

# A Spotlight on Friedreich Ataxia: Optimising the Patient Journey from Diagnosis to Disease Management

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## Meeting Summary

This symposium was held on the first day of the European Academy of Neurology (EAN) Congress, with four main objectives: to raise awareness of Friedreich ataxia (FA) as a rare, progressive neurodegenerative disorder; to summarise the patient journey from identifying first symptoms in childhood and adolescence to reaching an accurate diagnosis; to discuss the burden of living with FA and highlight the benefit of improved communication and collaboration between members of the multidisciplinary team on reducing this burden on patients and their

caregivers; and to summarise current management options within the field of FA and provide an overview of emerging therapies and active clinical trials.

The symposium was chaired by Sylvia Boesch, a neurologist and senior staff member at the Medical University of Innsbruck, Austria, and Head of the Centre for Rare Movement Disorders, Innsbruck, Austria, who presented an overview of rare diseases in general and of FA. Mathieu Anheim, a neurologist at the Movement Disorders Unit, University Hospital of Strasbourg, France, followed with a description of the aetiology and symptomatology of FA. Lastly, Paola Giunti, a professorial research associate in the Department of Clinical and Movement Neurosciences, University College London Queen Square Institute of Neurology, Faculty of Brain Sciences, University College London, UK, explained the best approach to FA management, including a summary of clinical trials for emerging therapies in FA.

## Introduction

### Sylvia Boesch

Boesch explained that in the European Union (EU), a rare disease is defined as a disease that affects less than one person in 2,000. Between 6,000–8,000 different rare diseases affect an estimated 30 million people in the EU.<sup>1</sup> In the USA, a rare disease can be defined as a disease or condition that impacts fewer than 200,000 people.<sup>2</sup> Of all rare diseases,  $\leq 5\%$  are estimated to have approved treatments, known as ‘orphan’ therapies,<sup>3</sup> yet 3.5–5.9% of the global population (263–446 million people) are affected with a rare disease at any one time.<sup>2</sup>

Based on their own clinical experience, Boesch described the unmet needs in rare neurological disease as a lack of available diagnoses; relatively unavailable, and ineffective treatment; a lack of research to develop treatment; poor disease awareness; and limited financial resources.<sup>4,5</sup>

FA is a rare neurodegenerative disorder that affects one in 20,000–50,000 individuals in Europe, and a total of approximately 22,000 people globally.<sup>6,7</sup> Anheim explained that FA is the most common inherited ataxia.<sup>8</sup> Disease onset typically occurs in childhood or adolescence, between 5–15 years of age,<sup>7</sup> and the condition affects multiple body systems including the central nervous system, peripheral nervous system, musculoskeletal system, heart, and pancreas.<sup>9</sup>

The disorder is characterised by progressive neurological and non-neurological symptoms, including effects on ambulation, speech, swallowing, hearing, and vision, as well as cardiomyopathy and skeletal abnormalities.<sup>10–12</sup> Loss of ambulation and the need for a wheelchair typically occur between 25–30 years of age, leading to loss of autonomy and an increasing requirement for assistive care.<sup>9,10,13</sup> As FA progresses, it results in an increasing need for complex multidisciplinary care.<sup>13</sup>

## Introducing Friedreich Ataxia: Discover the Journey to Diagnosis and the Burden of Illness

### Mathieu Anheim

FA is an autosomal recessive disease caused by mutations in the *FXN* gene.<sup>14</sup> In most cases (96%), the mutation is a homozygous GAA triplet expansion in intron 1; triplet repeats over 66 are considered pathogenic, and the expansion number correlates with age of onset and disease severity.<sup>10,15–18</sup> A minority of patients (4%) carry a heterozygous GAA expansion and a point mutation on the other allele.<sup>10</sup> Anheim emphasised that, in their experience, *FXN* GAA triplet-repeat expansion cannot be identified through targeted gene panels or whole exome sequencing, and that specific testing for these expansions is required.

Mutations in *FXN* in FA lead to reduced levels of functional frataxin,<sup>19</sup> a protein involved in mitochondrial iron homeostasis and the assembly

and transfer of iron–sulfur clusters to various mitochondrial components.<sup>8,19,20</sup> A reduced level of frataxin results in impaired mitochondrial function and increased sensitivity to oxidative stress.<sup>8,19</sup> This leads to the clinical features of FA, characterised by progressive degeneration of the peripheral nervous system and central nervous system, cardiomyopathy, and ataxia.<sup>8,9</sup>

In Anheim's clinical experience, the first signs of FA occur in the peripheral nervous system, with the loss of dorsal root ganglia, degeneration of the posterior column of the spinal cord, and peripheral neuropathy. Anheim explained that patients tend to present with a loss of tendon reflexes and ocular symptoms.

The neurological symptoms of FA include combined ataxia, cerebellar dysarthria (muscle-related speech difficulty), absent tendon reflexes, hypopallesthesia (a decreased ability to perceive vibration), sensory neuropathy, extensor plantar reflexes, and square wave jerks (involuntary, horizontal, saccadic intrusions that interrupt eye fixation).<sup>11,21</sup> Anheim explained that cerebellar ataxia progressively worsens in FA, evidenced by worsening instability when closing the eyes, and an impaired heel-shin test due to hypermetria.<sup>22</sup> Notably, MRI of the brain shows mild to no cerebellar atrophy in FA.<sup>21,23</sup> Extra-neurological signs of FA include hypertrophic cardiomyopathy, scoliosis, diabetes, optic neuropathy, hearing loss, and pes cavus (abnormally high plantar longitudinal arch).<sup>21</sup>

Anheim noted that in their clinical experience, clumsiness and unsteadiness worsen as the condition progresses. More advanced stages are severely disabling in many activities of daily living, with increased wheelchair use, marked dysarthria, and swallowing difficulties.

Differential diagnosis of FA can be supported by electroneuromyography to identify the type of neuropathy present; the recessive ataxias can be divided into those without peripheral neuropathy, those with both sensory and motor neuropathy, and those with sensory neuropathy alone (for which FA is the prototype).<sup>22</sup> Anheim stressed that, in their experience, the differential diagnosis should not neglect treatable entities, such as ataxia with vitamin E deficiency, which can be treated with vitamin E supplementation; Refsum disease, which can be treated with

phytanic acid; cerebrotendinous xanthomatosis, which can be treated with cholestanol; and others. In particular, Anheim highlighted that ataxia with vitamin E deficiency often mimics the clinical picture of FA.

Overall, FA is associated with a poor prognosis.<sup>13</sup> The mean duration of the disease is 15.0–20.0 years, and the mean age of death is 36.5 years (12.0–87.0 years).<sup>13</sup> The primary cause of death in patients with FA is cardiac dysfunction, most commonly from congestive heart failure or arrhythmia.<sup>24</sup>

Patients with FA require multidisciplinary clinical care,<sup>25</sup> and Anheim stressed the importance of co-ordination, collaboration, and communication between the disciplines involved. Anheim explained that spasticity can be managed with baclofen or botulinum toxin injections, neuropathic pain with gabapentin or pregabalin, urinary emergencies with oxybutynin, and cardiomyopathy with  $\beta$ -blockers or aldosterone antagonists. In Anheim's experience, orthopaedics is important for the management of scoliosis, and referral to cardiology, ophthalmology, audiology, and speech/physical/occupational therapy should be considered as needed.<sup>25</sup> Anheim also advocated assessment by dual-energy X-ray absorptiometry to detect osteoporosis, screening for fasting blood glucose and HbA1c on a yearly basis, and offering genetic counselling.<sup>25</sup>

Anheim emphasised the take home message that *FXN* mutations should be specifically searched for as soon as an autosomal recessive cerebellar ataxia with an FA-compatible phenotype is detected.<sup>21</sup> Anheim noted that this phenotype would include progressive worsening of combined ataxia arising in a young patient, with optional findings such as scoliosis, pes cavus, cardiomyopathy, lack of tendon reflexes, or bilateral extensor plantar reflexes.

## The Therapeutic Landscape: Navigating Disease Management and an Outlook on Key Clinical Trials

Paola Giunti

FA is a complex and multisystemic condition for which no treatment is currently available in Europe,<sup>9</sup> and Giunti explained that the management of FA requires a holistic approach within multidisciplinary clinics.<sup>9</sup>

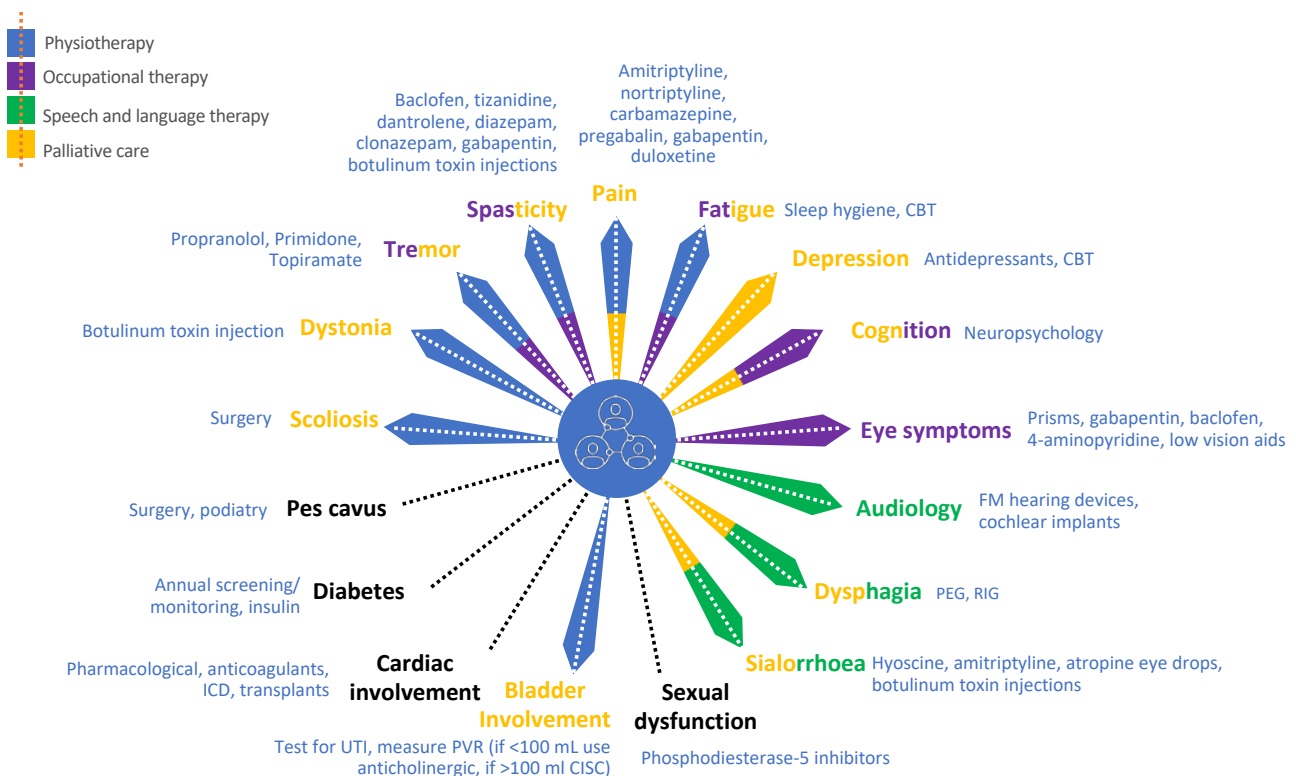
In Giunti's experience, specialist ataxia centres provide adapted treatment and care for patients with FA.<sup>9</sup> These centres co-ordinate patient care, involving neuro-ophthalmologists; neuro-ear, nose, and throat specialists; cardiologists; orthopaedic surgeons; physiotherapists; speech and language therapists; occupational therapists; neuropsychiatrists; and geneticists.<sup>9</sup> Giunti highlighted that such clinics should also

begin to deliver overall palliative care. Specialist centres can provide a holistic approach to disease management, with symptomatic treatments and patient education (Figure 1), and these sites can also be hubs for ataxia research and clinical trials.<sup>9</sup>

Guidelines for the best practice treatment of ataxias can be found on the Ataxia UK website,<sup>6</sup> and recommendations specifically for the diagnosis and management of the progressive ataxias have also been published.<sup>26,28</sup> Additional guidelines have been produced that focus specifically on FA.<sup>27</sup> Giunti highly recommended that clinicians refer to these publications.

Giunti explained that the clinical trial landscape for FA has changed considerably over the past decade, with many more trials now being conducted, mainly in Phase I or Phase II. Two trials of novel therapies in FA have recently

Figure 1: Symptom management with multidisciplinary team input.<sup>26,27</sup>



Adapted from de Silva et al.<sup>26</sup>

CBT: cognitive behavioural therapy; CISC: clean intermittent self-catheterisation; FM: frequency modulated; ICD: implantable cardioverter defibrillator; PEG: percutaneous endoscopic gastrostomy; PVR: post-void residual; RIG: radiologically inserted gastrostomy; UTI: urinary tract infection.

been completed, assessing vatiquinone and omaveloxolone, and the omaveloxolone trial has resulted in approval for marketing in the USA.<sup>29-31</sup> Some drugs being trialled in FA target upstream mechanisms, addressing the reduced frataxin levels through replacement or upregulation of expression, while other approaches focus on downstream mechanisms such as the effects on mitochondria.<sup>32</sup>

The modified Friedreich Ataxia Rating Scale (mFARS) is commonly used as a study endpoint in clinical trials. This validated tool assesses neurological function, with a higher score indicating worsened function. It measures upper and lower limb co-ordination, upright stability, and bulbar function (including strength and volume of coughing and clarity of speech).<sup>7,33</sup>

### Vatiquinone

Giunti explained that vatiquinone (previously known as EPI-743) is an oral, selective inhibitor of 15-lipoxygenase, an enzyme that regulates energetic and oxidative stress pathways.<sup>34,35</sup> Vatiquinone is also thought to target NAD(P)H quinone dehydrogenase 1.<sup>36</sup> In addition, vatiquinone has demonstrated nuclear factor-erythroid factor 2-related factor 2-mediated neuroprotective effects in frataxin-silenced motor neurons and in neural stem cells isolated from FA mouse models, and has been shown to prevent *in vitro* ferroptosis through the inhibition of 15-lipoxygenase.<sup>37</sup> While vatiquinone does not target FA-specific pathways directly, it helps to improve the regulation of energy metabolism.<sup>36</sup>

A recent randomised, double-blind, placebo-controlled study of vatiquinone in patients with FA (MOVE-FA) was designed to assess the change in total mFARS score from baseline to Week 72 (n=123).<sup>30,38</sup> Secondary endpoints included the change from baseline in Friedreich Ataxia Rating Scale Activities of Daily Living (FARS-ADL), mFARS sub-scores, and the Modified Fatigue Impact Scale (MFIS).<sup>38</sup> The primary analysis was conducted in patients between the ages of 7–21 years, and the study design included a 24-week open label extension phase.<sup>30</sup>

Results from MOVE-FA demonstrated a meaningful slowing of disease symptom progression with vatiquinone versus placebo,

including a difference of -0.18 in the mFARS bulbar subscore (p=0.044) and a difference of -1.26 in the mFARS upright stability subscore (p=0.021).<sup>38</sup> However, the study did not reach its primary endpoint, with a non-significant difference in total mFARS change from baseline of -1.61 (p=0.14). In a sensitivity analysis that excluded patients who discontinued treatment during the study (n=26), vatiquinone had a significant effect on MFIS, with difference in change from baseline of -4.73 (p=0.042). Treatment-related adverse events were generally mild to moderate in severity, and gastrointestinal symptoms were the most common. The safety profile was similar between vatiquinone and placebo groups, and also similar to other vatiquinone paediatric studies.

### Omaveloxolone

Giunti reiterated that frataxin is fundamental for the activity of the mitochondrial respiratory chain, particularly Complex I, and that reduced levels of frataxin inhibit these complexes, resulting in an increase in reactive O<sub>2</sub> species, increased lipid peroxidation, and deregulation of mitochondrial membrane potentials in fibroblasts from FA mouse models.<sup>39</sup> Omaveloxolone (previously known as RTA 408) is a nuclear factor-erythroid factor 2-related factor 2 activator that prevents Complex I inhibition in FA neurons in mouse models and in fibroblasts from patients with FA, evidenced by a normalisation of NADPH levels and NADPH redox state.<sup>39,40</sup>

The safety and efficacy of omaveloxolone in patients 16–40 years of age with genetically confirmed FA was assessed in the MOXle study.<sup>29</sup> The study was divided into three main parts:

- Part 1: a randomised, placebo-controlled, double-blind, dose-ranging, multicentre trial to determine the optimal dose of omaveloxolone and evaluate safety over 12 weeks.<sup>40</sup>
- Part 2: a randomised, placebo-controlled, double-blind, parallel-group study to evaluate the safety and efficacy of omaveloxolone at the 150 mg dose identified in Part 1 over 48 weeks.<sup>7</sup>
- Open-label extension: designed to assess the long-term safety and tolerability of

omaveloxolone following completion of Part 1 and Part 2 of the MOXle study.<sup>41</sup>

In Part 1, patients with FA were randomised 3:1 to omaveloxolone or placebo and treated for 12 weeks (N=69). Patients were randomised to omaveloxolone at doses of 2.5–300.0 mg/day (n=52) or placebo (n=17).<sup>40</sup> The primary endpoint was the change from baseline in peak work (watts/kg) attained during exercise testing at Week 12, along with safety and tolerability, and the secondary endpoint was the change in mFARS score at Week 12. Other measures included the Timed 25-Foot Walk Test (T25-FW), 9-Hole Peg Test (9HPT), low-contrast vision, and health-related quality of life.<sup>29,40</sup>

Despite no significant change in peak work in exercise testing compared with placebo (p=0.77), omaveloxolone significantly improved mFARS scores from baseline in a dose-dependent manner (p<0.001) and, when compared with the placebo-corrected change at 160 mg/day, mFARS improvements approached statistical significance (p=0.06). Omaveloxolone was well tolerated, and adverse events were generally mild. The optimal dose was determined to be 160 mg/day, so a 150 mg/day dose was examined in MOXle Part 2 as this would reduce the number and complexity of capsules that patients would need to take while still providing similar systemic exposure (Reata Pharmaceuticals, data on file).<sup>40</sup>

Part 2 included patients 16–40 years of age with genetically confirmed FA; baseline mFARS scores between 20–80; and the ability to complete maximal exercise testing on a recumbent stationary bicycle (N=103). Patients were randomised 1:1 to receive 150 mg/day omaveloxolone or placebo daily for 48 weeks, followed by a 4-week follow-up. The primary endpoint was the change from baseline in mFARS at Week 48 (excluding patients with severe pes cavus, as defined in the protocol; n=82), and secondary endpoints included the change in baseline at Week 48 in Patient Global Impression of Change (PGIC), Clinician Global Impression of Change (CGIC), 9-HPT, T25-FW, frequency of falls, peak work during maximal testing, and activities of daily living.<sup>7,29</sup>

In MOXle Part 2, changes from baseline in mFARS scores in omaveloxolone and placebo patients showed a difference between treatment groups

of -2.4 (p=0.014), indicating a neurological function benefit.<sup>7</sup> Improvements were consistent across individual components of mFARS, subgroups, including age, sex, GAA1 repeat length, and ambulatory status. Omaveloxolone was generally well tolerated with few serious adverse events or discontinuations; adverse events were generally mild to moderate in severity. The most common adverse events occurring more frequently in the omaveloxolone arm were headache, increased alanine aminotransferase, nausea, excoriation, fatigue, increased aspartate aminotransferase, abdominal pain, and diarrhoea. Four patients (8%) who received omaveloxolone discontinued treatment due to an adverse event, compared with two patients (4%) in the placebo group.<sup>7</sup>

Data from the open label extension part of MOXle were analysed to determine the effects of a delayed start to omaveloxolone in the study population.<sup>41</sup> To achieve this, mFARS scores at the end of the 48-week placebo-controlled period (MOXle Part 2) were compared with those at 72 weeks in the MOXle open-label extension (up to 144 weeks) for patients initially randomised to omaveloxolone compared with those initially randomised to placebo in MOXle Part 2. A non-inferiority test was performed to compare the difference between treatment groups (placebo to omaveloxolone [delayed start group] versus omaveloxolone to omaveloxolone [early start group]) using a mixed model for repeated measures. Slopes of the change in mFARS scores were compared between both groups in the open-label extension. The primary endpoint was the difference in the initial placebo and initial omaveloxolone groups in the 'delayed start period' (extension Week 72 change from baseline mFARS values) compared with the initial omaveloxolone-placebo difference in the 'placebo-controlled period' (MOXle Part 2 Week 48 change from baseline mFARS values).<sup>41</sup>

Results showed that the difference in mFARS between omaveloxolone and placebo observed at the end of placebo-controlled MOXle Part 2 was preserved after 72 weeks in the extension phase. The results support the outcome of MOXle Part 2 and indicate a persistent treatment benefit with omaveloxolone.<sup>41</sup>

Data from the open-label MOXle extension were also compared with propensity-matched

natural history data from FA-COMS.<sup>42</sup> Logistic regression was used to estimate propensity scores based on multiple covariates, including sex, baseline age, age of onset, baseline mFARS score, and baseline gait score. Selection of covariates was based on clinical relevance and availability. The primary endpoint was the change from baseline in mFARS at Year 3 for the MOXIe-extension patients compared with the matched FA-COMS patients using an mixed model for repeated measures.<sup>42</sup>

Results indicated that omaveloxolone provides a persistent benefit over 3 years when compared with an untreated, matched cohort from FA-COMS. In the primary pooled population by Year 3, mFARS scores for patients in the FA-COMS matched set progressed 6.6 points, whereas they progressed just three points for patients treated with omaveloxolone ( $p=0.0001$ ), suggesting a 55% slower progression in mFARS.<sup>42</sup>

Giunti explained that it is important for clinical trials to use measures of disease that best characterise this multisystem condition, and which best represent the burden of disease. An online survey of patients with FA in the USA and UK found that the symptoms they would most like to see addressed by a clinical trial differed by the patient's stage of disease.<sup>43</sup> Ambulatory patients would most like to see balance problems addressed (walking independently and walking with aids), whereas patients who were wheelchair-dependent were most likely to want to see slurred speech addressed. Giunti stressed that clinical trials need to include patients at different stages of their disease, particularly as the overall quality of life and lifespan of patients with FA increase. Giunti also felt that research is needed to develop predictive and prognostic

biomarkers, allowing clinical trials to include more targeted populations. Giunti described one recent study that used machine learning in combination with data from a wearable motion capture suit; this approach was more accurate than the Scale for the Assessment and Rating of Ataxia (SARA) scores in predicting *FXN* gene expression levels for each patient, and in predicting individual SARA scores 9 months into the future.<sup>44</sup>

Giunti concluded that due to the complexity of FA, disease management requires a holistic approach with multidisciplinary clinics, to achieve the best quality of life for these patients.<sup>9</sup> Giunti added that there are several pharmacological compounds with a wide range of mechanisms currently under clinical development,<sup>32</sup> and that both vatiquinone and omaveloxolone studies report promising efficacy data and safety.<sup>7,38</sup>

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## Closing Remarks

### Sylvia Boesch

Boesch summarised the key take aways from the symposium, reiterating that the most common mutation in FA is a homozygous triplet repeat in an intron of *FXN*, resulting in reduced levels of the frataxin protein. The mutation is quite common in the Western population, with an estimated carrier frequency of 1:60–1:110.<sup>14</sup> Boesch stressed that after many years of purely symptomatic treatment for FA, disease-modifying drugs are being developed and are expected to be available in the near future, offering hope to patients and their clinicians.

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