Journal of Clinical Medicine: Current Research **ISSN: 2832-7551**
Volume 2 (2022) 3 Pages
DOI: http://dx.doi.org/10.53043/2832-7551.JCMCR.2.008

Short Review* | *Open Access

Clinical Development Innovation in Rare Diseases: Overcoming Barriers to Successful Delivery of A Randomised Clinical Trial in Alkaptonuria

Ranganath LR[1,2*], Sireau N[3]

[1]Department of Clinical Biochemistry and Metabolic Medicine, Royal Liverpool University Hospital, Prescot Street, Liverpool, L7 8XP
[2]Department of Musculoskeletal Biology, University of Liverpool, L7 8TX
[3]The Alkaptonuria Society, Cambridge, UK

***Correspondence:** LR Ranganath, Department of Clinical Biochemistry and Metabolic Medicine, Liverpool Clinical Laboratories, Royal Liverpool University Hospital, Prescot Street, Liverpool, L7 8XP, UK

Received: August 25, 2022;
Accepted: September 06, 2022;
Published: September 09, 2022

Citation: Ranganath LR, Sireau N. Clinical Development Innovation in Rare Diseases: Overcoming Barriers to Successful Delivery of A Randomised Clinical Trial in Alkaptonuria. J Clin Med Current Res. (2022);2(2): 1-3

Key words: Alkaptonuria, nitisinone, homogentisic acid, SONIA 2, DevelopAKUre

1. Article

Alkaptonuria (AKU) (OMIM#203500) is a rare inherited disorder due to deficiency of homogentisate dioxygenase with resultant accumulation of homogentisic acid, occurring with a worldwide frequency of 1 in 100,000 to 250,000 [1].

1.1 Pre-study preparations

The rarity and the lack of serious morbidity in early years has hindered the advances in knowledge needed to develop effective therapies. While case reports of single or few cases continue to appear in the medical literature, reliable studies describing significant numbers of AKU cases remain scant. The natural history study of AKU at the National Institutes of Health in the USA, as well as the United Kingdom National Alkaptonuria Centre (NAC), have helped to increase our understanding of AKU. The pioneering suggestion by the NIH that a drug already treating another fatal inherited disorder, hereditary tyrosinaemia 1 (HT-1), could be used to treat AKU led to the initial development of the enzyme inhibitor nitisinone. However, the NIH outcomes study proved inconclusive and did not lead to FDA approval for use in AKU [2-4]. This made it harder to convince the marketing authorisation holder of nitisinone (Swedish Orphan Biovitrum, Sobi) to support a new clinical nitisinone trial. We realised from the NIH study that the barriers to a successful clinical nitisinone trial included low numbers of recruitable subjects, an incomplete understanding of the nature of AKU and lack of an appropriately representative outcome measure. These barriers were addressed and resolved by carrying out a population identification study which enabled identification of 75 UK patients and 626 outside the UK [5]. A natural history study in the UK re-emphasised the delayed slow inexorable progression of AKU, which led to the design of the European outcomes study being longer [6]. The UK natural history study recognised the multisystem nature of AKU and developed a composite score describing the burden of AKU disease in a patient that could serve as

an outcome measure instead of a single variable disease feature [7,8]. Further, the nitisinone license holder Sobi obtained regulatory approval for nitisinone use in treating HT-1 in 2002 in the USA and 2005 in Europe and UK [9]. When the new AKU clinical studies were being planned in 2011 it became clear that the 12-year market exclusivity for nitisinone in HT-1 would run out during the planned AKU repurposed nitisinone outcomes study, making it difficult to convince Sobi to support the study by providing expertise and nitisinone [10]. Drug repurposing is more economical than starting from scratch for orphan diseases, yet obtaining funding to study and develop effective treatments for rare diseases is challenging with more than 7,000 competing rare diseases. That's why we laud the European strategy on rare disease which offers funding hope for millions of rare disease sufferers. A barrier to success in new clinical therapy development can be overcome by engaging with the regulatory authorities to develop an acceptable study design and have seamless regulatory approval following conclusion of study. When we engaged with the European Medicines Agency, they understood the complexities of the development and guided us to use a realistic metabolic end point while also expecting us to show trends in clinical benefit. As a result, the European Commission (EC) Framework Programme 7 funded a European programme of studies entitled DevelopAKUre which commenced in November 2012.

1.2 Peri-study considerations

The DevelopAKUre programme had a 5.5-year duration to deliver on a dose-response as well as an outcomes study called Suitability of Nitisinone in Alkaptonuria 1 and 2 respectively (SONIA 1 and SONIA 2). The SONIA 1 confirmed the final dose that was used in SONIA 2 after 1.5 years from start of the programme. This required frequent communication with the EC to obtain approval to make changes to study logistics in order to finish as close to agreed timelines as possible, although the study still overran by nine months. Despite identifying 76 AKU patients in the UK, they could not be recruited to SONIA 2 due to the ethical dilemma of these patients being randomised to the control no-nitisinone arm when they were eligible to receive nitisinone for free at the UK NAC. This necessitated patient recruitment especially for the UK site from Europe, resulting in barriers such as overseas travel for disabled patients, language barriers requiring use of interpreters, as well as carefully planned safety rescue for patients if they suffered an adverse event. SONIA 2 was challenging due to a number of factors including lengthy multisystem assessments lasting from Monday to Friday of each study site visits. The SONIA 2 study sites were Liverpool (UK), Piešťany (Slovakia) and Paris (France). The study processes were harmonised to minimise variability in procedures such as serum sample acidification, ear cartilage biopsy and photographs of eyes and ears for HGA-pigment, to name a few. Site initiation visits before commencement were also used to minimise variability. Liverpool was an adult general hospital, Piešťany was a specialist national rheumatology centre, while France was a paediatric metabolic centre. We had effective patient societies assisting and supporting patients in Liverpool and Paris, but had difficulty in Piešťany. We recruited 139 out of the projected 140 patients in SONIA 2 over nine months thanks to the activism of our patient societies; this was helped by having weekly patient recruitment telemeetings. These changed to weekly retention meetings once full recruitment was achieved and were crucial to ensuring continued participation, especially of the untreated control group, for the success of the SONIA 2 study. Although travel, accommodation and food expenses for participants were paid from the EC grant, problems were experienced with hospital administration systems for prompt payment of minor incidental expenses to participants, which was eventually solved. There were 13 partners, including two AKU patient societies, in the DevelopAKUre consortium, and the weekly consortium telemeetings ensured effective communication. There were also seven face-to-face meetings during DevelopAKUre to ensure the project progressed smoothly.

1.3 Post-study considerations

The SONIA 2 study ended in February 2019, data analysis was completed and the main publication setting out the results of the study was published in 2020 [11]. At the same time a compilation of documents was sent to the European Medicines Agency for label extension of nitisinone to cover its use in adults with AKU, which was awarded in 2020 [12]. Further dissemination activities continued with more than 20 articles published so far. Sobi, RLUH and the AKU Society (UK) have assisted with national HTA assessments of nitisinone use in adults with AKU, often requiring several meetings with the national health regulatory authorities to ensure patient access to the study drug.

Carrying out a successful clinical trial in very rare diseases is challenging. It requires careful planning and trans-national coordination. The participation of a pharmaceutical partner as well as an effective consortium are crucial to success.

2. References

1. Lai CY, Tsai IJ, Chiu PC, Ascher DB, Chien YH, Huang YH, et al. A novel deep intronic variant strongly associates with Alkaptonuria. npj Genom. Med. 6, 89 (2021). https://doi.org/10.1038/s41525-021-00252-2
2. Anikster Y, Nyhan WL, Gahl WA. NTBC and alkaptonuria. Am J Hum Genet 1998; 63: 920-921
3. Phornphutkul C, Introne WJ, Perry MB, Bernardini I, Murphey MD, Fitzpatrick DL, et al. Natural history of alkaptonuria. N Engl J Med 2002; 347: 2111-21;
4. Introne WJ, Perry MB, Troendle J, Tsilou E, Kayser MA, Suwannarat P, O'Brien KE, et al. A 3-year randomized therapeutic trial of nitisinone in Alkaptonuria. Mol Genet Metab. 2011; 103: 307-14
5. Ranganath L, Taylor AM, Shenkin A, Fraser WD, Jarvis J, Gallagher JA, Sireau N. Identification of alkaptonuria in the general population: A United Kingdom experience describing the challenges, possible solutions and persistent barriers. J Inherit Metab Dis 2011; 34: 723-30
6. Ranganath RL, Cox TF. Natural history of alkaptonuria revisited: analyses based on scoring systems. J Inherit Metab Dis 2011; 34: 1141-51
7. Cox T, Ranganath L. A quantitative assessment of alkaptonuria: testing the reliability of two disease severity scoring systems. J Inherit Metab Dis 2011; 34: 1153-62
8. Cant HEO, Chatzidaki I, Olsson B, Rudebeck M, Arnoux JB, Imrich R, et al. Exploring the Alkaptonuria Severity Score Index to increase clinical accuracy and improve flexibility. JIMD Reports.2022;1-10.DOI:10.1002/jmd2.12290
9. https://www.ema.europa.eu/en/medicines/human/EPAR/orfadin
10. https://www.europeanpharmaceuticalreview.com/article/62846/orphan-drugs-regulation-eu/
11. Ranganath LR, Psarelli EE, Arnoux JB, Braconi D, Briggs M, Bröijersén A, et al. Suitability of Nitisinone in Alkaptonuria 2 (SONIA 2) - A randomised study on the efficacy and safety of nitisinone in alkaptonuria. The Lancet Diabetes & Endocrinology. 2020;8:762-772
12. https://www.ema.europa.eu/en/news/first-treatment-rare-metabolic-disorder-alkaptonuria#:~:text=EMA%20has%20recommended%20granting%20an,in%20certain%20areas%20of%20Slovakia