Pediatr Nephrol
DOI 10.1007/s00467-016-3438-x

ORIGINAL ARTICLE

Switching from immediate- to extended-release cysteamine in nephropathic cystinosis patients: a retrospective real-life single-center study

Thurid Ahlenstiel-Grunow[1] · Nele K. Kanzelmeyer[1] · Kerstin Froede[1] · Martin Kreuzer[1] · Jens Drube[1] · Christian Lerch[1] · Lars Pape[1]

Received: 4 April 2016 / Revised: 28 April 2016 / Accepted: 16 May 2016

Abstract
Background Nephropathic cystinosis is a rare lysosomal storage disease which is characterized by the accumulation of free cystine in lysosomes and subsequent intracellular crystal formation of cystine throughout the body. If not treated with cysteamine, a cystine-depleting agent, end-stage renal disease will develop early, followed by multiple organ failure as the disease progresses. The established cysteamine formulation requires a strict dosing regimen at 6-h intervals. An extended release (ER) twice-daily formulation has recently been developed. The aim of our study was to evaluate the implementation and outcomes of this option in routine care.
Methods All pediatric cystinosis patients' records in Hannover Medical School were screened, and data on cysteamine therapy, tolerability, dosing, estimated glomerular filtration rates (eGFR), white blood cell cystine levels, and proton pump inhibitor (PPI) use were extracted for the period January 2014 to January 2016.
Results The median age of the 12 patients enrolled in the study was 12.5 (range 1–18) years. At the end of the study period ten of these patients received ER-cysteamine. There were no additional side effects. Halitosis/bad breath was often subjectively judged as improved or eliminated, and PPI use could be stopped in one of three patients. The main reasons for switching to the ER formulation were difficult night-time administration and uncontrolled disease. Mean eGFR values remained stable with a median of 67 ml/min/1.73 m^2 before and after the transition. White blood cell (WBC) cystine values remained low after the switch (1 nmol/mg protein before and after transition; $p = 0.64$).
Conclusions In this single-center cohort, the switch from IR- to ER-cysteamine was safe and effective over the short term and provided advantages in terms of frequency of administration and less halitosis/bad breath. The long-term benefit of this option needs to be evaluated in future studies.

Keywords Nephropathic cystinosis · Cysteamine · Fanconi syndrome · Lysosomal storage disease · Cystine depleting agents

Introduction

Nephropathic cystinosis is a rare autosomal recessive lysosomal storage disease with an incidence of 1.0–2.0 per 200,000 live births [1]. It is caused by mutations in the *CTNS* gene which codes for the membrane transport protein cystinosin [2]. Cystinosin is responsible for transporting cystine out of the lysosomes, and non-function of this protein results in the the accumulation of free cystine in the lyosomes that ultimately leads to the widespread intracellular crystal formation of cystine throughout the body. The first severe consequence of crystal formation is generalized proximal tubular dysfunction, which is the single, most frequent cause of Fanconi Syndrome in children. If the disease is left untreated, kidney failure is in most cases inevitable, and multiple organ failure ensues over time. Diagnosis is confirmed by the measurement of elevated cystine levels in white blood cells (WBCs). The target level can vary from laboratory to laboratory, and each laboratory should therefore have its own reference values. In most cases, target levels are <1.0–1.5 nmol/mg protein. Our laboratory works with a target level of <1 nmol/mg protein, with the optimal level being <0.5 nmol/mg protein.

Values in healthy subjects can reach values of 0.2–0.6 nmol/mg protein. Higher concentrations are indicative of

✉ Lars Pape
Pape.Lars@mh-hannover.de

[1] Department of Pediatric Nephrology, Hannover Medical School, Carl-Neuberg-Strasse 1, 30625 Hannover, Germany

Published online: 27 June 2016

cystinosis, and values of <0.5–1 nmol/mg protein represent the therapeutic target level. Cysteamine, a specific cystine-depleting agent, is the cornerstone of cystinosis treatment [2–5]. Early therapy is essential, as it has been shown to delay the progression to end-stage renal disease (ESRD) on average by 5–10 years, the need for renal replacement therapy, such as dialysis or kidney transplantation, and the development of extra-renal complications and to improve growth. However, there is as yet no evidence that ESRD can be completely prevented.

An immediate-release (IR) formulation of cysteamine (IR-cysteamine; Cystagon; Orphan Europe, Paris, France) has been commercially available since 1997. Although effective in managing kidney damage and preserving kidney function, patients find the IR formulation difficult to use over the long-term due to its strict 6-h administration schedule. More recently, a novel extended-release (ER) formulation of cysteamine (ER-cysteamine;PROCYSBI; Raptor Pharmaceuticals Inc., Novato, CA) which needs only to be administered twice daily has been developed. This ER formulation was put on the market in 2013 in the USA and in 2014 in Europe, and its efficacy and safety was shown in a short-term, cross-over, non-inferiority trial [6]. Gastrointestinal symptoms were identified as the most frequently reported adverse events with both the IR and ER formulations, but compared to treatment with IR-cysteamine treatment with ER-cysteamine for identical periods of time resulted in a reduction of 87 % in the use of proton pump inhibitors (PPIs) [6]. These same authors analyzed 2-year follow-up data from 40 patients receiving ER-cysteamine and further demonstrated that cystine levels in WBCs could be effectively kept at <1 nmol/mg protein. There was no impairment of growth or kidney function in this cohort, and the quality of life of the patients was generally improved [7]. However, little is known to date on the implementation of ER-cysteamine therapy in the clinical setting and its implications for the clinical routine.

The aim of our study was to analyze the findings on the implementation of ER-cysteamine therapy in routine care at a single pediatric center, examine the main reasons for or against the switch from the IR to the ER formulation of cysteamine, and determine the impact switching had on the outcomes of the cystinosis patients.

Methods

Extended-release cysteamine as a new therapeutic option was discussed with the families of all affected patients in the Division of Pediatric Nephrology of Hannover Medical School in July 2014.

A short guidance paper was developed at our institution for the transition from IR- to ER-cysteamine treatment. It provided instructions on what information should be given to the patients, adequate dosing, and prescription modalities, as well as on the procedure for determining cystine levels in WBCs. The guidance paper also informed patients and their families that the reasons for the switch needed to be thoroughly documented for payors and that the patients were expected to provide information on adverse events at each follow-up visit, as well as their experience with halitosis.

The records of all pediatric cystinosis patients treated at our institution from January 2014 to January 2016 were screened. As a first step we collected the dates and reasons for or against a switch to the delayed-release (ER) formulation. Further data were extracted only in the case of a switch. Cysteamine treatments for the periods immediately before and after the change to the ER formulation were assessed. In addition, the dosing of ER-cysteamine at the 6- and 12-month follow-up and any dose adjustments were evaluated.

All available values for the estimated glomerular filtration rates (eGFR) during the study period were obtained. To evaluate if there were any significant changes in kidney function after the switch in medication, we compared the last determined eGFR values within 4 months before the transition to ER-cysteamine and those at 13–15 months after the switch in those patients for whom both values were available. Similarly, all available values for WBC cystine levels were obtained. To verify if there were any significant changes in WBC cystine levels, we compared the averages of all values before and after the switch. All eGFR values were calculated based on cystatin C, creatinine, and blood urea nitrogen (BUN) values using the method outlined by Schwartz et al. [8]. WBC cystine levels were determined directly at our center. Protein content was determined using the Lowry method, and cystine content was measured using tandem mass spectrometry. Leukocyte cystine content was calculated as nanomoles cystine per milligram protein. PPI use before and after the change in treatment was retrieved from patient records, and important tolerability issues were noted.

All data were assessed descriptively. Due to the small sample size data were presented as the median and range and compared using the Mann–Whitney U test. A P of <0.05 was considered to be statistically significant.

This study is based on routine clinical data retrieved from patient records and was therefore exempt from Ethics Committee approval.

Results

Baseline characteristics

Charts from 12 pediatric cystinosis patients with a median age of 12 (range 1–18) years were available for review. The study cohort consisted of six boys and six girls who had been diagnosed at the median age of 10.5 (2–56) months. Three had

successful kidney transplantation after having developed ESRD. All baseline characteristics are summarized in Table 1.

Switch to the ER formulation

Of the 12 families consulted about a change in cysteamine therapy, 11 consented to switch to the ER formulation. The most prominent reason for a switch was "difficulties with night-time administration of IR-cysteamine" ($n = 9$), followed by inadequate disease control in terms of excessively high WBC cystine levels ($n = 2$). Non-adherence and halitosis were further reasons for the medication change. The reason for not switching medication was a very stable condition and good tolerability of IR-cysteamine ($n = 1$).

Eight of the 11 patients who switched to the ER formulation encountered no difficulties, with no complications or additional side effects (Table 2). Halitosis and/or bad breath was assessed by four of six patients who switched to ER-cysteamine to be reduced or even eliminated. Three patients encountered difficulties in switching from IR- to ER-cysteamine. Table 2 gives an overview of the switch from IR- to ER-cysteamine in all patients.

Patient 1 was switched to ER-cysteamine for the first time in September 2014. He subsequently suffered from vomiting and weight loss and was changed back to IR-cysteamine in October 2014. However, night-time administration remained a major hurdle for the patient's parents. When a fructose malabsorption was identified as the cause of the patient's gastrointestinal problems, a new attempt with ER-cysteamine was made in January 2015. While the drug was readily tolerated this time, swallowing of the capsules was associated with dry heaving. Following a request from the parents, the patient was changed back to IR-cysteamine in July 2015. The therapy with the IR formulation is ongoing in this patient and is well tolerated.

Patient 2 switched to the ER formulation for the first time in October 2014. However, as the patient's parents were unable to administer the content of the capsules through the feeding tube, conversion to ER-cysteamine was stopped and the patient reverted to the IR formulation. Due to apparent difficulties with night-time administration, an unstable metabolic situation and very high WBC cystine levels, the parents were advised to reconsider a switch back to the ER-cysteamine formulation. In September 2015 they agreed, and this time the transition to ER-cysteamine was uneventful. Treatment with ER-cysteamine is still ongoing in this patient.

Patient 7 required a change back to the IR formulation after 13 months on ER-cysteamine because of frequent vomiting, which the parents felt was associated with the ER formulation of cysteamine. This patient is now successfully being treated with the IR formulation.

The median follow up time in the 11 patients, where a transition to ER-cysteamine was made at least transiently, was 14 (range 3–18) months.

PPI use

PPI use was generally infrequent in our patient cohort ($n = 3$). Of the three patients requiring PPI, one was able to stop using the medication after transition to ER-cysteamine therapy.

Cysteamine doses

All patients received prescriptions for oral cysteamine and eye drops for the whole study period. In those patients who switched from IR- to ER-cysteamine, the median oral doses normalized to body surface were 1.2 (range 0.2–1.9) g/m^2/day (IR) and 0.9 (range 0.1–1.2) g/m^2/day (ER). This represents a median ER-cysteamine start dose of 75 % (range 50–100 %) of the IR-cysteamine dose. While the overall dose can be

Table 1 Patients' baseline characteristics

Patient no.	Age in January 2016 (years)	Sex	Age at diagnosis (months)	Kidney transplant (year)
1	6	Male	11	
2	5	Male	8	
3	18	Female	2	
4	14	Female	6	2012
5	14	Male	26	
6	14	Female	6	2012
7	12	Male	10	
8	9	Male	56	2015
9	14	Female	18	
10	2	Male	6	
11	13	Female	18	
12	1	Female	15	

Table 2 Characteristics of switching from immediate-release- to extended-release cysteamine

Patient no.	Date of switch	Reason for switch	Side effects with IR-cysteamine	Side effects with ER-cysteamine	Proton pump inhibitor use
1	Several switches. Refer to text Currently on IR-cysteamine.	Extremely bad breath and halitosis Difficulties with night-time administration.	Halitosis	Vomiting, weight loss, retching when swallowing the capsules	–
2	Several switches. Refer to text Currently on ER-cysteamine	Cystine target levels not reached under IR-cysteamine Difficulties with night-time administration Unstable metabolic situation.	–	–	Yes, no change
3	December 2014	Non-compliance with IR-cysteamine Bad breath	Halitosis Bad breath	–	–
4	August 2014	Difficulties with night-time administration	Halitosis	–	–
5	September 2014	Difficulties with night-time administration	Halitosis	Halitosis	–
6	August 2014	Difficulties with night-time administration	Halitosis	Significantly less halitosis	–
7	November 2014 Back to IR-cysteamine in December 2015 Refer to text	Difficulties with night-time administration	Halitosis GI symptoms	Halitosis GI symptoms	–
8	March 2015?	Difficulties of night-time administration	–	–	Yes, could be stopped under ER-cysteamine in May 2015
9	n.a.	No switch Therapy with IR-cysteamine safe, tolerable, and effective.	–	n.a.	–
10	February 2015	Difficulties with night-time administration	–	–	Yes, no change
11	July 2014	Difficulties with night-time administration	–	–	–
12	October 2015	Cystine target levels not reached under IR-cysteamine	GI symptoms	GI symptoms	–

ER, Extended release; GI, gastrointestinal; IR, immediate release; n.a., not applicable

reduced with the ER formulation, the number of capsules that need to be taken at a time is increased with ER-cysteamine due to the 50 % lower drug content per capsule and the less frequent administration. The prescription ranged from one to four capsules with IR- and from one to ten capsules with ER-cysteamine. The higher pill load was generally accepted by the patients.

The initial ER-cysteamine dose was set to 100 % of the IR dose in two patients due to elevated WBC cystine levels. In one patient a lower start dose for the ER formulation was chosen as WBC cystine levels were largely <1 nmol/mg protein.

The target daily minimum dose of 1.3 mg/m^2 (IR) was not achieved in five of the 12 patients. Patient 3—a teenager—and one mother with a small child (Patient 12) were non-adherent with the prescribed doses and insisted on lower dosing. Patient 8 was an infant with gastrointestinal problems, which the parents attributed to the cysteamine treatment, so they would only accept lower doses. Cystine levels were <0.5 nmol/mg protein in Patient 7, and the physicians and parents together decided that there was no need for a dose increase. A similar decision was made for Patient 10 who presented with a very satisfactory overall condition and low WBC cystine values.

Information on doses at the 6- and 12–month follow-ups after the switch was available for seven and five patients, respectively. Median ER-cysteamine doses per body surface area per day at the 6- and 12-month follow-ups were 1.0 (range 0.6–1.4) and 0.9 g (range 0.5–1.4) g/ m^2/day, respectively.

The dose was adjusted over time for seven patients. Patient 3 refused the targeted dose, and the prescription was therefore set to lower doses. In the other six patients the nominal dose

was increased to account for the growth in these children and, in two patients who presented with elevated WBC cystine levels, to obtain better disease control.

Estimated glomerular filtration rates

The graphic depiction of the eGFR values from 2014 to 2016 suggests that they remained stable for all patients who switched to the delayed release formulation (Fig. 1). eGFR values at 13–15 months of follow-up were available for five patients. The median eGFR within 4 months prior to the switch in medication and at approximately 1 year after the transition (IR to ER) was 67 (range 26–90) and 67 (range 21–91) ml/min/1.73 m^2, respectively ((no significance at $p = 1$).

WBC cystine levels

The levels of cystine in the WBCs could be kept within the range of the therapeutic target after the change to ER-cysteamine. The values seen over the study period from 2014 to 2016 remained stable or were improved in most patients after the transition (Fig. 2). The median of all values before and after the switch was both 1 nmol/mg protein (range 0.2–5.7 and 0–2.5 nmol/mg protein, respectively). The Mann–Whitney *U* test confirmed that there was no statistical difference between the values ($p = 0.64$). Only one patient presented with higher average WBC cystine levels after the transition to ER-cysteamine. However, this patient's cystinosis was difficult to manage in general, and treatment was characterized by an insufficient understanding of the severity of disease, language problems, and a long history of non-adherence not only with therapy but also with scheduled visits.

Discussion

We found that in our real-life setting, most families of our 12 pediatric cystinosis patients were well informed about the new option from patient associations and were proactive in the change to ER-cysteamine. The switch from IR- to ER-cysteamine went well in most patients, leading to fewer side effects and better therapy control in some children.

In times of increasing restrictions on reimbursement, an increased number of alternative treatment options, and an abundance of medical information, the question of who decides on new options—whether it is a patient's parents, the patients themselves, local or national centers, private practice physicians, or sickness funds—and how decisions are made needs to be addressed. Thorough documentation and transparent decision-making is now of paramount importance so that the clinical team avoids refunding requests or litigation. The implementation of new evidence into healthcare policy and practice is generally very complex and there are no simple answers [9].

At our institution any new treatment option is thoroughly evaluated by the entire clinical team. In the case of the treatment of cystinosis patients, we scrutinized the significance of different factors which could justify a switch from IR- to ER-cysteamine. In general, unmet therapeutic goals and relevant side effects are the most common possible reasons for a change in therapy, but difficulties with drug administration and non-compliance are also relevant factors. Last but not least, the reimbursement situation has to be considered, and less expensive but similarly effective options need to be taken into account.

Compliance with IR-cysteamine treatment is generally challenging in cystinosis as it requires strict 6-hourly dosing to provide for effective cystine depletion [10]. While this may be successfully achieved in childhood, it gets increasingly difficult in adolescents and adults [11] when the dosing schedule not only interferes with patients' tasks and daily routines, but the most commonly observed adverse events become more import. Most cystinosis patients struggle with severe halitosis and/or bad breath under cysteamine treatment [3]. While this condition is always challenging in terms of maintaining adequate social relationships, it takes on special significance for adolescents and young adults. That non-adherence offers immediate benefit in terms of less halitosis

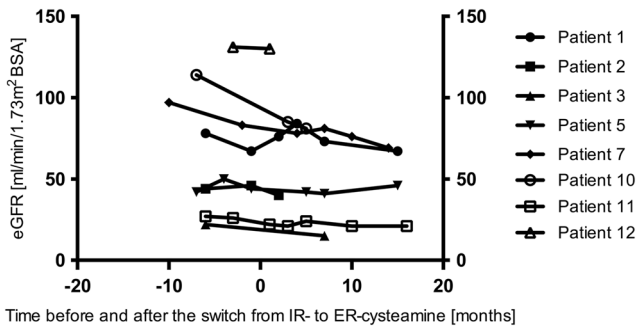

Fig. 1 Estimated glomerular filtration rate (*eGFR*) before and after the switch from immediate-release (*IR*)- to extended-release (*ER*)-cysteamine for all patients with native kidneys who changed to the new formulation. *BSA* Body surface area

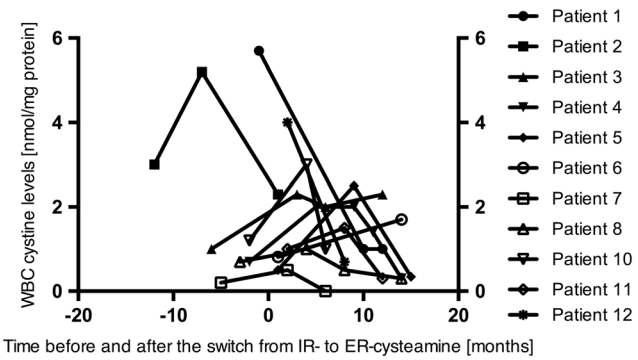

Fig. 2 Cystine levels in white blood cells (*WBCs*) before and after the switch from immediate release (IR)- to extended release (ER)-cysteamine for all patients who changed to the new formulation

but does not lead to immediate worsening of symptoms is especially unfavorable for adherence at this age.

Treatment with ER-cysteamine reduces halitosis and bad breath compared to treatment with IR-cysteamine [12]. Accordingly, while the most common reason that patients in our cohort gave for a switch was difficulty with night-time administration, reducing halitosis and/or bad breath was also cited as a motivating factor for the switch.

From the clinicians' perspective, assumed or manifest non-adherence as well as insufficient disease control were reasons for advising a transition to ER-cysteamine.

The main reasons against switching were that the patient was in a stable condition on IR-cysteamine therapy, tolerability to the current therapy was good, and there was adequate disease control. However, for small children receiving all of their medication four-times daily via gastrostomy or patients with a prescription for cysteamine eye drops four-times daily, there would be no advantage to switching in terms of administration schedule. This might change in the future, however, when new formulations of cysteamine eye drops that require less frequent dosing will become available.

The direct treatment costs with ER-cysteamine are significantly higher than those with standard IR-cysteamine. In Germany, treatment consisting of a daily dose of 1.5 g ER-cysteamine costs 574 € per day for a patient with a body surface of 1 m^2 as compared to 40 € per day for IR-cysteamine.

While ER-cysteamine is approved in Germany for the treatment of cystinosis and is generally reimbursed by public health insurances, the law also requires "economically reasonable" prescriptions. Better disease control may mean significant savings and outweigh the potentially higher cost of new drugs. For this reason it is necessary to document the reasons why ER-cysteamine therapy is thought to lead to better disease control than IR-cysteamine in individual patients. As we have shown in our cohort study, night-time administration of IR-cysteamine is a significant problem, eventually leading to non-compliance and inadequate disease control. For parents it can be an appreciable relief to switch to a therapy that only requires twice-daily administration. Ultimately, national health authorities will have to evaluate the significance of such innovative formulations of established therapies for the healthcare system. They will clearly need to verify the potential benefit provided by the new therapeutic option and weigh it against the additional costs involved. Meanwhile, pharmaceutical companies should remain motivated to continue research, especially on rare diseases. Only the joint efforts of legislators, reimbursement agencies, and manufacturers will enable patients to access medical innovation in both developed and developing countries.

On the whole, there were very few problems and no additional side effects after the switch to ER-cysteamine, which is in line with results from the approval and follow-up trials [6, 7]. Both eGFR and WBC cystine levels in leukocytes remained stable or improved under ER-cysteamine despite the lower total dosing. The exceptions observed are thought to be associated with other factors, such as transplant rejection or non-compliance, rather than a lack of treatment efficacy. Four of six patients reported less halitosis. While our findings are consistent with existing data, this subjective feedback in our cohort still warrants further substantiation before firm conclusions can be drawn. Results from a study showing that PPI use was reduced or at least not increased under treatment with a delayed release formulation [6] were reflected in our cohort. However, the number of patients in our cohort taking PPIs was too small to allow meaningful interpretation of the data.

There are a number of shortcomings to our study which could affect the validity of our results. It is a retrospective evaluation of a small number of patients without a control group. However, cystinosis is an extremely rare disease and to include adequate patient numbers for a well-designed randomized controlled trial is almost impossible. Hence, observing intraindividual changes after a medication switch in a real-life setting can provide relevant information for an orphan disease such as this. Notably, the results represent only short-term findings, and longer follow-up is needed to fully understand the impact which the ER-cysteamine formulation will have on future patient outcomes.

In conclusion, a switch from IR- to ER-cysteamine was feasible and safe in children in a real-life setting. Adolescents in particular may benefit from the twice-daily administration and a potential reduction in halitosis.

Conclusions

The main reasons for a switch from IR-cysteamine to ER-cysteamine in our cohort were difficulties with night-time administration and thereby worse disease control. The switch was safe and effective, and in some children there was the extra advantage of less halitosis/bad breath. We could not draw any clear conclusions regarding gastrointestinal tolerability; a larger sample size would have been required to confirm potential improvements. The high direct treatment costs for the new option may threaten its comprehensive availability to patients in need.

Acknowledgments The authors thank Susanne Merk who provided medical writing services and Felicity Kay for English language correction.

Compliance with ethical standards

Ethical approval For this type of study formal consent is not required.

Disclosure of potential conflicts of interest Lars Pape has received research grants, speaker's honoraria, and travel grants from Raptor Pharmaceuticals and Orphan Europe. All other authors declare no conflicts of interest.

Statement of financial support The study was supported by an unrestricted grant by Raptor Pharmaceuticals. Good Publication Practice Guidelines for pharmaceutical companies were adhered to [13]. The manuscript was not seen or reviewed at any stage by Raptor Pharmaceuticals.

References

1. Gahl WA, Thoene JG, Schneider JA (2002) Cystinosis. N Engl J Med 347:111–121
2. Kalatzis V, Cherqui S, Antignac C, Gasnier B (2001) Cystinosin, the protein defective in cystinosis, is a H(+)-driven lysosomal cystine transporter. EMBO J 20:5940–5949
3. Emma F, Nesterova G, Langman C, Labbé A, Cherqui S, Goodyer P, Janssen MC, Greco M, Topaloglu R, Elenberg E, Dohil R, Trauner D, Antignac C, Cochat P, Kaskel F, Servais A, Wühl E, Niaudet P, Van't Hoff W, Gahl W, Levtchenko E (2014) Nephropathic cystinosis: an international consensus document. Nephrol Dial Transplant 29:iv87–iv94
4. Markello TC, Bernardini IM, Gahl WA (1993) Improved renal function in children with cystinosis treated with cysteamine. N Engl J Med 328:1157–1162
5. Van Stralen KJ, Emma F, Jager KJ, Jager KJ, Verrina E, Schaefer F, Laube GF, Lewis MA, Levtchenko EN (2011) Improvement in the renal prognosis in nephropathic cystinosis. Clin J Am Soc Nephrol 6:2485–2491
6. Langman CB, Greenbaum LA, Sarwal M, Grimm P, Niaudet P, Deschênes G, Cornelissen E, Morin D, Cochat P, Matossian D, Gaillard S, Bagger MJ, Rioux P (2012) 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 7:1112–1120
7. Langman CB, Greenbaum LA, Grimm P, Sarwal M, Niaudet P, Deschenes G, Cornelissen EA, Morin D, Cochat P, Elenberg E, Hanna C, Gaillard S, Bagger MJ, Rioux P (2014) 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 165:528–533.e1
8. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL (2009) New equations to estimate GFR in children with CKD. J Am Soc Nephrol 20:629–637
9. Bucknall T, Fossum M (2015) It is not that simple nor compelling! Comment on "Translating evidence into healthcare policy and practice: single versus multi-faceted implementation strategies—is there a simple answer to a complex question?". Int J Health Policy Manag 4:787–788
10. Levtchenko EN, van Dael CM, de Graaf-Hess AC, Wilmer MJ, van den Heuvel LP, Monnens LA, Blom HJ (2006) Strict cysteamine dose regimen is required to prevent nocturnal cystine accumulation in cystinosis. Pediatr Nephrol 21:110–113
11. Ariceta G, Lara E, Camacho JA, Oppenheimer F, Vara J, Santos F, Muñoz MA, Cantarell C, Gil Calvo M, Romero R, Valenciano B, García-Nieto V, Sanahuja MJ, Crespo J, Justa ML, Urisarri A, Bedoya R, Bueno A, Daza A, Bravo J, Llamas F, Jiménez Del Cerro LA (2015) Cysteamine (Cystagon(R)) adherence in patients with cystinosis in Spain: successful in children and a challenge in adolescents and adults. Nephrol Dial Transplant 30:475–480
12. Besouw M, Tangerman A, Cornelissen E, Rioux P, Levtchenko E (2012) Halitosis in cystinosis patients after administration of immediate-release cysteamine bitartrate compared to delayed-release cysteamine bitartrate. Mol Genet Metab 107:234–236
13. Wager E, Field EA, Grossman L (2003) Good publication practice for pharmaceutical companies. Curr Med Res Opin 19:149–154