Poster No: P.71

Vamorolone has shown less impact than daily prednisone or deflazacort on height and body mass index in patients with Duchenne muscular dystrophy (DMD)

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Introduction

- Glucocorticoid (GC) treatment is recommended as a standard of care in Duchenne muscular dystrophy (DMD).[1] Daily regimens of GCs such as prednisone or deflazacort have been shown to be efficacious in the treatment of DMD by improving muscle function.[2]
- Weight gain and stunting of growth are among the most frequently reported side effects of the daily regimens of prednisone and deflazacort.[1]
- The efficacy and safety of prednisone and deflazacort were compared in the randomized, double-blind study, FOR-DMD:[2]
  - Treatment with daily prednisone or daily deflazacort, compared with intermittent prednisone alternating 10 days on and 10 days off, resulted in significant improvement in the efficacy outcomes over 3 years. There was no significant efficacy difference between the two daily GC regimens, which both outperformed the intermittent regimen.
- Vamorolone is a dissociative steroidal anti-inflammatory drug that seeks to retain efficacy and reduce safety concerns in patients with DMD compared to GCs via changes to structure/activity relationships with the GC receptor.[3]
- The efficacy and safety of vamorolone was investigated during the first 24 weeks (Period 1) of a randomized, double-blind study (VBP15-004, NCT03439670):
  - The results of the primary analysis at 24 weeks have been reported previously.[4]
  - The study met its primary endpoint; both doses of vamorolone (6 mg/kg/day and 2 mg/kg/day) showed statistically significant and clinically meaningful improvement in functional outcomes vs. placebo after 24 weeks of treatment.
- Through 48 weeks (Period 2), efficacy was maintained for the 6 mg/kg/day dose across all outcome measures, while only across some measures for the 2 mg/kg/day dose.
- The long-term effects of vamorolone were investigated in a 2.5-year study, VBP15-LTE:[5]
  - Vamorolone was associated with maintenance of muscle strength and function for up to 2.5 years.

Objective

- The objective of this analysis was to compare the effect of prednisone (PDN), deflazacort (DFZ) and vamorolone (VAM) on height and body mass index (BMI) in DMD patients aged 4 to <7 years at treatment initiation.

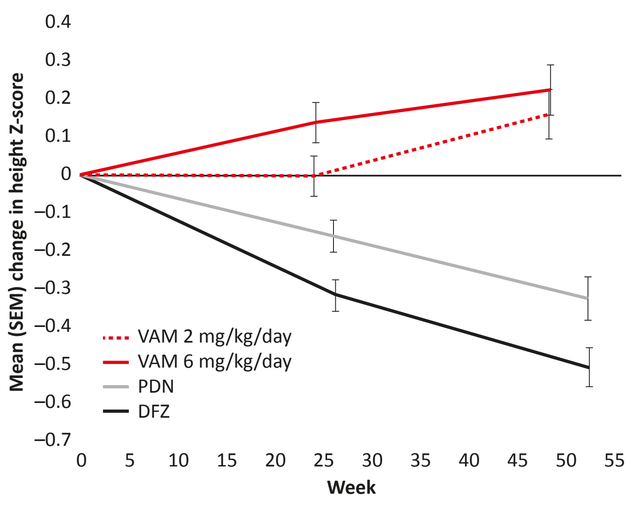
Methods

- In this post-hoc, cross-study comparison, data were analyzed from two randomized, double-blind studies (FOR-DMD[2] and VBP15-004[4]) and one open-label study (VBP15-LTE[5]). The data from the double-blind studies were compared during the 1-year (48–52 weeks) treatment period (VBP15-004 vs FOR-DMD). The long-term data were compared during the 2.5-year treatment period (FOR-DMD vs VBP15-LTE).
  - Patients treated with PDN 0.75 mg/kg/day (n=55) or DFZ 0.9 mg/kg/day (n=49) from the FOR-DMD study were compared to those treated with VAM 2 mg/kg/day (n=28) or VAM 6 mg/kg/day (n=28) in the VBP15-004 study (up to 48 weeks) or treated with 2–6 mg/kg/day flexible dosing in the VBP15-LTE study (n= 46; up to 2.5 years).
- The patients meeting the common inclusion criteria of all studies (subjects with confirmed DMD aged 4 to <7 years at baseline, able to walk independently and complete the time to stand test without assistance) were extracted for the analysis.
- Height and BMI Z-scores were calculated using the Centers for Disease Control and Prevention (CDC) growth data. Changes from baseline and annualized slopes of changes were analyzed with Mixed Model for Repeated Measures or as cumulative response plots.
- The BMI Z-scores were analyzed both as actual changes from baseline and as conditional changes from baseline by calculating baseline-adjusted changes in BMI Z-scores.[6] An annual change >1 standard deviation score (SDS) in the conditional BMI was defined as a clinically significant change.[6]

Results

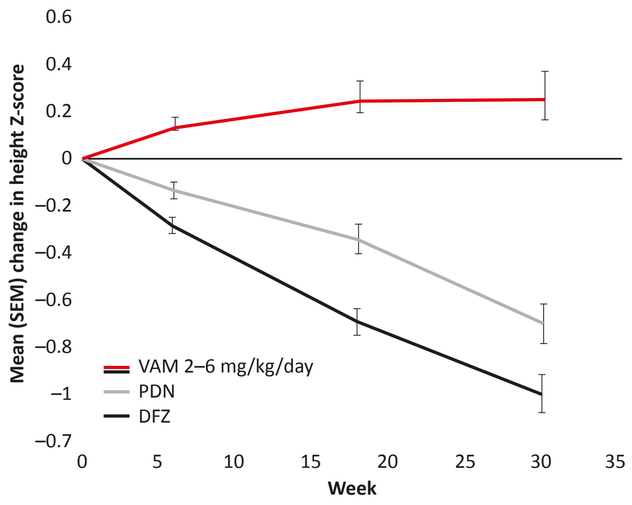
- At Weeks 48–52, the mean height Z-scores decreased in the PDN (-0.30 SDS) and DFZ groups (-0.50 SDS), whereas they increased in the VAM 2 mg/kg/day group (+0.16 SDS) and VAM 6 mg/kg/day group (+0.29 SDS) **(Figure 1)**.
- After 2.5 years of treatment, the height Z-scores continued to decrease in the PDN group (-0.69 SDS) and DFZ group (-1.0 SDS) and increase in the VAM group with flexible dosing (2–6 mg/kg/day; +0.09 SDS) in the VBPP15-LTE study. The mean difference between VAM and DFZ groups after 2.5 years was approximately 1.3 SDS, and between VAM and PDN groups was approximately 1.0 SDS **(Figure 2)**.
- At Weeks 48–52 and at 2.5 years, most of the patients (>70%) in all groups had higher BMI Z-scores than at baseline.
- After 2.5 years of treatment, large increases in BMI (>0.5, >0.75 or >1.0 SDS) were seen numerically more frequently in DFZ and PDN groups (**Figure 3**).
- When analyzed as conditional annualized changes in BMI Z-scores (i.e., by adjusting for baseline BMI), BMI increased less with VAM, compared with PDN and DFZ **(Figure 4)**.

Figure 1. Mean (SEM) change from baseline in height Z-scores during the 48–52 week treatment period (VBP15-004 and FOR-DMD studies, MMRM)



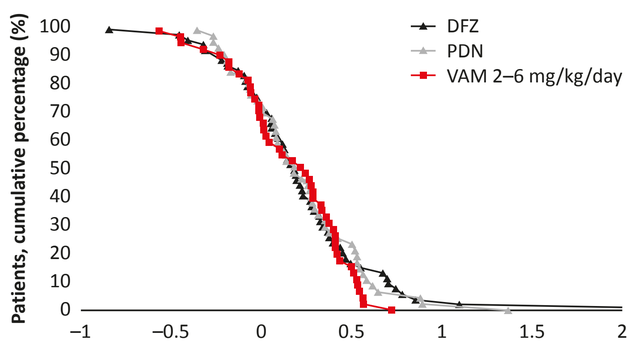
DFZ, deflazacort; MMRM, mixed model for repeated measures; PDN, prednisone; SEM, standard error of the mean; VAM, vamorolone.

Figure 2. Mean (SEM) change from baseline in height Z-scores during a 2.5-year treatment period (VBP15-LTE and FOR-DMD studies, MMRM)



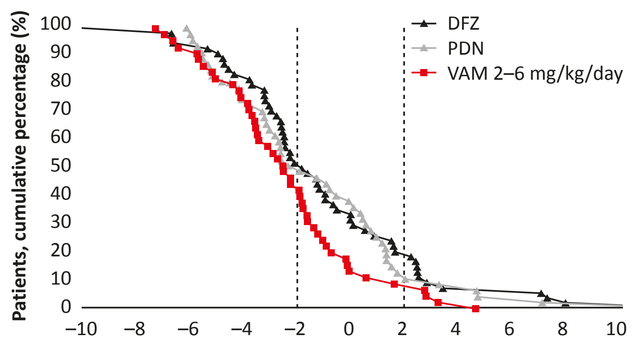
DFZ, deflazacort; MMRM, mixed model for repeated measures; PDN, prednisone; SEM, standard error of the mean; VAM, vamorolone.

Figure 3. Annualized individual changes from baseline in BMI Z-scores during a 2.5-year treatment period (VBP15-LTE and FOR-DMD studies, cumulative response plot)



DFZ, deflazacort; PDN, prednisone; VAM, vamorolone.

Figure 4. Annualized individual conditional changes in BMI Z-scores during a 2.5-year treatment period (VBP15-LTE and FOR-DMD studies, cumulative response plot); change in conditional Z-score >2 SDS is defined as abnormal



DFZ, deflazacort; PDN, prednisone; VAM, vamorolone.

Conclusion

- In conclusion, this post-hoc, cross-study comparison demonstrated that over 1-2.5 years height z-scores decreased with DFZ and PDN, but increased with VAM in patients with DMD. BMI numerically increased less with VAM than DFZ and PDN over that same period.
- Interpretation of the results are limited by this being a post-hoc, cross-study comparison and any conclusions should be made taking this factor into account, given the studies were conducted at different times, under different circumstances and in different protocols.

Acknowledgments

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