Relating Heterotopic Ossification Volume to Joint Function and Quality of Life: A Simulation Study in Fibrodysplasia Ossificans Progressiva

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Background

- Fibrodysplasia ossificans progressiva (FOP) is an ultra-rare, severely disabling genetic disease characterized by the formation of bone (heterotopic ossification [HO]) in muscles, tendons, ligaments, fascia, and aponeuroses.[1]
- HO leads to progressive disability, severe functional limitations in joint mobility, and a shortened lifespan.[1]
- With an estimated prevalence of 1.36 per million individuals worldwide (range: 0.036–1.428 per million individuals),[2] it is difficult to conduct clinical trials in this population:
  - Disease rarity may lead to insufficient power to find statistically significant effects for all except the largest treatment effects.[3,4]
  - Disease heterogeneity coupled with challenges related to validated trial outcomes might impact certainty in efficacy estimations.[3,5]
- In FOP, the relationship between HO volume and functional and quality of life (QoL) outcomes merits further investigation.
- Due to the small number of real-world patients, computer simulations can be used to enhance interpretation of trial data in FOP.

Objective

To determine whether significant differences in functional and QoL outcomes can be expected in a trial that showed substantial reductions in HO volume in patients with FOP.

Methods

- A patient-level model was used to simulate patient histories up to the end of a 2-year, 2-arm trial, varying the effect of the intervention on extra bone growth as measured by HO volume.
- Baseline estimates with treatment (n=99) were based on the phase 3 MOVE trial (NCT03312634), while baseline estimates without treatment (n=111) were based on the international FOP Natural History Study (NCT02322255).
- Outcomes of interest were the Cumulative Analogue Joint Involvement Scale (CAJIS), FOP-Physical Function Questionnaire (FOP-PFQ), and the Patient Reported Outcome Measure Information System (PROMIS).
- Sets of 1000 trial simulations were run, with varying levels of HO reduction and varying levels of random noise, while assuming linear relationships between HO volume and the outcome measures:
  - HO volume changes were derived from the FOP NHS.
  - The dependence structure between HO regions was maintained in the simulation and based on the FOP NHS and the MOVE trial.
  - Prevention of new HO volume in nine body regions was modelled as a percentage in the intervention arm, ranging from 0% to 100% in increments of 25%.
  - Random noise was included to simulate real-world heterogeneity; it was varied in scale by adjusting the standard deviation.
- **Figure 1** provides an overview of the three analyses performed on the model simulations:
  - Calculations assessed the likelihood of finding a relationship between HO volume and outcomes, and the likelihood of finding an intervention effect on outcomes.

Results

- **Figure 1** provides an overview of the results for each analysis.
- **Figure 2** and **Figure 3** provide more detail on analyses 2 and 3, respectively, where the probability is estimated by the percentage of simulated trials where statistically significant results are found ($p<0.05$). Each panel in **Figure 3** corresponds to a different scale of standard deviation.
- Overall, the simulations showed that there was a low probability of finding a significant effect of treatment ($p<0.05$) on CAJIS, FOP-PFQ or PROMIS in the simulated 2-year trials, although an implicit relationship could be found cross-sectionally (by pooling data from both groups).
- The low probability of finding a treatment effect was present, even when treatment completely halted all new HO volume, and no random noise was included.

Figure 1. Overview of the analyses and results

Analysis 1: Strength of the relationship between the endpoints

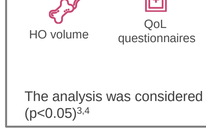
Assuming a linear relationship between HO volume and summary scores for CAJIS, FOP-PFQ and PROMIS, it was tested whether this relationship could consistently be detected.

Significant relationships ($p<0.05$) between HO volume and the functional and QoL questionnaires could be found at all points in time and over all levels of random noise.

Analysis 2: Treatment effect on HO volume

The HO volume between intervention and comparator groups was compared at baseline, at year 1 and year 2. The probability of finding a significant difference between the HO volume in these two groups is shown in **Figure 2**.

The analysis found that the trials were not powered to detect a significant difference ($p<0.05$) in HO volume between study groups, regardless of time and new HO volume prevention.



Analysis 3: Treatment effect on CAJIS, FOP-PFQ, and PROMIS

Given an assumed linear relationship between HO volume and the three outcome measures, it was tested whether study groups had significant differences when considering CAJIS, FOP-PFQ or PROMIS, rather than HO as in Analysis 2.

While a linear relationship between HO volume and outcome measures could be detected (Analysis 1), a significant difference ($p<0.05$) in CAJIS, FOP-PFQ, and PROMIS scores could not be found between the two study groups, even with no random noise and new HO volume prevention of 100%.

The analysis was considered to have enough power when more than 80% of simulated trials found a statistically significant treatment effect ($p<0.05$)[3,4]

CONCLUSIONS

- This analysis found that, given the limited number of observations used in the simulated trials, there was not enough power to reliably find a treatment effect in HO volume, even if present.
- When very strong relationships were imposed between HO volume and CAJIS, FOP-PFQ, and PROMIS, it was unlikely that a statistically significant treatment effect ($p<0.05$) would be found. This held true even when assuming a treatment effect of 100% and no random noise in the relationship between HO and CAJIS, FOP-PFQ, and PROMIS.
- Given the limited number of patients which can practically be enrolled in an FOP trial, a treatment effect on HO volume does not imply significant effects ($p<0.05$) on functional and QoL outcomes.
- This lack of power is a result of substantial HO volume heterogeneity, insufficient patient numbers and random noise. The lack of statistically significant results in the context of this simulation does not imply that there is no treatment effect.
- This study highlights the challenges of conducting clinical trials in ultra-rare diseases.

Figure 2. Treatment effect on HO volume

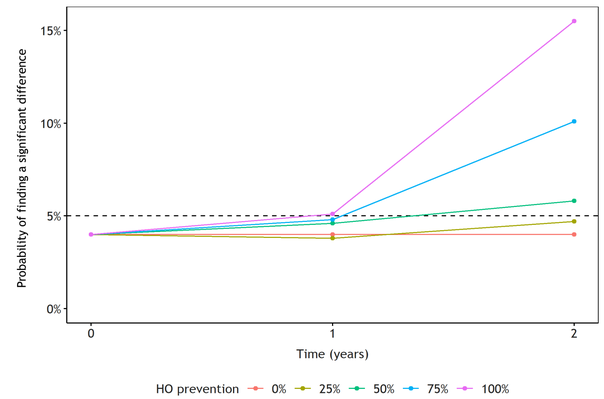
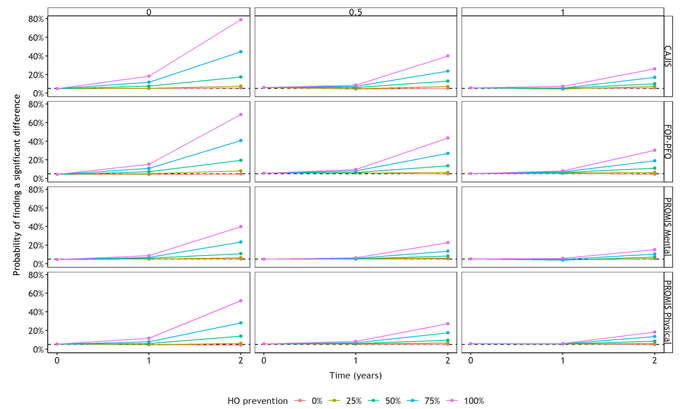


Figure 3. Treatment effect on CAJIS, FOP-PFQ, and PROMIS



The probability of finding a significant difference represents the likelihood of finding a statistically significant ($p<0.05$) treatment effect based on 1000 simulations.

Abbreviations CAJIS: Cumulative Analogue Joint Involvement Scale; FOP: fibrodysplasia ossificans progressiva; FOP-PFQ: FOP Physical Function Questionnaire; HO: heterotopic ossification; PROMIS: Patient-Reported Outcome Measurement Information System; QoL: quality of life.

References 1. Mahboubi S et al. Pediatr Radiols 2001;31(5):307–14; **2.** Baujat G et al. Orphanet J Rare Dis 2017;12(1):123; **3.** Nestler-Parr S et al. Value in Health 018;21(5):493–500; **4.** Jones SR et al. Emerg Med J 2003;20(5):453–8; **5.** Cox GF. Am J Med Genet A 2018;176(4):759–772.

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