Repurposing nitisinone for Black Bone Disease

Lessons from the EC-funded DevelopAKUre project

Dr Nicolas Sireau, Chairman and CEO, AKU Society
1902: Sir Archibald Garrod
The Croonian Lectures

ON

INBORN ERRORS OF METABOLISM.

Delivered before the Royal College of Physicians of London on June 18th, 23rd, 25th, and 30th, 1908,

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LECTURE II.¹

Delivered on June 23rd.

ALKAPTONURIA.

MR. PRESIDENT AND FELLOWS.—Of inborn errors of metabolism, alkaptonuria is that of which we know most, and from the study of which most has been learnt. In itself it is a trifling matter, inconvenient rather than harmful, which only attracts attention because an infant stains its clothing, or because an adult fails to effect an insurance of his life. The medical man merely needs to be aware of its existence and to be acquainted with the methods for its recognition in order that he may not mistake it for troubles of graver kinds; but for the chemical physiologist and pathologist it is one of the most interesting of metabolic
the early years of the nineteenth century was drawn in medical writing: black when passed and such as but it is difficult to suggest an alkaptonuria for some cases sixteenth and seventeenth century G. A. Scribonius⁴ (in 1584) of a man enjoyed good health, continuous that cited by Schenck⁵ (in 1606) of a similar peculiarity and stated life. The most interesting record in the work of Zacutus Lusitanus patient was a boy who passed his age of 14 years, was submitted to an experiment which had for its aim the examination of his viscera, which was supposed to have been in question by charring and the measures prescribed were cold and watery diet, and drugs that had any obvious effect, and eventuated to the futile and superfluous thera
ties their natural course. None of them married, begat a large family, and passed on life, always passing urine black as that alkaptonuria is a very old question, and many medical men have never met with it. Of its occurrence in a family and of its mode of transmission, spoken at sufficient length in the majority of instances it is present throughout life, and has been so
Harwa

Oldest AKU Patient
1500BC

Stenn et al 1977
Metabolic pathway

Phenylketonuria

Albinism

Alkaptonuria

Tyrosinaemia type 1
Lesson 1: Make sure you understand your disease
The AKU tetrad
Black Bone Disease
Effects on spine

Sofia Michopoulou & Andrew Todd Pokropek
A cell model

AKU Research Team
AKU mouse model
Lesson 2:

Build a global patient movement
A global patient movement

Worldwide: 950 patients and counting

Europe
- Belgium: 9
- France: 46
- Germany: 90
- Italy: 15
- Netherlands: 50
- Spain: 6
- Slovakia: 208
- Czech Republic: 11
- Poland: 35
- Switzerland: 5
- Other: 10

United Kingdom and Ireland
- 64

Canada
- 17

USA
- 92

Mexico
- 1

Dominican Republic
- 8

South America
- Brazil: 3
- Argentina: 4
- Other: 2

ASIA
- India: 100+
- Pakistan: 4
- South East Asia: 8
- China and Hong Kong: 3

Middle East
- Jordan: 54
- Qatar: 40
- Palestine: 5
- Israel: 3
- Turkey: 4
- Other: 6

Australia
- 13
AKU Societies in EU, Middle East and North America

- AKU Society UK
- ALCAP (France)
- AIMAKU (Italy)
- AKU Society Germany
- AKU Society Netherlands
- AKU Society Belgium (in progress)
- AKU Society Jordan
- AKU Society Slovakia (in progress)
- AKU Society India (in progress)
- AKU Society North America (USA and Canada)
Lesson 3:
Set up a strong clinical development programme for your proposal
Nitisinone reduces homogentisic acid by \(95\%)\).
Urinary HGA

Figure 1.

National Institutes of Health
Three stage development plan

- Drug response study
- Clinical efficacy phase 3 trial
- Cross-sectional study to determine age of treatment
Lesson 4:

Put together a solid EU consortium
The Royal Liverpool and Broadgreen University Hospitals NHS Trust

UNIVERSITY OF LIVERPOOL

Hôpital Necker Enfants Malades

PSR the orphan EXPERTS

UDOS Drug development consultancy

INSTITUT NECKER

UNIVERSITY OF SIENA

sobi SWEDISH ORPHAN BIOVITRUM

nordic bioscience

AKU Alkaptonuria Society

ALCAP Association pour la Lutte Contre l'Alcaptonurie
Lesson 5:

Set up a clinical reference centre
Lesson 6:
Launch the programme effectively
Rare Diseases: Challenges and Opportunities for Social Entrepreneurs

A new book out now!

With chapters from leaders in the rare disease sector.

For more information, go to the book stand in the posters section of the conference.
Thank you

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