

Cysteamine (Cystagon®) adherence in patients with cystinosis in Spain: successful in children and a challenge in adolescents and adults

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ABSTRACT

Background. Cysteamine has improved survival and prognosis in cystinosis. Increasing numbers of patients reach adulthood and face new challenges such as compliance that wanes over time. The aim of this study was to evaluate adherence to cysteamine treatment in a group of cystinotic patients in Spain in an attempt to identify potential therapy pitfalls and improve the overall care of affected individuals. Despite the impact of cysteamine on prognosis, there is a paucity of data regarding adherence.

Method. Thirty-four cystinotic patients (21 male) 38% ≥18 years were enrolled in a voluntary, anonymous survey. Replies were obtained from patients (15/34), mothers (11/34), fathers (4/34) and both parents (4/34).

Results. Patient age (median and interquartile range) at diagnosis was 1 year (0.57–1), and patient age at Cystagon® initiation was also 1 year (0.8–1.8). Sixteen (47%) were kidney

transplant (KTx) recipients; six were retransplanted. Age at first KTx 10 years (8.7–13.7). Patient understanding of multiorgan involvement in cystinosis: 4.1 organs reported; eye 97% and kidney 91%. Cysteamine was given by mother (100%) and father (83%) in <11 year olds, or self-administered (94%) in ≥11 year olds. Four daily doses in 89% versus 56% in <11 year olds or ≥11 year olds, with fixed schedule in 94% versus 50% in <11 or ≥11 year olds and progressive loss of reminders over time. Furthermore, 44% complained of unpleasant smell. Motivation for treatment compliance was 100% versus 40% in <11 versus ≥11 year olds, respectively. Disease impact in patients <18 years is as follows: school (29%), social (14%), 'feeling different' (10%); in patients ≥18 years: 'feeling different' (62%), professional (39%) and job absenteeism (31%). Referring physician: paediatric nephrologist (94%) and nephrologist (63%) in <11 versus ≥11 year olds. Ophthalmological follow-up: 83% versus 38% in <11 versus ≥11 year olds. Patient opinion of physician expertise: paediatric nephrologist (94%) and nephrologist (44%). New treatment options (65%) and better information (42%) were demanded to improve adherence.

Conclusion. Treatment with Cystagon is effective in young patients. However, adherence diminishes over time in adolescents and adults despite disease impact. Strategies such as better information on the disease, patient self-care promotion and facilitated transition to adult healthcare services are required to improve compliance and the clinical management of cystinosis.

Keywords: adherence, cysteamine, cystinosis, prognosis, transition

INTRODUCTION

Cystinosis is a rare autosomal recessive disorder of the lysosomal cystine transporter cystinosin [1] encoded by the *CTNS* gene (17p13) [2], which affects ~1–2 per 100 000 newborns [3]. Most patients exhibit the severe infantile form, leading to end-stage kidney disease (ESKD) by the end of the first decade in the absence of specific cystine-depleting treatment [1] and premature death before the second decade [4–7], whereas up to 5% present the milder late-onset form of the disease [8]. Treatment with Cysteamine (Cystagon®), the only available cystine-depleting drug from lysosomes in Spain, and renal transplantation have improved the prognosis of cystinosis [1]; consequently, increasing numbers of affected patients are reaching adulthood [9, 10]. Early and sustained treatment with cysteamine has improved renal outcome in cystinosis [11] by delaying progression to ESKD [4]. Furthermore, correct cysteamine administration also delays the onset and reduces the severity of extra-renal complications [5], leading to extended life expectancy and longer patient survival [6].

This changing scenario in cystinosis poses new challenges such as long-term compliance with a lifelong treatment [7], a difficult task in patients who take multiple medications and supplements [12], are exposed to potential cysteamine-related side effects (gastric intolerance, unpleasant smell and halitosis, among others) [13] and need to follow an ‘every 6 hour’ (Q6h) [14] dose schedule of immediately released cysteamine (Cystagon®) [15]. Last but not least, cystinosis is a good model of a rare ‘paediatric disease’ extending to adult practice [4, 6, 16]; however, few resources are in place to prevent inadequate transition to adult services [17], management of systemic disease involvement is poor, reference centres are lacking in many countries and, commonly, awareness among adult physicians is low [18]. Cystinotic patients are often transferred in a suboptimal process to adult services where they feel depressed and ‘lost in the system’ [19]. New therapeutic approaches are based on a patient-centred strategy of disease education, adherence, support by patient advocacy groups and a new culture of patient ‘self-care’ [20].

MATERIALS AND METHODS

Fifty-six individuals with cystinosis under the regular care of 29 different paediatric or adult nephrologists in 22 different hospitals received chronic treatment with cysteamine (Cystagon®) in Spain in 2012. All physicians caring for a patient with cystinosis were personally invited to participate in this study so that patients and families could be informed, give

their consent and be provided with a printed copy of the questionnaire.

An anonymous written survey was distributed among patients diagnosed with cystinosis at the time of a regular renal care follow-up visit at different hospitals in Spain in 2012. Patients and/or their parents, if applicable, were invited to voluntarily participate by completing a questionnaire, the estimated duration of which was ~10 min. In order to guarantee patient confidentiality and voluntary enrolment, a ‘take home’ option was offered and patients could later submit the document to a central site, thereby preserving individual information blinded to their physicians. Patients’ geographic location or centre identification data were not provided. The survey consisted of 21 multiple-choice questions covering four main areas: (i) knowledge of cystinosis and impact of the disease; (ii) adherence to cysteamine treatment; (iii) monitoring of cysteamine therapy and (iv) measures to improve compliance. The survey was promoted by Orphan Europe (a pharmaceutical company specialized in orphan diseases and a member of the *Recordati Group*), which created, designed and distributed it via company representatives to physicians caring for known cystinotic patients treated with cysteamine (Cystagon®). Another firm, A.C. Nielsen Company, made the overall analysis of the results in an independent manner. The results were expressed as median and inter-quartiles and patients were divided into two groups: those under and over 11 years of age.

RESULTS

Demographics

Thirty-four paediatric and adult patients (21 male and 13 female) with nephropathic cystinosis participated in the study, a figure representing 61% of the known treated cystinotic population in Spain. The questionnaire was completed by patients (15/34), their mother (11/34), father (4/34) or both parents (4/34). Age distribution was as follows: 12 patients (35%) 0–6 years, 6 (18%) 7–11 years, 3 (9%) 12–17 years and 13 (38%) ≥18 years old. All responders suffered from the infantile form of the disease. Out of 34 (47%), 16 had received at least one kidney transplant (KTx) and 6 (18%) had more than one. Remarkably, adult patients constituted almost 40% of the study cohort; indeed, 12 of 13 patients over 18 years of age were KTx recipients and half (6/12) had received more than one graft. At the time of the study, 22 patients were being followed up in paediatric nephrology services, whereas 12 were receiving care in adult nephrology departments. The main clinical characteristics of patients are described in Table 1.

This cohort belongs to the population of cystinotic patients in Spain that currently consists of 29% children, 16% teenagers and 55% adults. However, a lower percentage of cystinotic adults was enrolled in the study because ~32% of patients over the age of 18 did not participate.

Age at diagnosis and initiation of cysteamine

Cystinosis was diagnosed during infancy in 27 patients (79%); of them, 15 (44%) were diagnosed within the first year of life. In patients under the age of 11, treatment with

Table 1. Clinical characteristics of cystinotic patients at baseline (n = 34)

	n	Years (md; interquartile)
Age at the time of the study (years)		
<11	18 (53%)	
≥11	16 (47%)	
Age at diagnosis (years)		
		1 (0.57–1)
0–1	15 (44%)	
1–2	12 (35%)	
2–3	3 (9%)	
≥3	2 (6%)	
NR	2 (6%)	
Age at cysteamine initiation		
		1 (0.8–1.85)
<11 years age		
0–1	10 (56%)	
1–2	6 (33%)	
2–3	2 (11%)	
≥3	0 (0%)	
≥11 years age		
0–1	5 (31%)	
1–2	3 (19%)	
2–3	5 (31%)	
≥3	1 (6%)	
NR	2 (13%)	
Kidney transplant (KTx)		
Yes	16 (47%)	
1 KTx	8	10 (8.75–13.75)
2 KTx	4	
3 KTx	2	
No	18 (53%)	
Education		
Nursery/primary	13 (38%)	
Secondary	8 (24%)	
Former education	5 (15%)	
NR	8 (24%)	

NR, no reply.

cysteamine was initiated before the second year in 89% and within the first year in 56%. A significant difference was observed in age at cysteamine initiation between patients under or over 11 years of age at the time of the study, with earlier administration in patients diagnosed more recently (median 1 versus 2.7 years old, $P < 0.001$) (Table 1).

Knowledge on cystinosis and impact of the disease

Patients were aware of the systemic nature of cystinosis and reported the almost universal involvement of organs that occurs in cystinosis such as eyes (97% responders) and kidneys (91% responders), but also others such as muscles (44%), pancreas (35%), gastrointestinal (32%), central nervous system (CNS) (32%), neurological (24%), cardiovascular (21%) and testicular (15%), with a mean of 4.1 affected organs reported per patient.

The impact of the disease on quality of life (QOL) was reported to be greater in adults than in children. Thus, 62% of affected adults complained of feeling different, 39% expressed professional limitations, 31% required job absences and 8% referred to compromised social life and rejection, whereas in patients under 18 years old, cystinosis negatively influenced school attendance (29%), learning ability (5%) and social life (14%), but only 10% reported feeling different.

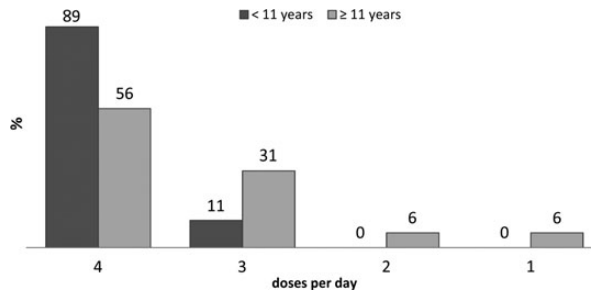


FIGURE 1: Number of self-reported daily cysteamine (Cystagon®) doses by patient age.

Adherence to cysteamine

In children under the age of 11, cysteamine was mainly administered by the mother (100%) and father (83%), but also by other relatives (28%) or by a teacher or school nurse (33%). In contrast, patients over 11 were largely responsible for their own treatment (94%), with less involvement of relatives (mother 25% and father 6%) or others.

With respect to treatment adherence, 89% of patients under 11 received cysteamine (Cystagon®) following a fixed four-daily dose schedule compared with only 56% of older patients who took the correct number of four doses per day (Figure 1). Furthermore, up to 41% of patients or their relatives had asked their doctor for a reduction in the number of daily doses: 27% stated their doctors had refused to reduce the number of doses, but 15% reported their physicians had agreed.

Nevertheless, whereas the majority of children under 11 followed the cysteamine prescription correctly (94%), the percentage dropped dramatically in older patients (50%) who reported frequent schedule changes (13%), missed doses (13%), never using the recommended doses (18%) or even not caring about drug prescription (6%) (Figure 2). Although up to 65% of patients took advantage of alarms or dose-reminder tools, the study demonstrated progressive waning in their use over time, as only 46% of adult patients used dose reminders.

Regarding patient motivation for treatment, 72% of patients under 11 were always motivated, and 39% expressed more motivation before a clinical appointment. In contrast, fewer older patients expressed feeling always motivated (38%) and, remarkably, 38% expressed no motivation at all, with low increased interest before/after a clinical appointment or before a blood test (Figure 3). Patients complained of unpleasant smell (44%), too many medications (44%), excessive number of daily doses (35%) and gastrointestinal side effects (24%), among others. New therapeutic strategies focussed on lower-frequency doses, fewer pills and/or reduced pill size (60%) as well as additional education on the disease (42%) were demanded to improve adherence to cystinosis therapy.

Adherence to medical control

For patients under the age of 11 years, paediatric nephrologists represented the referring physicians and 94% were considered disease experts. Remarkably, adult nephrologists were considered disease experts by only 44% of patients. Furthermore, patients stated that only 56% or 44% of paediatric or

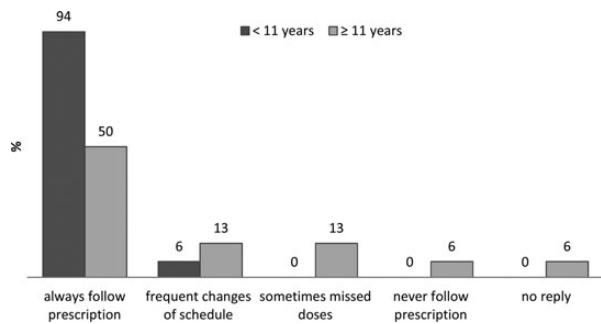


FIGURE 2: Self-reported adherence to cysteamine (Cystagon®) by patient age.

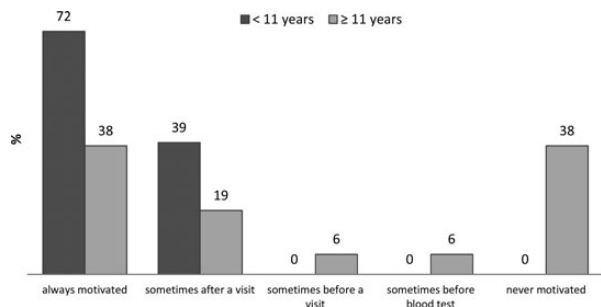


FIGURE 3: Patient motivation to follow cysteamine (Cystagon®) prescription by age.

adult nephrologists, respectively, provided them with sufficient information regarding cystinosis. Patients were under paediatric nephrologist care up to the age of 18, after which they were progressively transferred to adult nephrologists (13 of 34 patients). Several other medical specialists were also involved in the care of cystinotic patients: ophthalmologists (62%), endocrinologists (47%), transplant physicians (27%), neurologists (15%), dermatologists (6%) and others (18%). However, whereas 83% of younger cystinotic patients received regular ophthalmology care, the percentage dropped to 38% in those over 11 years of age.

DISCUSSION

We were able to collect self-reported data from 61% of the cystinotic patients receiving cysteamine in Spain. This study provides an insight into the current scenario of the disease in Spain, with a significant proportion (38%) of patients over 18 years of age, mostly kidney-transplanted recipients, being under the care of adult physicians. The main findings included good compliance in children under the age of 11 and a decline in cysteamine adherence after puberty associated with less parental supervision, decreasing use of dose reminders, very low motivation rates of treatment compliance in older patients, substantial impact on QOL and inadequate transition to adult medical care [19], with many centres caring for one individual patient. Specifically, our cohort of 34 individuals was under the care of 22 different doctors working at 20 different

hospitals, very telling of the dispersion of patients and consequent lack of physician/health system awareness of, and expertise in, cystinosis, which may also, at least in part, explain why a significant percentage of affected adults did not participate in the survey.

Most patients exhibit the severe infantile form of the disease and are at risk of developing premature ESKD and early death in the absence of specific cystine-depleting treatment [1], whereas up to 5% present the milder late-onset form [8]. Cysteamine treatment, which has been available since the 1980s, is able to preserve renal function and delay progression to renal failure [21] and later reduce systemic involvement of the disease [9, 10]. Oral cysteamine is able to achieve leucocyte cystine depletion of up to 95% [22, 23] and reduce the cystine parenchymal tissue content when adherence is consistent [21], with substantial beneficial effects on renal and extra-renal comorbidities [4–7] and patient life expectancy [16, 17]. Data on leucocyte cystine levels were not included in this study for their concordance with patient self-report information on adherence to be evaluated; however, the overall outcome of our cohort of cystinotic patients concurs with data of other recently published series [6, 16, 17]. Indeed, at the time of the study, 40% of cystinotic patients in this series were adults, a finding that reflects the impact of early diagnosis and cysteamine prescription in most cases. Our results also indicate an improvement in diagnosis and cysteamine initiation in this Spanish cohort of patients who started the specific treatment with Cystagon® during infancy and before 1 year of age in more than half of the contemporary new cases, a fact that presumably will be associated with better long-term outcome, as reported [5, 7, 11]. Our data also reflect the concept that cysteamine therapy should be started as early as possible after diagnosis [6, 17, 21]. Prompt diagnosis and education of parents and children from earlier ages on compliance would presumably also have a positive impact; hopefully, the children of today will be better adherents when teenagers tomorrow.

Cysteamine is known not to be able to reverse the associated Fanconi syndrome [3] or fully prevent progression to chronic kidney disease (CKD) [16–18]. We found that, even when treated, up to 47% of cystinotic patients progressed to ESKD during childhood, receiving a KTx at ~10 years of age (8.75–13.75), an experience similar to that described by the European ESPN-ERA registry [4]. In fact, almost 12 of 13 adult cystinotic patients in this series had been transplanted during childhood and retransplantation was also very common, as reported elsewhere [4, 6, 7]. Although data on renal function were not included in our survey, it seems reasonable to presume that a large number of cystinotic children also suffered CKD, as reported [10]. Therefore, most cystinotic patients would be transferred to adult KTx specialists who would need to be aware not only of this rare disease [1] but also that treatment will be lifelong, even after KTx [6, 17, 21].

This study confirms that patients understood the systemic nature of nephropathic cystinosis, with early universal kidney and eye involvement and progressive involvement of other organs such as the intestine, cardiovascular system and CNS, even after kidney transplantation [10] and mainly in low compliant individuals [6, 7], which may be beyond the scope of the

transplant specialist [18, 24]. In the present survey, the impact of the disease on QOL was reported to be greater in adults than in children, mainly affecting professional careers and social life; this may be due to the onset of extra-renal complications over time as expected [16–18] and cysteamine side effects, among other factors [15]. Indeed, around one-third of our patients were under the regular care of other physicians, mainly ophthalmologists and endocrinologists. In general, this kind of expertise may exceed the skills of the regular adult nephrologist, who is often focussed on transplantation. Therefore, the finding that only 44% of teenagers and adults with cystinosis in this study perceived their doctors to be experts in the disease is not surprising, in contrast to what occurs during childhood when the paediatric nephrologist is considered the main reference as he/she usually plays the role of patient care coordinator. As mentioned previously, systemic manifestations arising during adulthood warrant specialized cystinosis-specific outpatient care, because management usually requires expertise well beyond the skills of the individual physician [17]; this again underlies the need for adequate transfer of cystinotic patients to adult care [19].

Nevertheless, the major and most worrying finding of this study is the alarming waning of adherence to cysteamine treatment over time, predominantly in teenagers and adults [17]. In these patients, decreasing parental supervision, progressive loss of dose reminder use and, more importantly, lack of patient motivation coincide. It can be presumed, therefore, that older cystinotic patients will face significant disease progression [6, 7], as reported in the past, when high rates of extra-renal complications in adults with cystinosis [9] and limitations of their life expectancy owing to poor compliance were observed [17]. Despite the impact of treatment adherence on prognosis, data regarding adherence to cysteamine are lacking. Brief data presented as a poster recently reported missing Cystagon® doses, a sustained and progressive decrease in Cystagon®, refills with patient age and increasingly prolonged gaps between refills over time [25]. This may also be influenced by drug cost and availability, a factor not applicable in Spain where Cystagon® is universally provided free of cost by hospital pharmacies. Treatment with the new delayed-release cysteamine formulation would presumably have a positive impact on patient adherence [26, 27]. However, factors such as disease complexity and limited awareness of the long-term outcome of cystinosis may still determine patient compliance.

Nevertheless, suboptimal treatment adherence is not restricted to cystinosis. Indeed, recent studies reported that 52–67% of adult KTx recipients failed to follow their immunosuppressive medications correctly, which increased the probability of graft failure [28, 29]. These percentages were similar to those found in our study and may indicate common CKD-related scenarios. Moreover, measures targeting behavioural risk factors and active patient involvement have been advocated to improve treatment compliance in adult transplanted patients. Accordingly, similar strategies should be implemented in young and adult cystinotic patients [30].

It is to be hoped that new initiatives such as recently published guidelines regarding awareness of cystinosis and its impact on prognosis will lead to optimum, tailor-made care of these patients [31].

This study was limited by a bias of patient response, parental opinion and lack of leucocyte cystine level monitoring to ascertain actual compliance.

CONCLUSION

Despite severity of the disease and the impact of treatment on outcome, adherence to Cystagon® wanes over time in cystinosis, particularly during adolescence and adulthood.

Our results underline the concept that early initiation of cysteamine treatment and the implementation of patient education programmes stressing the benefits of good compliance are essential for the long-term prognosis. In our Spanish cohort, 89% of patients under the age of 11 comply well with cysteamine, although this compliance tends to wane with age.

Because patients are awaiting new approaches to their treatment, novel strategies such as patient self-care promotion, better information on the disease, facilitated transition to adult healthcare services guided by expert recommendations and multidisciplinary teams are urgently required to improve the clinical management of cystinosis.

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CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

- Gahl WA, Thoene JG, Schneider JA. Cystinosis. *N Eng J Med* 2002; 347: 111–121
- Town M, Jean G, Cherqui S *et al.* A novel gene encoding an integral membrane protein is mutated in nephropathic cystinosis. *Nat Gen* 1998; 18: 219–324
- Gahl WA. Cystinosis coming of age. *Adv Pediatr* 1986; 33: 95–126
- Van Stralen KJ, Emma F, Jager KJ *et al.* Improvement in the renal prognosis in nephropathic cystinosis. *Clin J Am Soc Nephrol* 2011; 6: 2485–2491
- Kleta R, Bernardini I, Ueda M *et al.* Long-term follow-up of well-treated nephropathic cystinosis patients. *J Pediatr* 2004; 145: 555–560
- Brodin-Sartorius A, Tête MJ, Niaudet P *et al.* Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults. *Kidney Int* 2012; 81: 179–189
- Gahl WA, Balog JZ, Kleta R. Nephropathic cystinosis in adults: natural history and effects of oral cysteamine therapy. *Ann Intern Med* 2007; 147: 242–250
- Servais A, Morinière V, Grünfeld JP *et al.* Late-onset nephropathic cystinosis: clinical presentation, outcome and genotyping. *Clin J Am Soc Nephrol* 2008; 3: 27–35
- Geelen JM, Monnens LAH, Levchenko E. Follow-up and treatment of adults with cystinosis in the Netherlands. *Nephrol Dial Transplant* 2002; 17: 1766–1770

10. Servais A, Brodin-Sartorius A, Tête MJ *et al.* Nephropathic cystinosis in adolescents and adults. *Eur Nephrol* 2012; 6: 3–7
11. Markello TC, Bernardini IM, Gahl WA. Improved function in children with cystinosis treated with cysteamine. *N Eng J Med* 1993; 328: 1157–1162
12. Wilmer MJ, Schoeber JP, van den Heuvel LP *et al.* Cystinosis: practical tools for diagnosis and treatment. *Pediatr Nephrol* 2011; 26: 205–215
13. Dohil R, Newbury RO, Sellers ZM *et al.* The evaluation and treatment of gastrointestinal disease in children with cystinosis receiving cysteamine. *J Pediatr* 2003; 143: 224–230
14. Belldina EB, Huang MY, Shneider JA *et al.* Steady-state pharmacokinetics and pharmacodynamics of cysteamine bitartrate in paediatric nephropathic cystinosis patients. *J Clin Pharmacol* 2003; 56: 520–525
15. Kleta R, Gahl WA. Pharmacological treatment of nephropathic cystinosis with cysteamine. *Expert Opin Pharmacother* 2004; 5: 2255–2262
16. Nesterova G, Gahl WA. Cystinosis: the evolution of a treatable disease. *Pediatr Nephrol* 2013; 28: 51–59
17. Goodyer P. The history of cystinosis: lessons for clinical management. *Int J Nephrol*. 2011; 2011: 929456. doi: 10.4061/2011/929456.
18. Nesterova G, Gahl WA. Nephropathic cystinosis: late complications of a multisystemic disease. *Pediatr Nephrol* 2008; 23: 863–878
19. Watson AR, Harden PN, Ferris ME *et al.* Transition from pediatric to adult renal services: a consensus statement by the International Society of Nephrology (ISN) and the International Pediatric Nephrology Association (IPNA). *Kidney Int* 2011; 80: 704–707
20. Forbes TA, Watson AR, Zurowska A *et al.* European Paediatric Dialysis Working Group. Adherence to transition guidelines in European paediatric nephrology units. *Pediatr Nephrol* 2014; 29: 1617–1624
21. Gahl WA, Reed GF, Thoene JG *et al.* Cysteamine therapy for children with nephropathic cystinosis. *N Engl J Med* 1987; 316: 971–977
22. Schneider JA, Bradley K, Seegmiller JE. Increased cystine in leukocytes from individuals homozygous and heterozygous for cystinosis. *Science* 1967; 157: 1321–1322
23. Smolin LA, Clark KF, Schneider JA. An improvement method for heterozygote detection of cystinosis using polymorphonuclear leucocytes. *Am J Hum Genet* 1987; 41: 266–275
24. Gahl WA, Nesterova G. Cystinosis. The post-transplant era. *Eur Nephrol* 2010; 4: 55–61
25. Cadieux B, Lapidus D, Greenbaum LA. Adherence to cysteamine and kidney outcomes among 224 cystinosis patients. In: Annual Meeting of the American Society of Pediatric Nephrology, Vancouver, 2014
26. Langman CB, Greenbaum LA, Sarwal M *et al.* A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety. *Clin J Am Soc Nephrol* 2012; 7: 1112–1120
27. Langman CB, Greenbaum LA, Grimm P *et al.* Quality of life is improved and kidney function preserved in patients with nephropathic cystinosis treated for 2 years with delayed-release cysteamine bitartrate. *J Pediatr* 2014; 165: 528–533
28. Chisholm MA, Mulloy LL, DiPiro JT. Comparing renal transplant patients' adherence to free cyclosporine and free tacrolimus immunosuppressant therapy. *Clin Transplant* 2005; 1: 77–82
29. Chisholm MA, Vollenweider LJ, Mulloy LL *et al.* Renal transplant patient compliance with free immunosuppressive medications. *Transplantation* 2000; 8: 1240–1244
30. Low JK, Williams A, Manias E *et al.* Interventions to improve medication adherence in adult kidney transplant recipients: a systematic review. *Nephrol Dial Transplant* 2014; doi: 10.1093/ndt/gfu204
31. Emma F, Nesterova G, Langman C *et al.* Nephropathic cystinosis: an international consensus document. *Nephrol Dial Transplant* 2014; 29: iv87–iv94.

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Circulating and renal vein levels of microRNAs in patients with renal artery stenosis

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ABSTRACT

Background. MicroRNAs (miRs) are small non-coding RNAs that are important regulators of gene expression and have

been implicated in atherosclerosis. Kidney injury distal to atherosclerotic renal artery stenosis (ARAS) is aggravated by atherosclerosis. Therefore, this study tested the hypothesis that renal miR expression would be altered in patients with ARAS.