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Nitisinone arrests ochronosis and decreases rate of progression of Alkaptonuria: Evaluation of the effect of nitisinone in the United Kingdom National Alkaptonuria Centre

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ABSTRACT

Question: Does Nitisinone prevent the clinical progression of the Alkaptonuria?
Findings: In this observational study on 39 patients, 2 mg of daily nitisinone inhibited ochronosis and significantly slowed the progression of AKU over a three-year period.
Meaning: Nitisinone is a beneficial therapy in Alkaptonuria.
Background: Nitisinone decreases homogentisic acid (HGA), but has not been shown to modify progression of Alkaptonuria (AKU).
Methods: Thirty-nine AKU patients attended the National AKU Centre (NAC) in Liverpool for assessments and treatment. Nitisinone was commenced at V1 or baseline. Thirty nine, 34 and 22 AKU patients completed 1, 2 and 3 years of monitoring respectively (V2, V3 and V4) in the VAR group. Seventeen patients also attended a pre-baseline visit (V0) in the VAR group. Within the 39 patients, a subgroup of the same ten patients attended V0, V1, V2, V3 and V4 visits constituting the SAME Group.

Severity of AKU was assessed by calculation of the AKU Severity Score Index (AKUSSI) allowing comparison between the pre-nitisinone and the nitisinone treatment phases.
Results: The ALL (sum of clinical, joint and spine AKUSSI features) AKUSSI rate of change of scores/patient/month, in the SAME group, was significantly lower at two (0.32 ± 0.19) and three (0.15 ± 0.13) years post-nitisinone when compared to pre-nitisinone (0.65 ± 0.15) ($p < .01$ for both comparisons). Similarly, the ALL AKUSSI rate of change of scores/patient/month, in the VAR group, was significantly lower at one (0.16 ± 0.08) and three (0.19 ± 0.06) years post-nitisinone when compared to pre-nitisinone (0.59 ± 0.13) ($p < .01$ for both comparisons). Combined ear and ocular ochronosis rate of change of scores/patient/month was significantly lower at one, two and three year's post-nitisinone in both VAR and SAME groups compared with pre-nitisinone ($p < .05$).

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Conclusion: This is the first indication that a 2 mg dose of nitisinone slows down the clinical progression of AKU. Combined ocular and ear ochronosis progression was arrested by nitisinone.

1. Introduction

Alkaptonuria (AKU) is a rare genetic deficiency of homogentisate dioxygenase (HGD), characterised by high circulating homogentisic acid (HGA), some of which is deposited in connective tissue as a pigmented polymer, during a process termed ochronosis [1, 2]. The effects of ochronosis include premature arthritis, lithiasis, cardiac valve disease, fractures, muscle and tendon ruptures and osteopenia [3, 4].

Current therapy is only palliative [5]. A potential agent called nitisinone has been shown to decrease circulating HGA [6–8] and to inhibit ochronosis in AKU mice [9, 10]. Nitisinone which inhibits *p*-hydroxyphenylpyruvate dioxygenase, the enzyme leading to formation of HGA, has been used for more than twenty years in the treatment of type-1 hereditary tyrosinaemia (HT-1) [11, 12]. The dose of nitisinone that decreases HGA by > 95% is 2 mg daily, based on the experience of using nitisinone in the National Institute of Health, USA [6–8], and the SONIA-1 clinical study [13], and approximately ten to fifty times lower than the doses used in HT-1. NHS England has approved the use of off-label nitisinone 2 mg daily for the management of AKU in the National Alkaptonuria Centre (NAC) Liverpool, UK [14].

A previous study employing 2 mg dose of nitisinone, failed to demonstrate a benefit on a single non-metabolic outcome, hip rotation [8]. The NAC is collecting data from a large number of assessments to calculate the severity of AKU using a validated semi-quantitative composite score termed AKUSSI (alkaptonuria severity scoring index) [15, 16], which increases the likelihood of detecting an effect of nitisinone.

1.1. Subjects and methods

The NAC was established in the Royal Liverpool University Hospital and funded by the Highly Specialised Services, NHS England, in April 2012. The lead author's institutional audit committee approved the analysis of the NAC data (Audit no. ACO3836).

Thirty-nine AKU patients attended the National AKU Centre (NAC) in Liverpool (Fig. 1). Varying numbers attended yearly visits in this VAR group (or VAR; variable number of patients at each visit). Nitisinone 2 mg was commenced at baseline (V1). Systematic assessments were carried out at all visits. Thirty-nine, 34 and 22 AKU patients completed 1, 2 and 3 years of monitoring respectively (V2, V3 and V4) after starting nitisinone. Seventeen patients (7 female and 10 male) also attended a pre-baseline visit (V0) in the VAR group; the duration between the V0 and V1 was 32.2 (± 2.3) months. V1 (n = 39; mean age 47.3 (± 2.3) years; 15 females; 24 male), V2 (n = 39; mean age 48.3 (± 2.3) years; 15 females; 24 male), V3 (n = 34; mean age 48.7 (± 2.6) years; 14 females; 20 male), and V4 (n = 22; mean age 47.3 (± 3.4) years; 9 females; 13 male) visits in the VAR group had a full data set in which the AKUSSI was calculated.

Within the 39 patients, a subgroup of the same ten patients attended V0, V1, V2, V3 and V4 visits constituting the SAME Group; the duration between V0 and the V1 was 36.7 ± 2.2 months. Attendance thereafter in the NAC was once a year.

Change in scores between V0 and V1, V1 and V2, V1 and V3, and V1 and V4 represent follow-up without nitisinone, as well as one, two and three years of nitisinone therapy, termed PRENIT, NIT 1, NIT 2, and NIT 3 respectively.

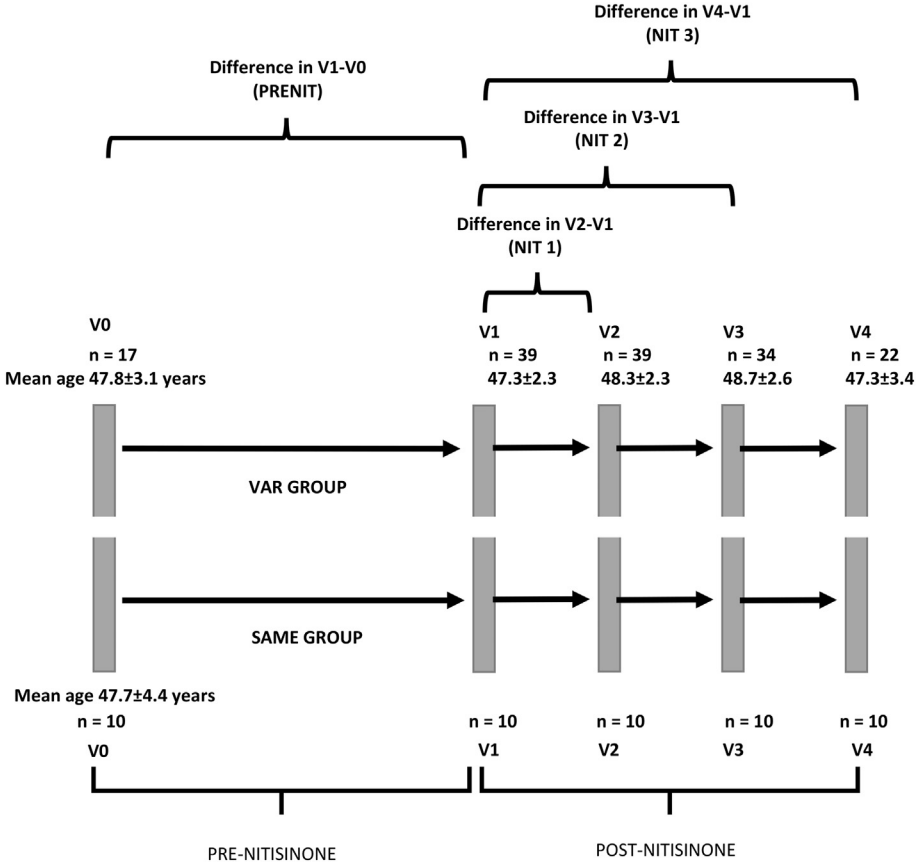

Fig. 1. Plan of the National Alkaptonuria Service: *The VAR group V0 visit consisted of the 10 patients from the SAME group plus seven additional patients who attended the NAC twice without receiving nitisinone. The SAME refers to ten patients attending the research study between 2008 and 2011. The V1, V2, V3 and V4 refer to yearly visits to the NAC. The NIT 1, NIT 2 and NIT 3 refer to change scores per patient per year after one, two and three years of nitisinone therapy. The numbers of patients in each group, their mean age and years of follow-up are also shown in the figure.