Efficacy and Safety of Dichlorphenamide in Adolescent Patients With Primary Periodic Paralysis

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Introduction

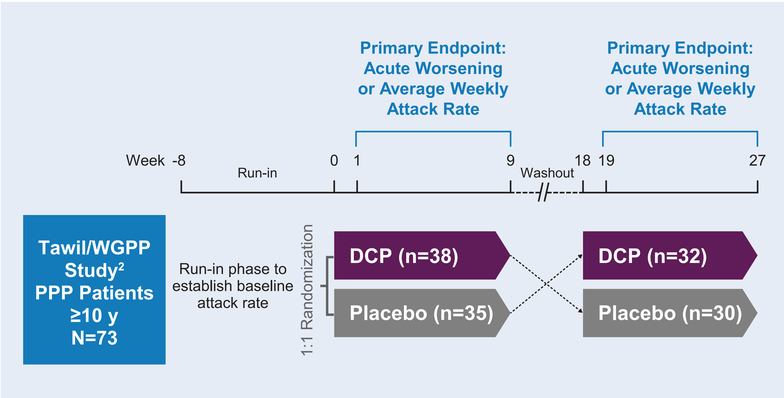
- The primary periodic paralyses (PPP) are ion channelopathies of skeletal muscle caused by point mutations in calcium, sodium, or potassium channel genes
- In adults with PPP, symptoms of muscle weakness and myotonia were often present in childhood
- PPP may be managed with lifestyle interventions; however, prophylactic drug therapy is often indicated
- Dichlorphenamide (DCP; Keveyis®, Strongbridge Biopharma) is the only FDA-approved drug for use in adults with PPP
- 2 multinational, placebo-controlled clinical trials demonstrated that DCP reduced the frequency, severity, and duration of PPP attacks of muscle weakness/paralysis when used daily[1,2]
  - One of these studies—the Tawil/Working Group on Periodic Paralysis (WGPP)[2]—enrolled adolescents as well as adults
- Results from the adolescent subgroup of the Tawil/WGPP have not been previously described

Objective

- To compare the effects of DCP in adolescents vs adults with PPP in a post-hoc analysis

Methods

Study Design



- Phase 3, double-blind, placebo-controlled, randomized crossover study
- After an 8-wk, run-in phase, 73 patients aged ≥10 y (mean 37) were randomly assigned to receive DCP or placebo for 9 wk, followed by washout (≥9 wk) and a switch to the other treatment for 9 wk
- This post-hoc analysis of study records compared the effects of DCP on weekly attack rates, weekly severity-weighted attack rates, and frequency of 9 prespecified adverse events (AEs) in adolescents vs adults

Results

Adolescent Characteristics and Disposition*

Patient #	Age at Entry, y	Gender	PPP Phenotype	Prestudy Medications	Treatment Sequence	Disposition
2	13	Male	Hypokalemic	Potassium	Placebo→DCP	Completed
3	15	Male	Hypokalemic	Potassium	DCP→placebo	Completed
18	17	Female	Potassium sensitive†	None	Placebo→DCP	Missing efficacy data; completed
19	10	Male	Potassium sensitive†	Acetazolamide	Placebo→DCP	No data; discontinued
33	16	Male	Hypokalemic	Acetazolamide + potassium	DCP→placebo	Completed
36	13	Male	Potassium sensitive†	None	DCP→placebo	Completed
58	16	Male	Potassium sensitive†	Acetazolamide	DCP→placebo	Completed

*Age at symptom onset and characteristics of paralytic or myotonic attacks, including triggers, were similar to those of adults (data not shown); †May have included hyperkalemic PPP or paramyotonia congenita.

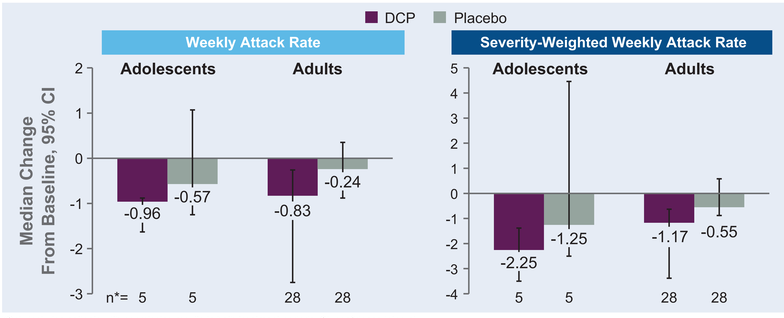
- 7/73 patients (10%) aged 10–17 y:
  - 1 patient (10 y) withdrew prior to receiving DCP
  - 1 patient (17 y) provided tolerability data only
  - 5 patients (13–16 y) provided efficacy/tolerability data
- Self-reported age of onset (mean 10–11 y) and attack characteristics were similar across age groups at baseline
  - Patients with reported age of onset of 0 were excluded from the calculation of mean age of onset

PPP Average Attacks/Week in Adolescents

Patient #	Weekly Attack Rate			Severity-Weighted Weekly Attack Rate*		
	Baseline	DCP	Placebo	Baseline	DCP	Placebo
2	0.88	0	0.13	2.75	0	0.25
3	1	0.13	1.25	3.63	0.13	2.38
18	NA	NA	1.71	NA	NA	2.43
19	2.63	NA	NA	4	NA	NA
33	1.25	0.29	0	2.38	0.29	0
36	1	0	0.43	1.38	0	0.43
58	2.5	0.88	3.57	3.25	1	7.71

*Severity was graded (range 1–4) by modified functional scale previously used in Guillian-Barré syndrome. NA, data not available.

Median Changes From Baseline in Weekly Attack Rates in Adolescents vs Adults



*Only includes patients with nonmissing results in both treatment periods. CI, confidence interval.

- Although the sample size was small, the direction and magnitude of attack frequency and severity improvements during DCP treatment were similar between adolescents and adults

Summary of Adverse Events in Adolescents

- All but 1 adolescent (DCP 50 mg) received a total daily dose of 100 mg; 6 adolescents received an average of 8.5 wk of DCP treatment
- Presence of 9 known AEs of carbonic anhydrase inhibitors was solicited at the end of each study phase (run-in, placebo and DCP treatment, and washout)
- 5 adolescents reported at least 1 AE during the study, with 3 reporting a total of 5 AEs during DCP treatment:
  - Patient 003: skin rash
  - Patient 033: skin rash, itchiness, and numbness
  - Patient 036: dizziness
- None of the adolescents reported a skin rash or itchiness during the other study phases
- None of the AEs were dose limiting or resulted in study withdrawal

Adverse Events Reported by Adolescents and Adults

AE, n (%)	DCP-Treated Adolescents n=6	DCP-Treated Adults n=54
Itchiness (pruritus)	1 (17)	7 (13)
Numbness (paresthesia)	1 (17)	24 (44)
Dizziness	1 (17)	9 (17)
Skin rash	2 (33)	9 (17)

- Patients were also asked about "other" AEs they experienced at the end of each phase, which were recorded as free text entries; 4 adolescents reported "other" AEs during DCP treatment:
  - Patient 003: weight loss
  - Patient 033: weakness (after 1st week of treatment only)
  - Patient 036: nausea, persistent or recurrent lightheadedness, and slow thinking
  - Patient 058: lightheadedness (during 1st week)
- Similar "other" AEs were reported by adults, including AEs related to cognitive changes (data not shown)

Conclusions

- **In this post-hoc analysis of a randomized, double-blind, placebo-controlled, crossover clinical study, adolescents and adults with PPP treated with DCP twice daily had similar improvements in short-term attack frequency and severity within the approved dosing range**
- **The frequency of class-related AEs was similar among adolescents and adults**
- **Based on the post-hoc analysis of these short-term data, a clinical trial evaluating the use of DCP in adolescents with PPP is warranted**

References: 1. Sansone VA, et al. Neurology. 2016;86:1408-16; 2. Tawil R, et al. Ann Neurol. 2000;47:46-53.

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