Heterotopic Ossification in Palovarotene-Treated and Untreated Individuals with Fibrodysplasia Ossificans Progressiva: Matched and Weighted Analyses

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Background

- Fibrodysplasia ossificans progressiva (FOP) is an ultra-rare, genetic disorder characterized by congenital skeletal malformations and episodic, abnormal bone formation in soft and connective tissues, known as heterotopic ossification (HO).[1,2]
- HO leads to progressive restriction of movement, cumulative disability, and a shortened life expectancy in individuals with FOP.[3–5]
- The current standard of care for individuals with FOP is mainly palliative, and limited to symptom management and flare-up prevention.[6]
- Palovarotene, an orally bioavailable retinoic acid receptor agonist, potently downregulates the bone morphogenetic protein (BMP) signalling pathway that is enhanced in FOP;[7] it is the first treatment shown to reduce new HO in individuals with FOP versus standard of care.[8,9]
- The open-label, phase III MOVE trial (NCT03312634) assessed the efficacy and safety of palovarotene in individuals with FOP,[9] and a non-interventional FOP natural history study (NHS; NCT02322255) evaluated disease progression over 36 months in individuals who were untreated beyond standard of care.[10]

Objective

To report post hoc matched and weighted analyses of HO volume changes observed in individuals with FOP treated with palovarotene during the phase III MOVE trial versus untreated individuals from the FOP NHS, to allow further evaluation of palovarotene for the treatment of FOP while accounting for differences between populations.

Methods

- Mean annualized new HO volume changes assessed by low-dose whole-body computed tomography from baseline until last available assessment were compared for individuals receiving palovarotene (MOVE) and individuals who did not receive treatment beyond standard of care (NHS).
  - This analysis excluded individuals who transitioned from the NHS to MOVE.
  - The MOVE Interim Analysis 3 (IA3) dataset was used, when all individuals had completed Month 18 assessments.
- Propensity score matching, and unstabilized and stabilized weighting, were conducted to adjust for baseline differences between the independent groups.
  - Propensity scores were estimated via multivariable logistic regression on baseline age, sex, age-adjusted baseline HO, baseline Cumulative Analogue Joint Involvement Scale (CAJIS) score, and time since last flare-up.
- Sensitivity analyses were conducted with HO volume reductions recoded as zero change and with square-root transformations applied to this outcome.

Results

- Overall, 61 untreated individuals (mean follow-up: 25.8 months) and 58 individuals receiving palovarotene (mean follow-up: 15.6 months) were included in the propensity score analyses.
  - From this, 39 untreated and treated individuals were successfully matched with balanced baseline characteristics **(Table 1)**.
  - Similarly balanced baseline characteristics were seen with unstabilized and stabilized propensity score weighting (data not shown).
- Mean annualized new HO volume was 76.9% lower in individuals treated with palovarotene versus untreated individuals after propensity score matching (p<0.05; **Figure 1**).
- Mean annualized new HO volume was 67.1% and 67.2% lower in treated versus untreated individuals after unstabilized (p<0.05) and stabilized (p<0.05) propensity score weighting, respectively **(Figure 2)**.
- Sensitivity analyses, with HO volume reductions recoded as zero and square-root transformation, yielded similar directions of effects as the primary analyses but with varying statistical significance **(Table 2)**.

CONCLUSIONS

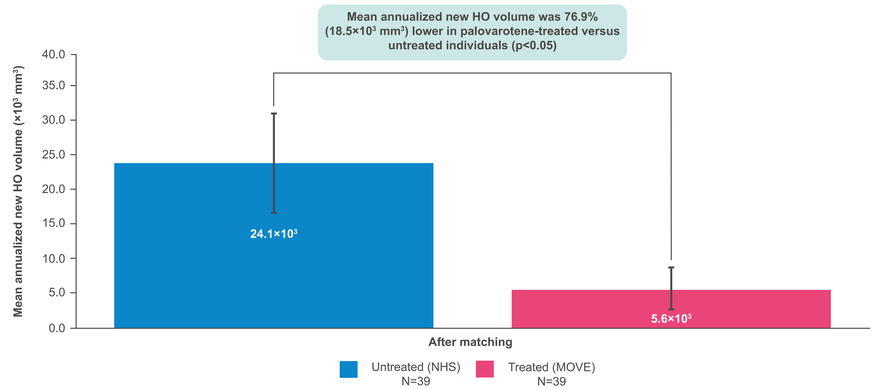
- Propensity score matched and weighted analyses revealed significantly lower mean annualized new HO volume in individuals who received palovarotene treatment versus individuals who were untreated beyond standard of care.
- While matched and weighted analyses adjusted for pre-specified prognostic factors, as a study of non-randomized treatment groups, there is a risk of confounding by unobserved factors.
- These post hoc results reinforce findings from the phase III MOVE trial,[9] and support the potential of palovarotene as a therapeutic option for individuals with FOP.

Table 1. Baseline characteristics in treated and untreated individuals before and after propensity score matching

	Before matching				After matching			
	Untreated (NHS) N=61	Treated (MOVE) N=58	Mean difference	Standardized mean difference (p-value)	Untreated (NHS) N=39	Treated (MOVE) N=39	Mean difference	Standardized mean difference (p-value)
Age at baseline (years), mean ± SD	20.7 ± 9.9	14.6 ± 9.5	−6.1 ± 1.8	0.630 (<0.001*)	17.0 ± 7.6	17.1 ± 10.4	0.1 ± 2.1	0.010 (0.965)
Female, n (%)	29 (47.5%)	31 (53.5%)	5.9%	0.118 (0.645)	18 (46.2%)	18 (46.2%)	0.0%	0.000 (1.000)
Male, n (%)	32 (52.5%)	27 (46.6%)	−5.9%	0.118 (0.645)	21 (53.9%)	21 (53.9%)	0.0%	0.000 (1.000)
Baseline CAJIS score, mean ± SD	13.3 ± 7.2	9.4 ± 6.0	−3.9 ± 1.2	0.586 (<0.01*)	10.7 ± 6.4	11.1 ± 6.3	0.4 ± 1.4	0.057 (0.803)
Age-adjusted baseline HO (×10³ mm³), mean ± SD	121.8 ± 54.6	100.2 ± 51.9	−21.7 ± 9.8	0.407 (<0.05*)	115.1 ± 58.7	113.3 ± 53.3	−1.9 ± 12.7	0.034 (0.882)
Time since last flare-up (months), mean ± SD	20.8 ± 34.1	26.8 ± 39.4	6.0 ± 6.8	0.164 (0.374)	24.0 ± 36.4	30.0 ± 43.7	5.9 ± 9.1	0.148 (0.516)

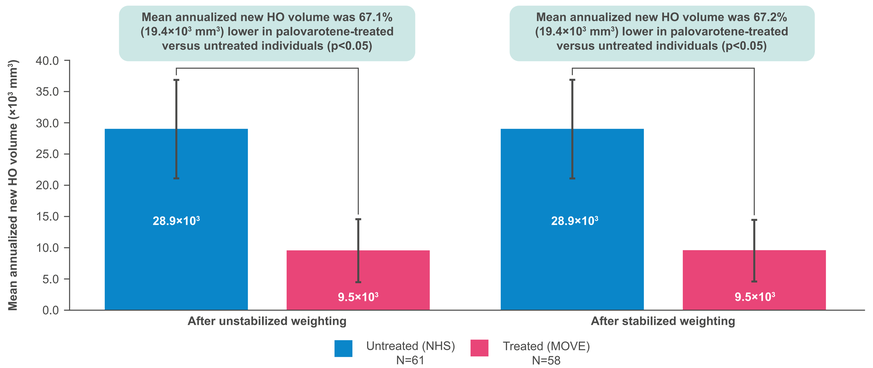
*Indicates statistical significance. Data are presented to one decimal place. Statistical comparisons were assessed using two sample t-tests for continuous variables, and chi-squared tests for categorical variables.

Figure 1. Mean annualized new HO volume in treated and untreated individuals after propensity score matching



Data are presented as mean ± SEM to one decimal place. Statistical comparisons were assessed using two sample t-tests.

Figure 2. Mean annualized new HO volume in treated and untreated individuals after unstabilized and stabilized propensity score weighting



Data are presented as mean ± SEM to one decimal place. Statistical comparisons were assessed using two sample t-tests. Unstabilized weights for individuals receiving palovarotene and untreated individuals were calculated as the inverse of the propensity score and the inverse of one minus the propensity score, respectively; stabilized weights were calculated by multiplying the unstabilized weights by the marginal probability of receiving treatment.

Table 2. Sensitivity analyses of matched and weighted analyses with HO volume reductions recoded as zero change and with square-root transformation

		After matching			After unstabilized weighting			After stabilized weighting		
		Untreated (NHS) N=39	Treated (MOVE) N=39	Mean difference (p-value)	Untreated (NHS) N=61	Treated (MOVE) N=58	Mean difference (p-value)	Untreated (NHS) N=61	Treated (MOVE) N=58	Mean difference (p-value)
Sensitivity analyses of mean annualized new HO volume	**With reductions recoded as zero (×10³ mm³), mean ± SEM**	25.8 ± 7.1	11.2 ± 3.3	−14.6 (0.06)	30.4 ± 7.4	15.8 ± 4.5	−14.5 (0.09)	30.4 ± 7.4	15.8 ± 4.5	−14.5 (0.09)
	With square-root transformation (×10³ mm³), mean ± SEM	0.2 ± 0.04	0.1 ± 0.03	−0.05 (0.25)	0.2 ± 0.03	0.1 ± 0.03	−0.03 (0.55)	0.2 ± 0.03	0.1 ± 0.03	−0.03 (0.54)

Data are presented to one decimal place. Statistical comparisons were assessed using two sample t-tests. Unstabilized weights for individuals receiving palovarotene and untreated individuals were calculated as the inverse of the propensity score and the inverse of one minus the propensity score, respectively; stabilized weights were calculated by multiplying the unstabilized weights by the marginal probability of receiving treatment.

Abbreviations BMP: bone morphogenetic protein; CAJIS: Cumulative Analogue Joint Involvement Scale; FOP: fibrodysplasia ossificans progressiva; HO: heterotopic ossification; IA3: interim analysis 3; NHS: natural history study; SD: standard deviation; SEM: standard error of the mean.

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