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Received 1 April 2020
Revised 5 May 2020
Published Online First 27 June 2020

To cite: Liang H, Labbé A, Baudouin C, *et al*. *Br J Ophthalmol* 2021;**105**:608–613.

ABSTRACT

Background/Aims Cystinosis is a rare, autosomal recessive disorder causing defective transport of cystine out of lysosomes. Cystadrops (0.55% cysteamine hydrochloride in viscous solution) has been used on a named-patient basis to treat the accumulation of cystine crystals in the cornea in patients with cystinosis.

Methods Retrospective analysis of the Temporary Authorisation for Use cohort of 130 patients who received Cystadrops between 2013 and 2017 in France.

Results Patients received an average dosage of 3.3 (±0.94) instillations per eye per day. Over the duration of follow-up, of up to 45 months, patients maintained visual acuity scores of 0.0, which approximated normal. Corneal cystine crystal scores tended to decrease over time, stabilising after around 27 months between 1.22 and 1.87. Photophobia decreased within 3 months, stabilising on scores of around 1.5 and 1.7. 47 non-serious adverse reactions were reported, which were generally transient irritation, stinging or blurred vision. Four serious adverse events were reported, including keratitis and corneal ulcer, but these may have been caused by the underlying disease.

Conclusion This large safety cohort confirms the efficacy, safety and tolerability of Cystadrops in real-world clinical practice.

INTRODUCTION

Cystinosis is a rare recessive autosomal disorder affecting lysosomal storage of the amino acid cystine.[1] It affects about 1 person in 100–200 000 around the world[2] and approximately 1 in 330 000 in France, although in the Brittany region, there is an incidence of 1 in 25 000.[3]

In healthy people, cystine is transported through cellular membranes and out of the lysosomes by the transmembrane protein, cystinosin. In patients with cystinosis, mutations or defects in the cystinosin gene result in the accumulation of cystine crystals in the lysosome, which in turn results in eventual tissue damage, particularly in the kidneys, pancreas, brain, muscle, thyroid, testis and the eyes.[4] In the eyes, the accumulation of cystine crystals occurs in all ocular structures, including the cornea, the conjunctiva, the iris and also the retina causing symptoms of photophobia, blepharospasm and other serious complications.[5–7] These corneal crystals may be visible on ophthalmological investigation from around 16 months of age in most patients with cystinosis; indeed, this is a diagnostic sign of nephropathic cystinosis.[5 8] If untreated, patients develop increasingly severe photophobia and refractory blepharospasm, progressing eventually to involvement of the posterior segment of the eye with hypopigmentary mottling of the retinal pigment epithelium, peripheral corneal neovascularisation, band keratopathy, glaucoma and visual impairment.[7]

Patients with nephropathic cystinosis are treated with oral cysteamine. Cysteamine binds to cystine to form cysteine and cysteine–cysteamine mixed disulfhides, which can then be transported out of the lysosome.[1 9 10] Oral cysteamine has been clinically proven to slow the disease progression, increasing patients' life expectancies.[4] However, because of the poor vascular system in the cornea, oral cysteamine is ineffective in reducing the ocular accumulation of cystine crystals.[11] Topical cysteamine hydrochloride (CH) is therefore routinely administered to dissolve cystine crystals.[5] A 6.5 mg/mL (0.65%) CH solution—equivalent to 4.4 mg/mL (0.44%) cysteamine—(Cystaran; Sigma-Tau Pharmaceuticals, Gaithersburg, MD, USA) was approved for the treatment of corneal cystine accumulation in the USA in 2012.[12] However, the utility of this formulation is limited by its inconveniently frequent administration (of either every waking hour, or 6–12 times per day). In this formulation, cysteamine readily oxidises at room temperature, necessitating cold storage, which complicates its packaging and distribution.[12]

In the European Union, locally prepared 0.5% and 0.55% CH formulations have been used off-licence, but with limited efficacy, possibly because of the inconvenience of frequent administration which may have contributed to poor adherence.[13 14] In addition, difficulties in manufacturing a stable compound have limited new product approval in Europe.[15] In 2013, the French National Agency of Medicines Safety and Health Products granted a Temporary Authorisation for Use (ATU, 'authorisation temporaire d'utilisation') to Recordati Rare Diseases to provide named patients with 0.55% CH—equivalent to 3.8 mg/mL or 0.38% of cysteamine—viscous solution (Cystadrops, Recordati Rare Diseases, Puteaux, France). By using carboxymethylcellulose (carmellose) sodium as a viscous agent, the duration of contact of the active ingredient with the surface of the eye could be extended, reducing the need for frequent administration down to four times per day. The chemical stability of the formulation was also improved, allowing the 0.55% CH drops to be kept at

room temperature for up to 7 days after opening, although refrigeration is still required for long-term storage. This formulation was shown to be more effective than standard CH preparations, and with considerable convenience advantages.[16 17] In a pivotal phase III comparative study, the 0.55% CH viscous formulation reduced corneal crystal density by 40% compared with a 0.10% CH formulation at 90 days ($p<0.0001$), and with a decrease in crystal density in all corneal layers. The formulation was generally well tolerated, with adverse events being mild stinging and burning.[17] These are typical symptoms with all ocular cysteamine formulations.[8] On the basis of the phase III study efficacy and safety results, as well as the pharmacovigilance record from analysis of the ATU cohort follow-up, this formulation, under the commercial name Cystadrops was approved for use in the European Union in 2017.[18] This manuscript presents the final safety and efficacy results from the ATU cohort of patients receiving Cystadrops from September 2013 until the granting of the marketing approval in June 2017.

Materials and methods

This is a retrospective qualitative observational analysis of the ATU pharmacovigilance cohort of patients with cystinosis in France. The qualitative report monitored the use of Cystadrops on a named-patient basis in patients with cystinosis in advance of its marketing authorisation. The ATU cohort included 130 patients with cystinosis from all regions in France who had been granted permission to receive Cystadrops 0.55% CH in viscous solution between 24 September 2013 and 16 June 2017. This qualitative report included a comparative analysis of a second group of patients (N=3) who had been added to the ATU cohort between 24 December 2016 and 16 June 2017. The ATU cohort enrolled patients older than 2 years of age with a diagnosis of cystinosis who had been prescribed Cystadrops on a named-patient basis and who had undergone an ophthalmological assessment with slit-lamp examination of crystal density, and assessments of visual acuity and photophobia.[19] There was no washout period following use of a different cysteamine formulation to avoid a potentially dangerous treatment interruption. Patients were seen every 3 months or more frequently if necessary. However, the duration of the follow-up was different for each patient depending upon when they joined the ATU cohort. The primary outcome was to assess adverse events. Ophthalmic evaluation included assessments of

1. visual acuity (measured using the LogMAR scale from +2.3 to −0.3),
2. the Cystinosis Corneal Crystal Score (CCCS) developed by Gahl *et al*[5] and
3. the severity of photophobia (from 0 to 5).[19]

Patients or their parents were informed about this inclusion by their treating physician and all gave informed consent. Recordati Rare Diseases registries and sharing of personal patient information were authorised for the ATU cohort by the 'Commission Nationale Informatique et Libertés' (ATU number: 34009 589 332 71).

RESULTS

Patient and disease characteristics at baseline

The patient cohort was evenly divided between men (49.2%) and women (50.8%). The mean age (±SD) at the time of the prescribed ATU request was 19.5 (±13.8) years, with a median of 17 years (range: 2–78). Patients under the age of 18 years were relatively evenly distributed across age categories: 24 patients between 2 and 6 years (18.5%); 17 patients (13.1%) between 6 and 12 years, and 25 patients (19.2%) between 12 and 18 years (table 1).

Mean age at diagnosis was available for 125 patients. Average age at diagnosis was 3.3 (±8.1) with a median of 1 year (range: 0–76 years). In 92.8% (N=116) of the patients, diagnosis was made before the age of 12. This type of cystinosis presenting in childhood is the most common and the most severe form of the disease, accounting for over 95% of cases.[4 20] One patient in this cohort was diagnosed with cystinosis at the age of 76, which is indicative of the late form of the disease, presenting with only ophthalmic symptoms. The mean time between diagnosis of cystinosis until the ATU prescription request (available for 125 patients) was 15.6 (±12.3) years, with a median of 14 years (range: 0–54 years).

In terms of previous ophthalmic treatment with cysteamine prior to inclusion in the ATU cohort, 14 patients had received no prior cysteamine eye-drops and 89.2% had received a cysteamine eye-drop formulation. In 24.1% of the patients, prior therapy was with a hospital preparation of CH 0.1% solution; in 70.7% of the patients, the CH concentration was not specified. It was most likely a 0.1% solution as this was commonly prepared in France. One patient had previously received Cystaran in the US, and three patients had received Cystadrops prior to joining the cohort (table 1). Duration of treatment prior to inclusion was on average 12.8 (±9.1) years, with a median of 10.7 years (range: 0–36.7). The prescribed average dosage was 4.9 (±1.93) instillations per eye per day, with a median of 4 (range: 1–12). Forty-six per cent (N=52) received more than four instillations per day, of whom, four patients received 10–12 drops per day.

On ophthalmic evaluation before inclusion to the ATU cohort, patients had a mean (± SD) visual acuity of 0.13 (±0.28) with a median of 0.0, which corresponds to normal vision; a mean CCCS of 22.13 (±0.72), with a median of 2.00 illustrating a high density of corneal crystals; and a mean photophobia score of 2.16 (±1.34) with a median of 2.00, which corresponds to mild-to-moderate discomfort with light.

In the ATU cohort, the majority of patients (65.1%) received a first prescription of four instillations per day (table 2).

Since the start of the ATU cohort, data from 239 follow-up visits for 85 patients were collected, and 59 patients had more than one visit. After initiation of Cystadrops, the average number instillations was 3.3 (±0.94) with a median of 4.0. More than half (55.4%) received the recommended dosage of 4 drops per eye per day, with 43.4% receiving dosages ranging from 1 to 3 drops per eye per day.

Evolution of ocular parameters on Cystadrops

In three patients, the treatment duration could not be calculated due to missing data; hence, the analysis was restricted to 82 patients and 164 eyes (table 3).

Adverse events

Of the 130 patients in the ATU cohort, 25 patients reported a total of 47 adverse events (4 serious and 43 non-serious) (table 4).

The most commonly reported adverse events were labelled as 'eye disorders' and accounted for 89.1% of the adverse events, and were reported by 29.5% of the patient cohort. Among these side effects, 'eye irritation' accounted for 29.8% of adverse events, reported by 10% of patients. 'Eye pain' accounted for 17%, occurring in 5.4% of patients and 8.5%

Table 1 Patient demographics and characteristics (N=130)

Characteristics (N=130)		Treatments (N=116)*		Outcomes (N=130)	
Sex		Previous treatment		Visual acuity: log scale	
Female	66 (50.8%)	Cystadrops	3 (2.6%)	N (missing)	230 (30)
Male	64 (49.2%)	Cystaran	1 (0.9%)	Mean (SD)	0.13 (0.28)
		Cysteamine 0.1%	28 (24.1%)	Median (range)	0.00 (–0.52* to –2.00)
		Unspecified cysteamine concentration	82 (70.7%)		
		Unnamed cysteamine treatment	2 (1.7%)		
Age at ATU prescription request (years)		Previous treatment period (years)		Cystinosis Corneal Crystal Score	
NOT	130	N (missing data)	112 (4)	N (missing)	180 (80)
Average (±SD)	19.5 (±13.8)	Mean (SD)	12.8 (9.1)	Mean (SD)	2.13 (0.72)
Median (range)	17.0 (2.0–78.0)	Median (range)	10.7 (0.0–36.7)	Median (range)	2.00 (0.00–3.00)
Age at ATU prescription request (years)		Frequency of instillations per day per eye		Photophobia	
2–6	24 (18.5%)	Missing data	3	N (missing)	250 (10)
6–12	17 (13.1%)	1	2 (1.8%)	Mean (SD)	2.16 (1.34)
12–18	25 (19.2%)	2	7 (6.2%)	Median (range)	2.00 (0–5)
≥18	64 (49.2%)	3	10 (8.8%)		
		4	42 (37.2%)		
		5	11 (9.7%)		
		6	30 (26.5%)		
		8	7 (6.2%)		
		10	2 (1.8%)		
		12	2 (1.8%)		
Age at diagnosis (years)		Number of instillations per day per eye			
N (missing)	125 (5)	N (missing)	113 (3)		
Mean (SD)	3.3 (8.1)	Mean (SD)	4.9 (1.93)		
Median (range)	1.0 (0.0–76.0)	Median (range)	4.0 (1–12)		
Age stratification at diagnosis (years)					
Missing data	5				
0–1	38 (30.4%)				
1–2	40 (32.0%)				
2–6	28 (22.4%)				
6–12	10 (8.0%)				
12–18	5 (4.0%)				
≥18	4 (3.2%)				
Disease duration (years)					
Missing data	125 (5)				
Mean (SD)	15.6 (12.3)				
Median (range)	14.0 (0.0–54.0)				

*Fourteen patients did not receive ophthalmic treatment with cysteamine before initiating treatment Cystadrops.
ATU, Temporary Authorisation for Use.

of adverse events were labelled as 'blurred vision', occurring in 3.1% of patients.

Eight patients temporarily interrupted Cystadrops, in two cases because of adverse events. One of these patients reported redness, tingling, burning and blurred vision, and the other patient described burning and pain with treatment. The other reasons for temporary discontinuation included an administration difficulty with one patient; pollen allergy; hospitalisation due to septic shock; and going on holiday as the reason for discontinuation in the remaining three cases. Two patients permanently discontinued treatment due to adverse events related to Cystadrops. One of these cases was because of repeated keratitis followed by corneal ulcer, and the other was because of persistent local intolerance. One patient was lost to follow-up. Two patients discontinued, one for personal reasons before recommencing at 4 instillations per day per eye. Three patients died during the observation period. One patient died of cardiac arrest following cardiomyopathy with chronic pulmonary arterial hypertension. One patient died following an infection. The third patient died in a foreign country of severe dehydration. None of these events were considered to be linked to Cystadrops treatment.

DISCUSSION

The ophthalmic efficacy results from this qualitative safety cohort of patients with cystinosis receiving the Cystradrops formulation of 0.55% CH in viscous carmellose sodium solution suggest that these patients had either a progressive improvement in ocular signs and symptoms of cystinosis over time, or they experienced a stabilisation of ophthalmic symptoms. No worsening of visual acuity was reported over time with Cystadrops treatment, which is a particularly important finding given that cystinosis is a progressive disease. The ATU cohort showed a slight decrease in CCCS over time compared to baseline, which again is a clinically meaningful finding for this progressive disease. A corresponding improvement in photophobia scores, reported within several months of starting treatment, illustrates that in addition to stabilising clinical signs, Cystadrops also improved clinical symptoms,

Table 2 Cystadrops treatment

Cystadrops treatment prescribed on request	Total (N=130)
Frequency of instillations per day and per eye	
N (missing)	1
1	1 (0.8%)
2	13 (10.1%)
3	28 (21.7%)
4	84 (65.1%)
5	2 (1.6%)
6	1 (0.8%)
Number of instillations per day per eye prescribed	
N (missing)	129 (1)
Mean (SD)	3.6 (0.76)
Median (range)	4.0 (1–6)
Cystadrops treatment during follow-up	**Total (N=85)**
Frequency of instillations per day and per eye	
N (missing)	2
1	5 (6.0%)
2	11 (13.3%)
3	20 (24.1%)
4	46 (55.4%)
5	1 (1.2%)
Number of instillations per day per eye prescribed	
Missing (N)	83 (2)
Mean (SD)	3.3 (0.94)
Median (range)	4.0 (1–5)

and thus potentially also helps improve patient quality of life relatively soon after starting treatment. Some patients were treated for over 44 months, suggesting that improvements were sustained over the long term, which is another particularly significant finding as untreated cystinosis results in the slow progressive deterioration of ocular faculties as cystine crystals accumulate in the eye.

These efficacy results are particularly interesting given that several previous studies that have only shown very limited efficacy of topical cysteamine in the treatment of severe corneal cystinosis.[21 22] The study by MacDonald *et al*[21] showing no efficacy in four patients receiving a 0.3% cysteamine solution in normal saline is arguably of limited relevance, because the study is 30 years old and used a significantly different formulation to the 0.55% CH in viscous solution used in the present report. These traditional formulations have inconsistent efficacy, possibly due to oxidation of cysteamine and poor absorption because of the short period that aqueous eye-drops remain on the cornea.[13–15] Conversely, Cystadrops are industrially produced, ensuring consistency of formulation, and the viscous solution prolongs the precorneal residence time of the cysteamine.[17] Al-Hemidan *et al* showed in their study, in 32 patients with nephropathic cystinosis receiving an in-house preparation of 0.55% cysteamine eye-drops instilled five to six times per day, that the improvement in photophobia was not clinically significant and that patients displayed statistically significant worsening of corneal cystine deposits.[22] A factor to bear in mind is that patients with cystinosis have multiple organ dysfunction, and compliance with frequent topical treatment is difficult to maintain, particularly in the very young. Cysteamine is used to decrease the corneal crystal load, but it is not effective in treating severe complications such as neoVx or band keratopathy, which require different treatments. Thus, for those patients who had more severe conditions, the therapeutic response would have been insufficient. However, in early and moderate stages, the previous study has shown efficacy in reducing the crystal load, thus decreasing the risk of irreversible corneal complications.[17]

Table 3 Results of ophthalmic evaluations over the duration of treatment for patients with at least one follow-up visit (N=eyes)

	Duration of treatment								
	Start N=164	0–3 months N=30	3–9 months N=102	9–15 months N=64	15–21 months N=78	21–27 months N=58	27–33 months N=50	33–39 months N=34	39–45 months N=8
Visual acuity: Log scale									
N (missing)	148 (16)	26 (4)	94 (8)	64 (0)	78 (0)	58 (0)	50 (0)	34 (0)	8 (0)
Mean (± SD)	0.14 (±0.31)	0.01 (±0.19)	0.09 (±0.28)	0.11 (±0.34)	0.04 (±0.16)	0.05 (±0.19)	0.07 (±0.16)	0.06 (±0.14)	0.00 (±0.00)
Median (range)	0.00 (−0.15–2.00)	0.00 (−0.25–0.50)	0.00 (−0.25–1.00)	0.00 (−0.25–1.30)	0.00 (−0.20–0.70)	0.00 (−0.10–1.30)	0.00 (0.00–1.00)	0.00 (0.00–0.70)	0.00 (0.00–0.00)
Cystinosis Corneal Crystal Score (CCCS)									
N (missing)	120 (44)	29 (1)	88 (14)	55 (9)	70 (8)	51 (7)	48 (2)	34 (0)	8 (0)
Mean (SD)	2.19 (±0.64)	2.19 (±0.75)	1.99 (±0.77)	1.91 (±0.77)	1.84 (±0.89)	2.01 (±0.82)	1.87 (±0.76)	1.84 (±0.79)	1.22 (±0.67)
Median	2.00	2.25	2.00	2.00	2.00	2.00	2.00	2.00	1.13
Range	0.5–3.0	0.5–3.0	0.00–3.0	0.25–3.0	0.00–3.0	0.50–3.0	0.25–3.0	0.25–3.0	0.50–2.25
Photophobia									
N (missing)	160 (4)	28 (2)	96 (6)	61 (3)	74 (4)	51 (7)	48 (2)	34 (0)	8 (0)
Mean (SD)	2.19 (±1.34)	1.46 (±0.92)	1.77 (±1.22)	1.64 (±1.24)	1.70 (±1.33)	1.51 (±1.04)	2.17 (±1.33)	1.53 (±1.05)	1.75 (±0.89)
Median	2.00	1.00	2.00	2.00	2.00	1.00	2.00	1.00	1.50
Range	0–5	0–4	−0–5	0–4	0–5	0–5	0–5	0–3	1–3

In the ATU cohort, the average visual acuity score decreased over time and tended to 0.0, which corresponds to normal sharpness of vision. Mean CCCS scores tended to decrease over time, stabilising after around 27 months of treatment, between 1.87 and 1.22 with a median of 2.0. Photophobia decreased after 0–3 months and stabilised around 1.7 and 1.5 over time.
ATU, Temporary Authorisation for Use.

Table 4 All adverse events (N=130)

	Preferred term	Patients (%)
Eye disorders	Eye irritation (burning)	13 (10)
	Eye pain (tingling, itchy)	7 (5.4)
	Blurry vision	4 (3.1)
	Ocular hyperaemia	3 (2.3)
	Keratitis	1 (0.8)
	Ulcerative keratitis	1 (0.8)
	Eye deposit	2 (1.5)
	Increased lacrimation	1 (0.8)
	Itching of the eye	1 (0.8)
	Dry eye	1 (0.8)
	Glare	1 (0.8)
	Ocular discomfort (cornea)	1 (0.8)
	Ocular discomfort	1 (0.8)
General disorders and administration site	Discomfort at instillation site	3 (2.3)
	Drug intolerance	1 (0.8)
Psychiatric disorders	Psychiatric disorders	1 (0.8)
Death (not considered related to the medication)	Death (unrelated causes)	3 (2.3)

In the present report, Cystadrops was found to be safe and generally well tolerated. It also improved the daily lives of patients by requiring fewer instillations per day. Side effects that had been reported previously in the clinical trial programme[16 17] were considered as 'expected'. Cumulatively, 42 adverse effects were reported in the ATU cohort. Four were classified as 'serious and unexpected', 1 was 'unexpected and non-serious' and the remaining 37 were 'expected' adverse events, such as mild stinging, redness and blurred vision, which have been reported previously with this class of treatment and are generally mild and transient.[13 16] These transient events are thought to be due to the increased viscosity, increasing the residence time of the CH, and possibly because of the higher concentration.[23] One patient experienced blurred vision on application of Cystadrops, which recurred with each application preventing the patient from driving and resulting in discontinuation. In terms of non-ocular adverse events, one case of 'psychiatric conditions' was reported. 'Non-expected' side effects included keratitis, corneal ulcer and psychotic disorders. These events were not considered to be related to the cohort medication, and in the case of keratitis, this is an established complication of cystinosis.[6]

Although this observational cohort is limited in that it was a retrospective, non-interventional clinical data analysis, given the rarity of this disease and the lack of availability of an approved and effective commercial preparation in some parts of the world, this qualitative report may be of particular interest to nephrologists and ophthalmologists in countries where Cystadrops is only available on a named-patient basis or where the only treatment possibilities are hospital preparations of CH. It has been estimated that there are some 184 patients currently receiving Cystadrops outside of Europe.

CONCLUSION

This qualitative cohort analysis, reporting on 130 cystinosis patients in France until June 2017 who were receiving Cystadrops to manage the accumulation of cystine crystals in the cornea, confirmed that the demographic data and ophthalmic parameters were generally consistent within the cohort and with data from the Cystadrops clinical trial populations. Analysis of 239 follow-up visits, with patients receiving a median of 4 instillations per eye per day confirmed that Cystadrops has a sustained efficacy on ophthalmic parameters, maintaining visual acuity, improving cystine corneal crystal scores, and improving photophobia. Cystadrops was found to be safe and well tolerated, with a total of 47 non-serious adverse reactions being reported. Corneal ulcer and keratitis were serious adverse events but were not thought to be related to the cohort drug. This large cohort confirms the safety and tolerability of Cystadrops in real-world clinical practice.

Correction notice This paper has been corrected since it was published online. Two small changes were made to table 2.

Acknowledgements The authors would like to thank Recordati Rare Diseases for providing the cohort medication and for offering unrestricted access to all data required for this analysis. The authors are also grateful to Guy Ramsay for providing editorial assistance in the preparation of this manuscript.

Contributors All listed authors contributed to the conception or design of this study; or the acquisition, analysis or interpretation of patient data; drafted or revised the work critically; and approved this version to be published. HL and VG are responsible for the overall content as guarantors. Guy Ramsay provided editorial assistance.

Funding No specific grant or funding from any source or agency was received for this work.

Competing interests HL has received speaker honoraria from Recordati Rare Diseases, HL has received research funding from October-1 and CHOC clinical trials honoraria. AL has received speaker honoraria from Recordati Rare Diseases, and research funding from October-1 honoraria. CB has received honoraria from Orphan Europe. CP and VG are both employees of Recordati Rare Diseases.

Patient or parental consent for publication Not required.

Data sharing statement Data are available in a public, open-access repository. Data are available upon reasonable request.

Data availability statement The data that supports the findings of this study are available from the corresponding author, HL, upon reasonable request and upon approval of Recordati Rare Diseases, CP.

Provenance and peer review Not commissioned.

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