on April 2021 to present and discuss the survey results.

Survey Structure

The survey consisted of 26 sections, divided into the following thematic areas: general information regarding the participant centers (four questions); OA patients' features (nine questions); information on the therapeutic approaches (three questions), use of carglumic acid (ten questions; see supplementary materials for the full-text survey). One response per center was considered. Within the survey, MMA, PA and IVA OAs were intended as the disorders suitable for the treatment with carglumic acid and related to a methylmalonyl-coenzyme A (CoA) mutase, propionyl-CoA carboxylase and Isovaleryl-CoA dehydrogenase deficiency, respectively. These forms are collectively referred to as OAs in the following sections. Decompensation episodes were intended as severe episodes of hyperammonaemia requiring hospitalization or emergency home therapy.

Statistical Analysis

Descriptive statistics were used to analyze the data collected from the survey. The results were presented as a percentage of answers on the total number of participating centers. All the ranges of patients were calculated considering the minimum and the maximum number of patients for each group. For the multiple answers questions in which a maximum number of patients was not foreseen, a plausible maximum was chosen from time to time.

Results

In total, 13 centers (100% of invited centers) of expertise in the management of OAs participated in the survey. Most of the centers (n=9, 70%) had

physicians with more than 10 years of experience treating OAs. Based on the collected data, it can be estimated that the responders globally perform 54-91 OAs evaluations each year.

Italian Patients with OAs

Italian patients with OAs were uniformly distributed into the four considered age groups: 0-5 years (26%), 6-10 years (22%), 11-16 years (17%) and >16 years (35%).

From the survey results, it can be estimated that the total number of patients with OAs at the referral centers was between 116 and 186. MMA resulted more widespread than PA and IVA (Figure 1). Furthermore, MMA patients were estimated between 71 and 130 (55% of the total), followed by patients with PA (31-80 patients, 26%) and IVA (21-64 patients, 19%).

In 12 centers (92%), more than 80% of patients received genetic confirmation of the diagnosis. More than 80% of patients received genetic confirmation of the diagnosis after newborn screening in six centers. In three centers (23%), no patients were diagnosed because of positive neonatal screening.

Regardless of the patients' age and the type of OAs, the overall mortality rate was estimated by responders as <10% in 84% of cases, 11-50% in 16% of cases; only one center reported a mortality rate >50%. Mortality rate by type of OA, strat-

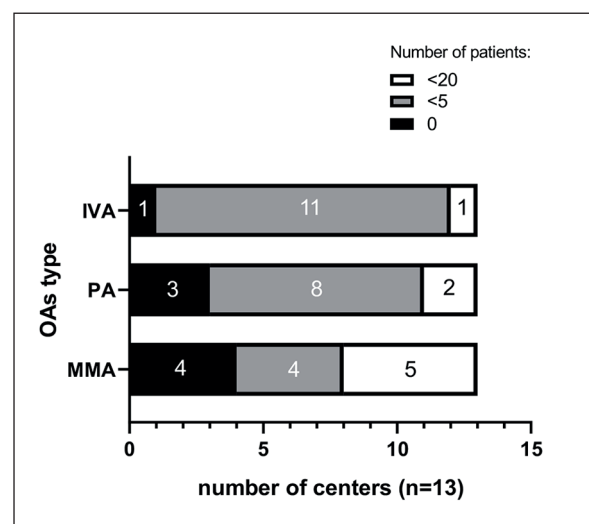


Figure 1. Number of patients in care at the 13 referral centers, stratified by the organic aciduria type. For each OA (y-axis), the number of centers following a specific number of patients (i.e., <20 or <5 or 0) is shown (x-axis). IVA: Isovaleric aciduria; MMA: Methylmalonic aciduria; OA: Organic aciduria; PA: Propionic aciduria.

ified by age groups, is reported in Table I. The reported mortality rate in patients with IVA was lower than in MMA and PA patients (Table I).

Therapeutic Approach

In six centers (46%), none of the treated patients underwent a transplant (liver, kidney, or both). In the remaining centers, the number of transplant patients was <5.

The most common dietary treatment was the reduction of natural proteins together with the adjunction of synthetic amino acids (77% of the centers, n=10), followed by the sole reduction of natural proteins (23% of the centers, n=3).

With respect to the pharmacological treatment, carnitine was the most commonly used drug (70% of treatments), followed by carglumic acid (20%), sodium benzoate (10%) and metronidazole (10%). Vitamin B12, biotin and glycine were the most reported treatments for MMA, PA and IVA OAs, respectively.

Carglumic Acid Therapy

All the participating centers reported using carglumic acid to treat MMA and PA OAs in all the considered age groups. The age groups with the highest use of carglumic acid were 0-5 years (39% of patients in a total of five centers) and >16 years (31% of patients in four centers, as regards the PA). No patients with IVA OAs were treated with carglumic acid in any participant centers.

In almost all centers (12 out of 13), carglumic acid was used for the acute treatment in >50% of the patients. One center reported not to have experience with the use of carglumic acid in the acute phase (Figure 2).

The 54% (n=7) of centers used carglumic acid as a chronic treatment in 10-50% of patients with MMA or PA. In 2 (15%) centers, carglumic acid was used for the chronic treatment in >50% of the patients. Two (15%) centers reported not having experience with the chronic use of carglumic acid (Figure 2).

In the chronic treatment, all participating centers used a dosage of carglumic acid between 50 and 100 mg/kg/day. The most used dosage was 50 mg/kg/day, prescribed by 66% of centers (n=8). A dosage between 50 and 100 mg/kg/day was used by three centers (25%). Most physicians (77%, n=10) indicated the change in ammonium levels as the main reason for dose adjustment over time in chronic carglumic acid therapy. Other reported reasons were glutamine levels variation (70%, n=9) and increased protein intake (54%, n=7).

Before using carglumic acid, the annual global number of decompensation episodes was between 1 and 5 in 70% of the centers (n=9) and between 6 and 10 in 15% of the centers.

After carglumic acid initiation, the number of annual decompensation episodes dropped to zero for most centers (70%, n=9) and was between 1 and 5 for the remainders (30%, n=4; Figure 3).

Table I. Mortality rate by type of OA, stratified by age groups.

OA type	Mortality rate			
	0%	1-10%	11-30%	31-50%
Age group: 0-5 years				
MMA; n (%)	1 (7)	8 (61)	2 (15)	2 (15)
PA; n (%)	1 (7)	8 (61)	2 (15)	2 (15)
IVA; n (%)	9 (70)	3 (23)	–	1 (7)
Age group: 6-10 years				
MMA; n (%)	2 (15)	10 (77)	1 (7)	–
PA; n (%)	3 (23)	9 (70)	1 (7)	–
IVA; n (%)	3 (23)	9 (70)	1 (7)	–
Age group: 11-16 years				
MMA; n (%)	3 (23)	6 (46)	4 (31)	–
PA; n (%)	3 (23)	9 (70)	1 (7)	–
IVA; n (%)	12 (92)	1 (7)	–	–
Age group: >16 years				
MMA; n (%)	3 (23)	7 (54)	1 (7)	2 (15)
PA; n (%)	4 (31)	4 (31)	2 (15)	3 (23)
IVA; n (%)	12 (92)	1 (7)	–	–

IVA: Isovaleric aciduria; MMA: Methylmalonic aciduria; OA: Organic aciduria; PA: Propionic aciduria.

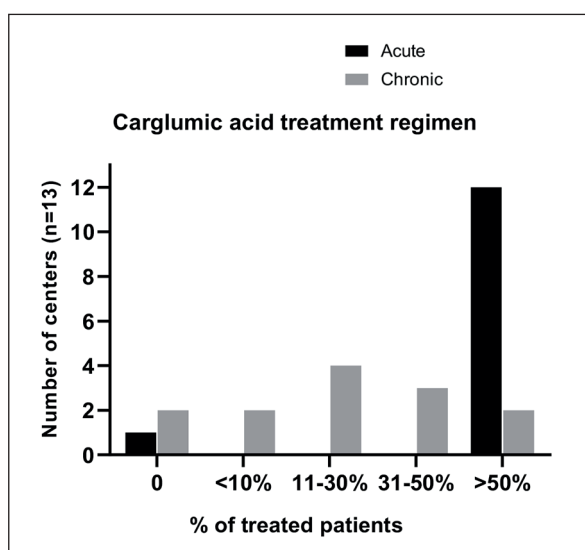


Figure 2. Percentage of patients for acute and chronic carglumic acid treatment among the 13 participating centers.

Most centers (70%, n=9) did not report difficulties during long-term treatment with carglumic acid. The obstacles reported by the other centers were related to the need for multiple daily, high-dose administrations and the taste of the drug.

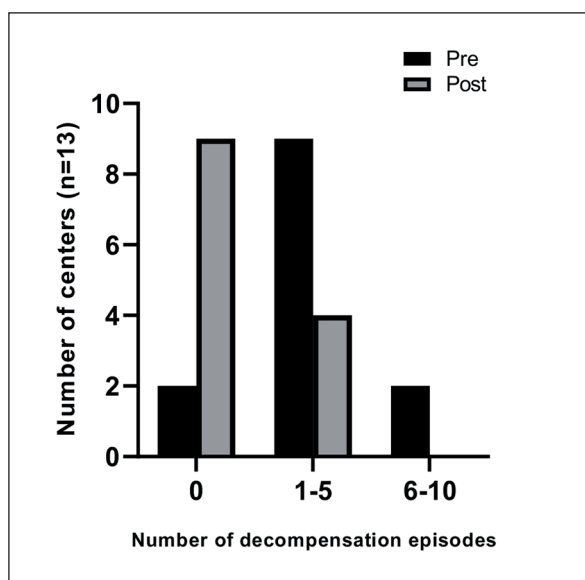


Figure 3. Number of decompensation episodes/year before (pre-) and after (post-) carglumic acid use. For each center the cumulative amount of decompensation episodes/year is shown.

Discussion

A group of Italian experts in managing patients with OAs met and discussed the current OAs management. The characteristics of the Italian patients with OAs and the main treatment modalities were qualitatively described through a survey, which focused on the long-term use of carglumic acid.

According to the estimated incidence, about 320 patients with OAs are expected in Italy. The survey showed that between 116-186 OA patients were followed-up. This discrepancy may be partially explained by missing or wrong diagnosis at any age; another issue could be related to patients with an unexplained death, especially in neonatal age. It has also had to be considered that the newborn screening is a recent tool not uniformly carried out in the different Italian regions consequently, there could be potentially affected patients (i.e., late-onset forms) who have not been diagnosed.

Patients with MMA resulted the most numerous, followed by patients with PA and IVA. Regardless of age and type of OA, the mortality rate was <10% in the majority of the referral centers, in agreement with literature data²². For instance, data relating to children who died in the first days of life due to particularly severe forms of OA were not included. Therefore, the mortality rate may show a bias related to the absence of this type of patient.

Since 2016, newborn screening for OAs has been mandatory in all regions of Italy. Before this year, there were only a few pilot projects in some regions (Toscana, Veneto). Of note, in about half of the participating referral centers, more than 80% of patients aged between 0 and 5 years received genetic confirmation of the diagnosis through newborn screening.

The survey results made it possible to estimate that 70% of the OAs treatments are based on carnitine. Reducing natural proteins with the adjunction of synthetic amino acids was the most suggested dietary regimen, according to the most recent guidelines¹⁰.

Almost all centers reported using carglumic acid in the acute phase of the disease, and 54% of centers used carglumic acid as a chronic treatment in up to 50% of patients. Participating centers reported a reduction between 69% and 81% in the annual number of metabolic decompensations with the chronic use of carglumic acid and an improvement in protein intake due to the

reduction of decompensation episodes. Most centers reported no difficulty using carglumic acid as a long-term therapy, reporting great compliance and a good tolerability profile. Most referral centers obtained satisfactory clinical results with a chronic dose between 50 and 100 mg/kg/day, and, in any case, a dose lower than 250 mg/kg/day is always used. The main reported reason for the change in dosage of chronic carglumic acid therapy was the change in ammonia levels (77%), followed by changes in glutamine levels (70%) and the increase in protein intake (54%).

Limitations

This study presents some limitations. First, the survey is not a scientific tool to assess treatment data and, in particular, the survey structure used in this project allowed only a qualitative description of results. The results were mainly based on a numerical estimate, and, consequently, there is a limited possibility of a formal statistical analysis. In addition, the use of different dosages of carglumic acid in the different referral centers could represent a limitation in the interpretation of the results, along with the lack of biomarkers data, useful for monitoring the therapy. Nevertheless, in the context of this project, the qualitative survey was a useful tool to collect data about clinicians' practice and obtained results align with the literature, suggesting a positive clinical experience with the long-term carglumic acid administration. Available evidence in this topic is related to one prospective randomized trial, retrospective studies^{3,13} and two case reports¹⁵⁻¹⁷. Burlina et al¹³ reported eight patients with PA and MMA treated with carglumic acid for 7-16 months with a 50 mg/kg/day dosage with favorable effect¹³. The authors also found a decrease in hyperammonemia episodes, the peak of ammonia levels and, therefore, hospitalization rate. In addition, an improvement in protein tolerance was reported. Tummolo et al¹⁵ reported a decreased number of hyperammonemia episodes in a PA patient due to carglumic acid treatment, performed initially at 100 mg/kg and after 6 months at 50 mg/kg¹⁵. Kiykim et al³ reported a clinical improvement in all the 21 observed PA and MMA patients treated with long-term carglumic acid, with a significant decrease in plasma ammonia levels and a reduction of hyperammonemia episodes at the end of the observation period. The mean carglumic acid dosage was 85 mg/kg/day. In a recent multicenter, randomized clinical trial¹⁶ on 38 PA and MMA patients, the long-term treat-

ment with carglumic acid at 50 mg/kg/day, in addition to standard therapies, significantly reduced the number of emergency room accesses caused by hyperammonemia. Kido et al¹⁷ reported a case of severe PA where long-term treatment with carglumic acid (50 mg/kg/day), in combination with carnitine supplementation and protein restriction, prevented metabolic decompensation and resulted in improved quality of life and developmental outcomes¹⁷.

Of note, to better understand the long-term management of OAs with the carglumic acid, a prospective mixed-design study which provides for the enrollment of 80 patients and a 36-month follow-up is ongoing among patients diagnosed with PA or MMA and treated ≥ 6 months with carglumic acid (PROTECT study, NCT04176523). Currently, 71 patients are already included in the study. The primary analysis will compare the incidence and duration of decompensation episodes pre- and post-carglumic acid therapy. Additional analysis will include healthcare resource utilization around individual decompensation events, patient/caregiver burden, and patient/caregiver satisfaction with treatment.

Conclusions

The scientific evidence for including carglumic acid in the guidelines for the long treatment of OAs has increased. Over the last decade, the Italian referral centers for the management of OAs were pioneers of the chronic use of carglumic acid, and the long-term therapy with carglumic acid has become a reference in treating OAs hyperammonemia. In current clinical practice and literature experiences, the use of carglumic acid can be prolonged without any time limitation, given the high safety profile shown by the drug^{3,13,15-17}. According to literature data, most of patients were treated with 50 mg/kg/day in the long term. Nevertheless, additional studies aimed at better defining a proper dosage for the chronic administration of carglumic acid and the clinical and biochemical characteristics of patients treated chronically are ongoing. In addition, the potential impact of this treatment regimen on the neurological development and growth of patients should be elucidate. Of note, the use of carglumic acid as a stabilizer of the clinical picture before organ transplantation should be further investigated, as organ transplantation is a therapeutic option that still present some limitations²³.

Conflict of Interest

Dr. Bordugo, Dr. Gasperini, Dr. Menni, Dr. Paci, Dr. Procopio and Dr. Tummolo received honoraria from Recordati Rare Diseases Italy Srl. Dr. Rossi received travel grant from Recordati Rare Diseases Italy Srl.

Acknowledgements

Editorial, statistical and graphical assistance were provided by Simonetta Papa, Ph.D, Valentina Mirisola, Ph.D, Massimiliano Pianta and Aashni Shah (Polistudium SRL, Milan, Italy). This assistance was supported by Recordati Rare Diseases Italy Srl.

Funding

This study was conducted with the non-conditioning assistance of Recordati Rare Diseases Italy Srl.

Authors' Contribution

Conceptualization: AB, IB, GB, AB, SG, LLS, EM, CM, FM, SP, EP, AR, LR, MS, FT, AT; Data curation: AB, IB, GB, AB, SG, LLS, EM, CM, FM, SP, EP, AR, LR, MS, FT, AT; Formal analysis: AB, IB, GB, AB, SG, LLS, EM, CM, FM, SP, EP, AR, LR, MS, FT, AT; Funding acquisition: N/A; Investigation: AB, IB, GB, AB, SG, LLS, EM, CM, FM, SP, EP, AR, LR, MS, FT, AT; Methodology: Alberto Burlina; Project administration: N/A; Resources: N/A; Software: N/A; Supervision: N/A; Validation: N/A; Visualization: N/A; Roles/Writing - original draft: Alberto Burlina; Writing - review & editing: AB, IB, GB, AB, SG, LLS, EM, CM, FM, SP, EP, AR, LR, MS, FT, AT. All Authors have read and approved the final version of the paper before submission.

Ethics Approval

Not required as this manuscript does not include details, images or videos related to the participants.

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