TR-F 12c: Pharmacological treatment of episodic ataxia type 2: Comparison of effectiveness of 4-aminopyridine sustained release (Fampyra™) and acetazolamide versus placebo

C. Adrion1, J. Claassen1,2, R. Feuerecker1,2, O. Bayer1, H.-H. Müller3, U. Mansmann3, K. Jahn1,2, M. Strupp1,2

1: IFB-MNI, Ludwig-Maximilians-University, Munich, Germany
2: Department of Neurology, Ludwig-Maximilians-University, Munich, Germany
3: IBE, Ludwig-Maximilians-University, Munich, Germany

Background

Episodic ataxia type 2 (EA2)  
- autosomal dominant hereditary disorder caused by heterozygous mutations of the gene CACNA1A on chromosome 19p13  
- familial episodic ataxia (EA) represents a genetically and phenotypically diverse group of rare hereditary disorders  
- EA2 is the most common and the best characterized of all the EA syndromes  
- recurrent attacks of ataxia which last for several hours to days

Evidence  
- drug of first choice: carbonic anhydrase inhibitor acetazolamide (ACTZ), which prevents attacks in 50-75% of all EA2 patients. However, efficacy of ACTZ never proven in randomized controlled trials  
- alternative treatment: potassium channel blocker 4-aminopyridine (4AP). An exploratory study and a recent randomized placebo-controlled pilot study showed that 4AP significantly reduced the frequency and duration of attacks  
- Fampyra™ recently approved by the FDA and EMA for symptomatic treatment of gait disorders in multiple sclerosis

The need for a trial  
- no confirmatory placebo-controlled trials conducted on the treatment of EA2 with ACTZ or 4AP, no trials comparing the effects of both treatment options for EA2 with inclusion of a placebo control group available so far

Objectives and design aspects

Objective:  
- To demonstrate efficacy of both active treatments (4AP, ACTZ) in reducing the frequency of attacks compared to placebo  
- To estimate differences between the 2 active treatments regarding frequency of attacks and side effects  
- To explore differences in gait performance

Interventions:  
- Fampyra™ (4AP sustained release form) and Acetazolamide (ACTZ) versus Placebo  
- Duration of intervention per patient: 9 month  
- 3 month-long treatment periods, separated by 1-month-long wash-out periods, 1 month follow-up

Study type:  
- Monocenter, randomized, double-blind, 3 way cross-over, placebo-controlled efficacy of treatment trial

Outcome measures

Primary efficacy endpoint:  
- number of attacks per months (recorded in patient diaries)

Primary efficacy outcome measure:  
- number of attacks during the last 30 days of a treatment period of 3 months

Key secondary endpoints:  
- Median duration of the attacks during the last 30 days during a treatment period of 3 months (recorded in patient diaries)  
- Gait performance: gait velocity, stride length, gait variability (coefficient of variation of stride time) measured at each end of treatment-period visits  
- Quality of life measured with a standardized questionnaires (at the end of each treatment period)

Statistical Analysis

Primary efficacy analysis: intention-to-treat principle  
- Subject-specific modeling approach (Poisson mixed-effects model, based upon the 3 treatment periods of all the 3 treatments)  
- 3 pairwise comparisons (two active treatments vs. placebo) using closed testing procedure for all 3 hypotheses  
- 2 preferred comparisons (Bonferroni α/2); Hochberg procedure more efficient (however, maintenance of type I error to be checked)  
  - Fampyra™ vs. Placebo  
  - ACTZ vs. Placebo

Sample size

Prior results used (Strupp et al. 2007; 10 patients with EA2, intervention 4AP)

standard error of log(effect size) estimator = 0.4

Result:  
- Reduction of mean number of attacks from 100% to 34%, 95% CI [15%;79%]

- To be assessed for eligibility: n = 36  
- To be allocated to trial: n = 30  
- To be analyzed: n = 30 (24 expected to complete all 3 phases)

References


Schlupp R, Wuehr M, Acioli N, Dannik T, Brandt T, Strupp M, Jahn K. 4-aminopyridine improves gait variability in cerebellar ataxia due to CACNA 1A mutation. J Neurol Neurosurg Psychiatry 2011; 82:569-75

Basic science research  
- Mouse models for vestibular and cerebellar diseases

Clinical research  
- Neurology, ENT, CSC®, IBE, CSC®, Interdisciplinary dizziness outpatient clinic

Translational research  
- Statistics, Translational Pharmacology, Clinical Pharmacology, Epidemiology

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