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Long-term efficacy and safety of dichlorphenamide for treatment of primary periodic paralysis

Valeria A. Sansone MD[1] | Nicholas E. Johnson MD[2] | Michael G. Hanna MD[3] | Emma Ciafaloni MD[4] | Jeffrey M. Statland MD[5] | Perry B. Shieh MD[6] | Fredric Cohen MD[7] | Robert C. Griggs MD[4]

[1]Neuromuscular Omnicentre, Neurorehabilitation Unit, University of Milan, Niguarda Hospital, Milan, Italy

[2]Department of Neurology, Virginia Commonwealth University, Richmond, Virginia, USA

[3]MRC Centre for Neuromuscular Diseases, Department of Neuromuscular Diseases, UCL Institute of Neurology, London, UK

[4]Department of Neurology, University of Rochester Medical Center, Rochester, New York, USA

[5]Department of Neurology, University of Kansas Medical Center, Kansas City, Kansas, USA

[6]Department of Neurology, Ronald Reagan UCLA Medical Center, Los Angeles, California, USA

[7]Strongbridge Biopharma, Trevose, Pennsylvania, USA

Correspondence
Valeria A. Sansone, Neuromuscular Omnicentre, Neurorehabilitation Unit, University of Milan, Niguarda Hospital, Piazza Ospedale Maggiore, 3, Milano 20162, Italy.
Email: valesans65@gmail.com

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Abstract

Introduction/Aim: Long-term efficacy and safety of dichlorphenamide (DCP) were characterized in patients with primary periodic paralysis (PPP).

Methods: Patients with PPP in a double-blind, placebo-controlled study were randomly assigned to receive DCP 50 mg twice daily or placebo for 9 weeks, followed by a 52-week open-label DCP treatment phase (DCP/DCP and placebo/DCP populations). Efficacy (attack rate, severity-weighted attack rate) and safety were assessed in patients completing the study (61 weeks). In this post hoc analysis, efficacy and safety data were pooled from hyperkalemic and hypokalemic substudies.

Results: Sixty-three adults (age, 19-76 years) completed the double-blind phase; 47 (74.6%) of these patients completed 61 weeks. There were median decreases in weekly attack and severity-weighted attack rates from baseline to week 61 (DCP/DCP [n = 25], −1.00 [$P < .0001$]; placebo/DCP [n = 20], −0.63 [$P = .01$] and DCP/DCP, −2.25 [$P < .0001$]; placebo/DCP, −1.69 [$P = .01$]). Relatively smaller median decreases in weekly attack and severity-weighted attack rates occurred from weeks 9 to 61 among patients receiving DCP continuously (n = 26; −0.14 [$P = .1$] and −0.24 [$P = .09$]) than among those switching from placebo to DCP after 9 weeks (n = 16; −1.04 [$P = .049$] and −2.72 [$P = .08$]). Common adverse events (AEs) were paresthesia and cognition-related events, which typically first occurred within 1 month of blinded treatment initiation and in rare cases led to treatment discontinuation. Dose reductions were frequently associated with common AE resolution.

Discussion: One-year open-label DCP treatment after a 9-week randomized, controlled study confirmed long-term DCP remains safe and effective for chronic use. Tolerability issues (paresthesia, cognition-related AEs) were manageable in most patients.

KEYWORDS
efficacy, hypokalemic periodic, paralysis, paralysis, safety, weakness

Abbreviations: AE, adverse event; DCP, dichlorphenamide; ITT, intent to treat; NA, not applicable; PPP, primary periodic paralysis.

This research was presented in part at the Muscle Study Group Annual Scientific Meeting, September 2018, Oxford, UK, and at the 71st Annual Meeting of the American Academy of Neurology, May 2019, Philadelphia, Pennsylvania.

1 | INTRODUCTION

Primary periodic paralyses (PPP; hyperkalemic and hypokalemic paralysis) are rare, hereditary skeletal muscle ion channelopathies that lead to attacks of muscle weakness.[1] Management of PPP includes long-term pharmacologic therapy to minimize attack frequency and severity.[1] The oral carbonic anhydrase inhibitor dichlorphenamide (DCP) is approved for treatment of hyperkalemic and hypokalemic periodic paralyses and related variants.[1,2]

Two randomized, double-blind, placebo-controlled studies, each with hyperkalemic and hypokalemic PPP substudies, demonstrated the effectiveness of DCP to prevent attacks of muscle weakness. The first study demonstrated that 9-week daily DCP treatment decreased attack frequency and severity in 73 patients with hypokalemic and hyperkalemic paralysis (age, 10-75 years).[3] In the second study, HYPHOP, daily DCP treatment reduced the frequency, severity, and duration of paralytic attacks in 65 adults during weeks 2 to 9 of a 9-week double-blind, placebo-controlled treatment period among patients with hypokalemic paralysis, and also during weeks 54 to 61 of a 1-year open-label extension.[4] Common adverse events (AEs) in both studies were paresthesia and cognitive changes (ie, confusion, depression, disorientation, memory issues, slowed mentation).[3,4] However, as the number of patients within each disease phenotype was relatively small by week 61, the current analysis addresses this sample size limitation by pooling key study data from the disease phenotype substudies to examine persistency of treatment benefit and further characterize the tolerability of DCP in PPP using pooled data from hyperkalemic and hypokalemic substudies of HYPHOP.[4]

2 | METHODS

2.1 | Study design and patients

Population and study details from HYPHOP have been described elsewhere.[4] Briefly, adults with hyperkalemic or hypokalemic PPP were randomized to receive double-blind DCP 50 mg or placebo twice daily for 9 weeks, followed by 52-week open-label DCP treatment (DCP/DCP and placebo/DCP populations, respectively).[4] In the double-blind phase, patients treated with DCP at enrollment continued their current DCP dose; those treated with acetazolamide received a DCP dose equivalent to 20% of acetazolamide dosing.[4] After 9 weeks, investigators could reduce or increase DCP dosing as needed. The HYPHOP (ClinicalTrials.gov Identifier NCT00494507) protocol was approved by the institutional review boards of 12 study centers. All patients provided written informed consent.

2.2 | Assessments and statistical analyses

Study completers comprised patients in the intent-to-treat (ITT) population (patients receiving at least one dose of double-blind or open-label DCP treatment) completing the 52-week extension period. Changes in weekly attack rates and severity-weighted attack rates (ie, sum of attack severity scores from 1 to 10 divided by the number of weeks) from baseline to week 61 and from weeks 9 to 61 were analyzed.[4] Within-treatment changes were assessed using the Wilcoxon signed-rank test. Treatment comparisons were analyzed with the blocked Wilcoxon rank-sum test, adjusting for PPP type.

AEs occurring during the 9-week, double-blind phase and the 52-week, open-label extension phase were summarized for the ITT population using the Medical Dictionary for Regulatory Activities version 11.0. For patients who received placebo during the double-blind phase, only AEs occurring during open-label DCP treatment were reported. Kaplan-Meier methods were used to estimate the percentages of patients without an AE over time.

3 | RESULTS

The ITT population comprised 63 patients who received at least one dose of DCP. Of these, 47 completed 61 weeks of treatment. The majority of study completers were male and had hypokalemic PPP (Table 1). The baseline median weekly attack rates and median severity-weighted attack rates were greater in the placebo/DCP group than in the DCP/DCP group. Median decreases in weekly attack and severity-weighted attack rates occurred from baseline to week 61 in both groups (Table 2). Relatively smaller median decreases in weekly attack and severity-weighted attack rates occurred from weeks 9 to 61 among participants receiving DCP continuously than among those switching from placebo to DCP after 9 weeks. Median attack and severity-weighted attack rates did not differ significantly between treatments at week 61 (Table 2 and Figure S1).

Approximately three quarters of patients reported at least one AE during DCP treatment (Table 3), most commonly paresthesia. AEs reported with placebo have been described previously.[4] Fewer than half of the DCP-treated patients reported at least one paresthesia over 61 weeks, the majority of whom had at least one event considered possibly related to the study drug, but none considered severe (Table S1). [Correction added on August 18, 2021 after first online publication: The preceding sentence has been revised from, "..., the majority of whom considered their AE(s) possibly related to the study drug..."] Paresthesia prompted study discontinuation in a single patient, and approximately three quarters of patients reported resolution of the last reported paresthesia during the study. Six of 25 (24.0%) patients reporting paresthesia were managed with DCP dose reduction (range, 25-100 mg); of these, 5 (83.3%) had resolution after dose reduction. Onset of paresthesia typically was within the first month of receiving DCP (Figure S2A and B).

The second most common were cognition-related AEs, reported for approximately one quarter of DCP-treated patients over 61 weeks (Table S1). The majority of cognition-related AEs were mild, with severe events and AE-related study discontinuations rarely occurring. Approximately two thirds of patients with cognition-related AEs reported the last event resolved while they participated in the study. Six (37.5%) patients were managed with DCP dose reduction (range, 25-50 mg), with all having resolution thereafter. One patient

TABLE 1 Patient disposition and double-blind baseline demographic and disease state characteristics

	ITT population (n = 63)		Study completer population (n = 47)	
Parameter	**DCP/DCP (n = 36)**	**Placebo/DCP (n = 27)**	**DCP/DCP (n = 26)**	**Placebo/DCP (n = 21)**
Patient disposition, n (%)				
Completion of 9-week double-blind phase	31 (86.1)	27 (100)	NA	NA
Completion of 52-week open-label phase	26 (72.2)	21 (77.8)	NA	NA
Age, years				
Mean (SD)	42.9 (13.3)	45.2 (15.6)	40.9 (14.2)	43.4 (15.9)
Range	19-76	19-76	19-76	19-76
Male, n (%)	22 (61.1)	17 (63.0)	17 (65.4)	13 (61.9)
Race, n (%)				
White	30 (83.3)	23 (85.2)	22 (84.6)	17 (81.0)
Hispanic	4 (11.1)	2 (7.4)	3 (11.5)	2 (9.5)
Other	2 (5.6)	1 (3.7)	1 (3.8)	1 (4.8)
Not reported	0	1 (3.7)	0	1 (4.8)
Type of PPP, n (%)				
Hypokalemic	24 (66.7)	19 (70.4)	17 (65.4)	14 (66.7)
Hyperkalemic	12 (33.3)	8 (29.6)	9 (34.6)	7 (33.3)
Median weekly attack rate	1.75	2.25[a]	1.75	3.00[b]
Median severity-weighted weekly attack rate	3.25	5.88[a]	2.25	5.88[c]

Abbreviations: DCP, dichlorphenamide; ITT, intent-to-treat; NA, not applicable; PPP, primary periodic paralysis; SD, standard deviation.
[a]$P = .5$ (between-treatment comparison for the ITT population based on blocked Wilcoxon rank-sum test).
[b]$P = .2$ (between-treatment comparison for the study completer population based on blocked Wilcoxon rank-sum test).
[c]$P = .3$ (between-treatment comparison for the study completer population based on blocked Wilcoxon rank-sum test).

discontinued treatment twice (ie, motor vehicle accident, hospitalization for thyroid cancer surgery), which resulted in a dose reduction from 150 to 0 mg each time; treatment was reinitiated, but an increase in DCP dosing from 150 to 200 mg resulted in cognitive disturbance, leading to a dose reduction to 150 mg. In addition to this patient, one patient increased DCP dosing after dose reduction (50 mg). Onset of cognition-related AEs typically was within the first month of DCP treatment (Figure **S2**C and D).

Nephrolithiasis as an AE was reported by three patients in the study (Table 3). One patient withdrew from the study due to this AE, although ultrasound did not indicate any changes from baseline in the appearance of the kidney stones at the time of study withdrawal. At baseline, eight patients had ultrasound evidence of nephrolithiasis. During treatment, one of the eight patients had an increase in size or number of kidney stones, whereas four had a decrease in the number of kidney stones during the study. Of the 57 patients with post-baseline data available for nephrolithiasis, 10 (17.5%) had an increase in the size or number of kidney stones. Only one of these 10 patients had baseline evidence of kidney stones. Incident nephrolithiasis was benign in all patients and was not associated with AEs.

4 | DISCUSSION

These post-hoc analyses extend findings from the original HYPHOP study by demonstrating that efficacy was maintained over the 61-week study with no evidence of waning over time. Indeed, there was evidence of further reduction in median weekly attacks among continuous DCP users to nearly none by study end. Likewise, patients who were switched from placebo to open-label DCP after week 9 nearly "caught up" with those who had been continuously treated with DCP over the entire study.

AE analyses indicated no new safety signals during the final 52 weeks of the study vs the first 9 weeks, and paresthesia and cognition-related AEs, which were the most commonly reported AEs during the first 9 weeks, were generally not reported during the extension. Clinicians can advise patients starting DCP that most patients who had one of these events initially reported it within the first month of treatment. Temporary dose reduction seems to be a reasonable maneuver to manage bothersome paresthesia or cognition-related AEs, given that patients with these AEs who were investigator-managed with dose reduction had subsequent symptom resolution. Likewise, it may be helpful to titrate slowly when escalation above the starting dose is needed to achieve efficacy. Treatment was associated with development of incident nephrolithiasis, which was mostly benign in nature, and an increase in stone size or growth during treatment was common. Surprisingly, among the eight patients with prevalent nephrolithiasis at study entry, kidney stone size or number was more often reduced rather than increased during treatment, suggesting that the stones in these patients may not have been influenced by the same pathogenesis that led to incident stone formation and growth.

TABLE 2 Summary of efficacy (study completer population)

	DCP/ DCP (n = 26)	Placebo/ DCP (n = 21)
Median weekly attack rate		
Baseline	1.75[a]	3.00[b]
Week 9	0.32	2.13[c]
Week 61[d]	0.06	0.25
Median change from baseline to week 61	−1.00	−0.63
Median percent decrease from baseline to week 61	93.8	75.0
P value of the median decrease	<.0001	.01
Median change from week 9 to week 61	−0.14	−1.04
Median percent decrease from week 9 to week 61	77.1	62.6
P value of the median decrease	.1	.049
Median severity-weighted attack rate		
Baseline	2.25[a]	5.88[b]
Week 9	0.58	5.02[c]
Week 61[e]	0.06	0.50
Median change from baseline to week 61	−2.25	−1.69
Median percent decrease from baseline to week 61	97.1	80.8
P value of the median decrease	<.0001	.01
Median change from week 9 to week 61	−0.24	−2.72
Median percent decrease from week 9 to week 61	72.6	57.8
P value of the median decrease	.09	.08

Abbreviations: DCP, dichlorphenamide.
[a]n = 25 (diary data missing for 1 patient).
[b]n = 20 (diary data missing for 1 patient).
[c]n = 16 (5 patients reached the endpoint of acute worsening of attacks during the double-blind phase, necessitating protocol-specified withdrawal and initiation of participation in the open-label extension phase).[4]
[d]*P* = .04 for the between-treatment difference for the change from week 9 to week 61. *P* = .14 for between-treatment difference at week 61 (blocked Wilcoxon rank-sum test).
[e]*P* = .08 for the between-treatment difference at week 61 (blocked Wilcoxon rank-sum test).
[Correction added on August 18, 2021 after first online publication: The values in the first part of Table 2 have been moved down by one row.]

Limitations include subjective measures of efficacy, lack of a comparator arm throughout the study, and lack of interim efficacy determination between weeks 9 and 61.

In conclusion, these analyses support long-term daily DCP to prevent attacks of muscle weakness in PPP, and they provide potentially useful information for patient counseling and management.

TABLE 3 Summary of AEs with DCP treatment (ITT population)

AEs	Patients, n (%)	
	Baseline to week 61 (n = 63)	Week 9 to week 61 (n = 58)
≥1 AE	47 (74.6)	35 (60.3)
≥1 treatment-related AE	38 (60.3)	20 (34.5)
≥1 serious AE	4 (6.3)	3 (5.2)
AEs reported in ≥5% of patients in either treatment period		
Paresthesia	25 (39.7)	9 (15.5)[a]
Cognitive disorder[b]	9 (14.3)	5 (8.6)
Fall	7 (11.1)	6 (10.3)
Headache	7 (11.1)	3 (5.2)
Diarrhea	6 (9.5)	4 (6.9)
Dysgeusia	6 (9.5)	2 (3.4)
Fatigue	6 (9.5)	2 (3.4)
Pruritus	5 (7.9)	2 (3.4)
Rash	5 (7.9)	2 (3.4)
Confusional state[c]	4 (6.3)	0
Muscle spasms	4 (6.3)	1 (1.7)
Nasopharyngitis	3 (4.8)	3 (5.2)
Nephrolithiasis[d]	3 (4.8)	3 (5.2)
Pain in extremity	3 (4.8)	3 (5.2)

Abbreviations: AE, adverse event; DCP, dichlorphenamide; ITT, intent-to-treat.
[a]Eight patients received placebo during the 9-week double-blind phase.
[b]AEs classified under Medical Dictionary for Regulatory Activities (MedDRA; version 11.0) Preferred Term "cognitive disorder" include cognitive disturbance, cognitive impairment, confusion/feels foggier, fogginess, mental fog, and spacey/foggy.
[c]AEs classified under MedDRA (version 11.0) Preferred Term "confusional state" include confusion and mental confusion.
[d]One patient discontinued from the study due to this AE, which was not associated with any visible ultrasound changes from baseline at the time of study withdrawal.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Nicholas E. Johnson https://orcid.org/0000-0002-3917-4257
Jeffrey M. Statland https://orcid.org/0000-0003-0790-5315
Perry B. Shieh https://orcid.org/0000-0001-7145-7663

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Relative effects of forced vital capacity and ALSFRS-R on survival in ALS

Salah A. Daghlas BS[1] | Raghav Govindarajan MD[2] | the Pooled Resource Open-Access ALS Clinical Trials Consortium

[1]University of Missouri-Columbia, School of Medicine, Columbia, Missouri

[2]Department of Neurology, University of Missouri-Columbia, Columbia, Missouri

Abstract

Introduction/Aim: Amyotrophic lateral sclerosis (ALS) is a degenerative neuromuscular disease with marked clinical heterogeneity. This heterogeneity can be partly captured by clinical measures, such as the forced vital capacity (FVC) and ALS Functional Rating

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; AUC, area under the curve; BMI, body mass index; CI, confidence interval; FVC, forced vital capacity; HR, hazard ratio; PRO-ACT, Pooled Resource Open-Access ALS Clinical Trials; ROC, receiver operator characteristic.