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Research article

Examining Patient Outcomes after the End of the Suitability of Nitisinone in Alkaptonuria 2 Study Employing Questionnaires

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Abstract

Introduction: The Questionnaire Follow-up study (Q-FU study) was designed to collect information on study drug access post-study as well as impact on pain symptoms both in those who received nitisinone as well as those who did not receive nitisinone. Patients and methods: Only UK and Slovak SONIA 2 patients, controls and nitisinone groups, participated in the present postal questionnaire study. Responses were analysed simple descriptive statistics. Results: 37 participants responded to the questionnaires in the Q-FU study. The proportions accessing nitisinone in the control and nitisinone groups in Q-FU study were 14.3 & 30% in the Liverpool site and 62.5 and 80% in the Piešťany site. The proportion gaining access to nitisinone in the combined control group after SONIA 2 completion, was low at 31.8%. The self-declared pain in the combined control group (Liverpool & Piešťany) decreased or stayed the same in equal proportion among those accessing nitisinone, with these changes occurred within 2 months of starting nitisinone. In the combined nitisinone group after SONIA 2 nitisinone access was 46.7%. The subjective pain experiences in the combined nitisinone group of the Q-FU study before access to nitisinone showed more of an increase while also showing a decrease in those regaining access to nitisinone. Conclusion: Participants accessed nitisinone post-study even prior to regulatory approvals due to proactive actions from the team. Participants noted an increase in pain when they stopped nitisinone at end of SONIA 2, and those able to access nitisinone post-study found relief in pain, both occurring within weeks.

Key words: Alkaptonuria, nitisinone, access, questionnaire

Introduction

An international, multicenter, randomized, evaluator-blinded, no-treatment controlled, parallel-group study to assess the efficacy and safety of once daily nitisinone for 4-years in patients with alkaptonuria was carried out between 2014 and 2019 [1]. A total of 138 AKU patients were recruited into SONIA 2. 69 AKU patients administered nitisinone 10 mg daily for 4 years in the treatment arm and 69 AKU patients were allocated to the no-treatment arm, also followed up over 4 years. Nitisinone was withdrawn once the 4-year study participation was completed. The marketing authorization for nitisinone in AKU was granted by the European Medicines Agency in September 2020 following the beneficial results of SONIA 2, which showed sustained decrease in urine HGA at 12 months (99.7% decrease achieved) as well as demonstration of trends in clinical benefit from nitisinone [2].

Alkaptonuria (AKU) (frequency <1 in 250,000) is a genetic error of metabolism in the breakdown of tyrosine, resulting from a deficiency of the enzyme homogentisic oxidase. It is charac-

terised by accumulation of homogentisic acid (HGA) and related compounds in body fluids and massive urinary excretion of HGA. Accumulation of HGA leads to the formation of a benzoquinone polymer (BQA) catalysed by the enzyme polyphenol oxidase. The polymer accumulates in the tissues leading to pigmentation (ochronosis) and tissue damage [3]. Ochronotic pigment is deposited in connective tissues and lead to damage [4]. The accumulation of HGA-pigment leads to symptomatic early-onset and severe joint disease, affecting predominantly the spinal column, hips and knees. Similarly, accumulation of HGA in the sub endothelial tissues of the aortic valve leads to fibrosis, calcification and deformity of the valve, sometimes requiring valve replacement. Renal and urinary stones and rupture of the Achilles tendon have also been associated with AKU. An assessment of severity tool namely the AKU Severity Score Index or AKUSSI can provide semi-quantitative data on disease burden [5,6]. In addition to dietary restriction of protein, antioxidant measures employing ascorbic acid, analgesia, and palliative surgery, the first HGA-lowering therapy employing nitisinone was tested in the Suitability of Nitisinone in Alkaptonuria 2 study (SONIA 2) after showing promise in real-world data analysis from the UK National Alkaptonuria Centre [7,8].

Patients had to obtain nitisinone upon returning to their countries. The main objective of the current Questionnaire Follow-up study (Q-FU study) was to collect information regarding their health from patients completing SONIA 2 study, both those who received nitisinone as well as those who did not receive nitisinone. This was via a questionnaire on a single occasion only, to collect information on their health status since completing participation in SONIA 2.

Patients and Study Design

Q-FU study is cross-sectional in design. 110 AKU patients completed all visits in the SONIA 2 study at present out of 138 recruited after 4 years of participation and only these were eligible to participate in the current Q-FU study (Figure 1). Of the three study sites in SONIA 2, namely Liverpool (UK), Piešťany (Slovakia) and Paris (France), only UK and Slovak patients participated in the present study. The SONIA 2 study centres in UK and Slovakia recruited 41 and 65 patients out of the total of 138 initially recruited. Questionnaires, for those who received nitisinone in SONIA 2, as well as those who did not receive nitisinone, were administered. Questionnaires were posted between 19th September and 19th December 2019, and responses received between 26th September and 27th August 2020. Questionnaires were translated into the language of the patient. Questionnaires were posted to patients along with a return-addressed stamped envelope. Responses were collected in Liverpool. Responses were then analysed. Simple descriptive statistics was used to assess responses.

The Q-FU study used the pain scores from SONIA 2 study at baseline and at the end of 4 years of study [1]. The musculoskeletal system was evaluated for symptoms (pain) in 14 joint areas (hips, knees, ankles, feet, shoulders, elbows and hands) and 4 spine areas (cervical, thoracic, lumber and sacroiliac); a score of 1 was given for presence of pain in the joint areas within the previous week and a score of 2 was given for pain in spine areas similarly. The pain scores used in the Q-FU study was the combined joint and spine pain scores.

Ethics approval was obtained in Liverpool (UK) to carry out the Questionnaire study to analyse data from UK and Slovak

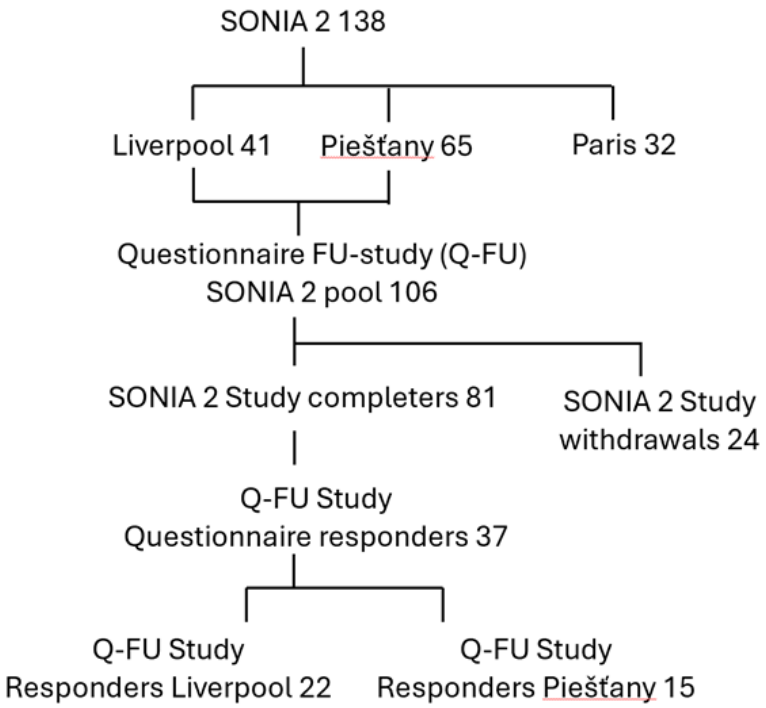

Figure 1: CONSORT Flow diagram for the Q-FU study

sites in January 2020. Informed consent was obtained from all participating patients (UK REC 19/EM/0204; UK IRAS project ID – 262550).

Results

The three study sites in SONIA 2 recruited 138 patients with Liverpool, Piešťany and Paris contributing 41, 65 and 32 respectively. Liverpool and Piešťany patients participating in the SONIA 2 Questionnaire Follow-up study (Q-FU), provided a potential pool of 106 (Figure 1). Since there were 24 patient withdrawals in SONIA 2 this then left a potential number of 81 patients, to whom questionnaires were sent. The questionnaires sought responses to success in obtaining nitisinone post-SONIA 2 from controls and nitisinone-treated eligible SONIA 2 patients, as well as their symptoms (pain). In the control group the main issue was to assess what effect the obtained nitisinone had on the pain, whereas in the nitisinone group the focus was to document what effect discontinuing nitisinone immediately after SONIA 2 had on the pain.

Out of 81 SONIA 2 completers, 37 responded to the questionnaires in the Q-FU study, 22 from those attending the Liverpool site and 15 from the Piešťany site, an overall response rate of 45.7%. The responder rate was 53.7 and 30.6% respectively in the Liverpool and Piešťany sites. All the study activities were carried out at the Liverpool site, such as posting the questionnaires, receiving the responses, collecting and analysing the data.

The age at baseline in the control and nitisinone groups in the Liverpool, Piešťany and combined sites is shown in Table 1 and were similar. Overall, there were 10 males and 12 females in the control group and 9 and 6 respectively in the nitisinone group. Baseline pain scores were comparable in the control and nitisinone groups in the Q-FU study with all patients having positive pain score. As already published in the SONIA 2 publication [1], pain scores at end of SONIA 2 study were lower than at the baseline, and this was also true of the responders in the Q-FU study.

Nitisinone was only provided for the nitisinone group in SONIA 2 until the end of four years of study. In the Q-FU study it was found that 31.8% of controls and 46.7% of nitisinone treated groups from SONIA 2 managed to obtain nitisinone locally post-SONIA 2 (Table 2). The proportions accessing nitisinone in the control and nitisinone groups in Q-FU study were 14.3 & 30% in the Liverpool site and 62.5 and 80% in the Piešťany site, while noting that the number of patients gaining access was greater for the Liverpool site.

The proportion gaining access to nitisinone in the combined control group after SONIA 2 completion i.e., the Q-FU study,

Table 1: Demographic and pain scores in Questionnaire Follow-up study

Study sites	Age at baseline yrs	Male/ Female	Baseline Pain score *	End study Pain score *				
	Controls	Nitisinone	Controls	Nitisinone	Controls	Nitisinone	Controls	Nitisinone
Liverpool	47.1±10.2	49.3±14.7	8/6	7/3	9.6±4.2	10.9±5	8.1±5.7	5.9±3.5
Piešťany	50.1±9.5	51.4±14.1	2/6	3/4	8.9±5.1	11±5.2	10.4±7	8.8±6.4
Combined	48.2±9.8	50±14	10/12	10/7	9.3 ±4.4	10.9±4.9	8.9±6.1	6.9±4.6

*Refers to pain scores from the original SONIA 2 study but only including patients in the Q-FU study cohort

Table 2: Access to and effects of nitisinone in Questionnaire Follow-up study in Control group

Study sites	Access to nitisinone	Pain post-SONIA 2 *	Pain post-SONIA 2 after nitisinone access **	Change analgesia medications after nitisinone
	Controls	Controls	Controls	Controls
Liverpool	14.30%	I =42.9%	S = 66.7%	S=28.6%
		D = 7.1%	NA=33.3%	NA=71.4%
		S = 7.1%		
		NA=42.9%		
Piešťany	62.50%	D = 12.5%	D = 60%	I=12/5%
		S = 62.5%	S = 40%	D=25%
		NA=25%		S=37.5%
				NA=25%
Combined	31.80%	I =27.3%	S = 40%	I=4.5%
		D = 4.5%	D = 37.5%	D=9%
		S = 27.3%	NA=22.5%	S=31.8%
		NA=40.9%		NA=54.5%

D = decreased; I = increased; S = same; NA = no response

* Change in pain within 8 weeks of end of study, ** Change in pain within 8 weeks of access to nitisinone

Table 3: Access to and effects of nitisinone in Questionnaire Follow-up study in Nitisinone group

Study sites	Access to nitisinone	Pain post-SONIA 2 *	Pain post-SONIA 2 after nitisinone access **	Change analgesia medications
	Nitisinone	Nitisinone	Nitisinone	Nitisinone
Liverpool	30%	I = 10%	I = 33.3%	I=10%
		S = 20%	D = 33.3%	S=20%
		NA = 70%	S = 33.3%	NA=70%
Piešťany	80%	I = 57.1%	D = 80%	I=28.6%
		NA=42.9%	S = 20%	D=14.3%
Combined	46.70%	I = 29.4%	I = 13.3%	I-17.6%
		S =11.8%	D = 66.7%	D=5.9%
		NA = 58.8%	S = 20%	S=17.7%
				NA=58.8%

D = decreased; I = increased; S = same; NA = no response
*Change in pain within 8 weeks of end of study
** Change in pain within 8 weeks of access to nitisinone

was 31.8%. The self-declared pain in the combined control group (Liverpool & Piešťany) after end of SONIA 2 study participation either increased or stayed the same in roughly equal proportions, while noting no response from some participants. In this combined control group (Liverpool & Piešťany) pain decreased or stayed the same in equal proportion among those accessing nitisinone, with these changes occurred within 2 months of starting nitisinone; the change in analgesic medications either remained the same or decreased in those providing a response (Table 2).

The proportion gaining access to nitisinone in the combined nitisinone group after SONIA 2 completion i.e., the Q-FU study, was higher than in the control group at 46.7%. The subjective pain experiences in the combined nitisinone group of the Q-FU study before access to nitisinone showed mostly an increase in those where there was a response (Table 3). This group reported the majority showing a decrease in those regaining access to nitisinone, with these changes occurred within 2 months of starting nitisinone; the change in analgesic medications either remained the same or increased in those providing a response.

Discussion

There is a strong school of thought that access to study drugs after completion of participation in a drug trial should be made available [9,10]. During SONIA 2 study it was possible to provide the study drug nitisinone only for the duration of the study period. This was because of the potential for adverse events in the event nitisinone was provided since it was not possible to monitor these patients' post-participation. Specifically, there was a 14.5% prevalence of painful corneal keratopathy during SONIA 2 where diet of patients was not adjusted to minimise tyrosinaemia; however, these patients had slit-lamp examinations and 6-monthly questionnaires to monitor safety. This was not possible after SONIA 2 with no possibility of ensuring safety if just given access to the study drug and hence nitisinone was not provided upon completion of SONIA 2.

Nitisinone was only provided for the nitisinone group per-protocol in SONIA 2 until the end of four years of study, namely January 2019. European Medicines Agency approved nitisinone for alkaptonuria in September 2020 [2] followed by European Commission in October 2020 [11] to make nitisinone 10mg daily available for adults with alkaptonuria. In the Q-FU study, which included only data from the Liverpool and Piešťany site it was found that 31.8% of controls and 46.7% of nitisinone-treated groups managed to obtain nitisinone locally after SONIA 2 which is gratifying. (Table 2). The proportions accessing nitisinone in the control and nitisinone groups at the Liverpool site were14.3% and 30%, while those at the Piešťany sites were 62.5% and 80%, while noting that the responder number was lower at the Piešťany site. It is therefore gratifying that many SONIA 2 participants were able to access nitisinone in their home countries even prior to securing regulatory approvals. AKU patients in the UK were already attending the UK National Alkaptonuria Centre (NAC) and it was unethical to recruit these to SONIA 2 (and therefore also for the Q-FU study) given the risk of placing these patients in the no-nitisinone arm as they would have been eligible to receive nitisinone in the NAC. Therefore, most patients in Q-FU study were non-UK, including those who attended the Liverpool site. To address nitisinone access post-SONIA 2, the pharmaceutical partner in SONIA 2, Swedish Orphan Biovitrum (Sobi), undertook the MoCA process (mechanism of coordinated access to orphan medical products) to facilitate access by engaging with European stakeholders [12].

The Q-FU study was a postal questionnaire study. The overall response rate of 45.7% in the Q-FU study was acceptable for a postal questionnaire study. An earlier identification study caried out by the lead investigator yielded a response rate of 18.2% [13]. One postal survey reported a response rate of 29.5% [14], while another reported an increase in response to repeated mailing so that at third mailing the response rate was 55.4% [15]. Others support the use postal questionnaire studies compared to studies collecting data online [16,17]. The responder rate was 53.7 and 30.6% respectively in the Liverpool and Piešťany sites. All the study activities were carried out at the Liverpool site, such as posting the questionnaires, receiving the responses, collecting and analysing the data. Recent publications suggest that on-line surveys yield higher responses rates and are also easier to re-administer.

The age at baseline in the control and nitisinone groups in

the Liverpool, Piešťany, and combined sites was similar and is shown in Table 1. Overall, there were 10 males and 12 females in the control groups, and 9 and 6 respectively in the nitisinone group in the Q-FU study. Baseline pain scores recalculated for the groups excluding Paris in the Q-FU study showed that all patients had a positive pain score. Like the full data set from SONIA 2, this abbreviated Q-FU study dataset also showed that pain score at end of SONIA 2 study was lower than those at baseline [1].

The self-declared pain experiences in the combined control group of the Q-FU study before access to nitisinone showed in equal proportion an increase or remaining the same in those where there was a response (Table 2); in the combined nitisinone group of the Q-FU study, almost equal proportions showed a decrease or no change in those gaining access to nitisinone, with these changes occurred within 2 months of starting nitisinone; likewise, the change in analgesic medications either remained the same or decreased in those providing a response.

In the combined nitisinone group of the Q-FU study before access to nitisinone, more showed an increase in subjective pain in patients providing a response (Table 3). This group reported mostly a decrease in pain in those regaining access to nitisinone, with these changes occurred within 2 months of starting nitisinone; the change in analgesic medications either remained the same or increased in those providing a response. It has been reported already 1 that nitisinone group was older and had more severe disease at baseline than the control group and may explained the analgesia requirements even in the Q-FU study.

There were limitations in the data. This was a study where a postal questionnaire was administered only once, and practicalities such as obtaining further ethics approvals and related logistics meant that these patients could not be resurveyed. The original SONIA 2 study even though is the largest ever conducted in this field of inherited metabolic diseases was still small compared to other reported questionnaire studies [18]. Like many questionnaire studies there was a problem with incomplete responders and responses. With most participants being from outside UK, care was taken to use suitably translated questionnaires to minimise barriers due to language and understanding. Even though the Q-FU study was initiated during the completion of SONIA 2, the eventual study only concluded sometime after the end of SONIA 2 and we cannot exclude difficulties in recalling information requested in the questionnaires.

In summary, accessing study drug nitisinone post-trial proved less difficult than anticipated within the initial eighteen months of the post-SONIA 2 period when this Q-FU study was conducted, assisted by planning by the consortium to address this issue. Participants noted an increase in pain when they stopped nitisinone at end of SONIA 2, and those able to access nitisinone post-trial found relief in pain, both occurring within weeks.

Author Contributions

LRR – pioneered the idea, secured funding, and managed the study, drafting manuscript and final approval of the manuscript.

MK assessed SONIA 2 patients and edited the manuscript.

HB and EL sent and received questionnaires, organized the data for suitable analyses, edited and approved the manuscript.

RI assisted with conduct of the SONIA 2 study in Piešťany, organizing the questionnaires for the Slovak patients, drafting manuscript and final approval of the manuscript.

NS was involved in drafting and approving the manuscript.

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We thank the substantial number of people (too many to name individually) for their invaluable support during SONIA 2.

Data Sharing Statement for SONIA 2

Granting SONIA 2 data access will be considered in response to qualified research requests. All de-identified individual participant data, for patients with separate consent signed for this purpose, may be available to researchers if project deemed appropriate. Data will be shared based on: the scientific merit of the proposal – i.e. the proposal should be scientifically sound, ethical, and have the potential to contribute to the advancement of public health as well as the feasibility of the research proposal – i.e. the requesting research team must be scientifically qualified and have the resources to conduct the proposed project. The data files would exclude data dictionaries that require user licenses. Data access is potentially available for projects deemed appropriate following finalized regulatory authority review and end of any data exclusivity periods and ending after 36 months or until the corresponding author can fulfil this obligation whichever is earlier. Proposals should be directed to lrang@liv.ac.uk to request access.

Declaration of interests

LRR received fees for lectures and consultations from Swedish Orphan Biovitrum.

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