Modeling Duchenne muscular dystrophy (DMD) disease progression as assessed by the 6-minute walk test (6MWT)

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Objectives & Methods

Objectives: To quantitatively describe the longitudinal mean and variability of DMD disease progression natural history, and clinical trial placebo and active drug treatment for all current investigational therapeutics with publicly available data.
Methods: PubMed and ClinicalTrials.gov were searched using PRISMA 2009 standards to obtain all publicly available individual-level natural history and treatment arm clinical trial data of the 6MWT in boys under 18 with DMD. Nonlinear mixed effects models were implemented with NONMEM(R) V7.3. Investigational treatment arm data were available from efficacy trials of eteplirsen, drisapersen and ataluren. A model-based meta analysis (MBMA) was conducted to estimate natural history, placebo and drug effect, treating each individual and trial arm as a unique unit (indicated with a subscript (i). A baseline model (BL_i) was fit with initial estimates based on summary statistics of literature population values. The baseline model was exponential function of baseline age (AGE_0), with a sigmoid Emax maturational effect (MAT_i). Final estimates of the baseline model were fixed in the fitting of a longitudinal disease progression model for the 6MWT endpoint ($6MWT_i$). Baseline, longitudinal and placebo effect parameters were fixed when estimating the full drug effect model ($Y_{i,j}$). The residual error ($\epsilon_{i,j}$) and random effects ($\eta_{1-3,i}$) were weighted by the square root of unit sample size.

Background

There are no DMD disease-modifying drugs on the US market, but 3 drugs in development have taken the spotlight. Ataluren (Translarna, PTC Therapeutics) is an oral compound targeting nonsense mutations. In 2014, Ataluren was given accelerated approval in Europe, but the FDA recently presented PTC with a refuse to file letter due to lack of efficacy shown in the back-to-back Ph.2b and Ph.3 trials. Drisapersen (Biomarin Pharmaceutical) is a subcutaneous exon 51 skipping drug. In April, the FDA denied Biomarin's NDA due to lack of efficacy demonstrated in the Ph.2 trial. Eteplirsen (Sarepta Therapeutics), an exon 51 skipping intravenous drug, was rejected by the FDA in both late 2015 and April 2016 due to failure to show efficacy in the Ph.2b trial. These trials all used the 6 minute walk test (6MWT) as the primary endpoint to measure efficacy.

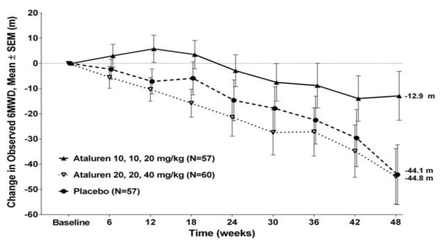

Figure 1: Published summary level clinical trial data from the ataluren Ph.2/3 efficacy trial with 174 total patients [1].

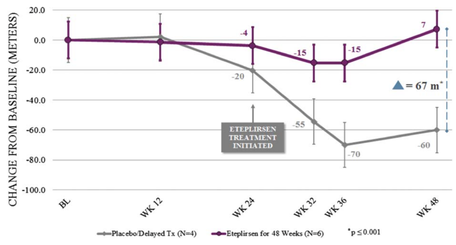

Figure 2: Published summary level clinical trial data from the eteplirsen Ph.2 efficacy trial with 53 total patients [2].

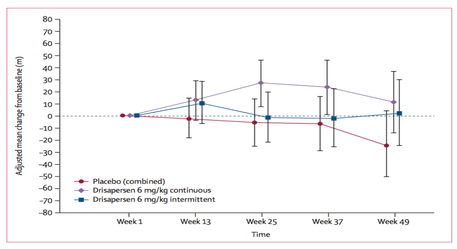

Figure 3: Published summary level clinical trial data from the drisapersen Ph.2 efficacy trial with 12 total patients [3].

Results

Natural history data were available for 194 boys from 4 unique studies [4-7]. 5 boys were excluded due to inability to capture data. 159 boys had baseline data only. γ and θ_2 were highly correlated and difficult to estimate. A sensitivity analysis was conducted to estimate γ, which was then fixed in the estimation of the full baseline model. The standard deviation of the residual error was fixed to the literature value of 4m [8]. The final parameter estimates are shown in Table 1. The ataluren high dose arm drug effect could not be estimated using the current model. The mean response of the high dose arm was lower than that of the placebo arm, causing problems in estimation. Eteplirsen treatment data were as omitted from the drug effect model because of the complexity of the trial design. Week 0-24 placebo data were included in placebo effect estimation.

Parameter	γ	θ_1	θ_2	α	Age_{50}	θ_3	θ_4	PE	$DEFF_1$	$DEFF_2$	$\omega_{1,1}$	$\omega_{2,2}$	$\omega_{3,3}$	σ
Estimate	8	390.4	4.06	-0.023	3.35	-4.12	-4.73	3.80	1.47	5.96e-01	6074	87	0.01	16
RSE (%)	.	6.34	241	65	14.7	34.1	34.3	9.34	193	129	8.34e+04	1.64e+08	1.15e+10	1e+13

$$MAT_i = \theta_1 + \theta_2 * (1 - e^{-\alpha * Age_{0,i}})$$

$$BL_i = MATi * \frac{Age_{0,i}^{\gamma}}{Age_{50}^{\gamma} + Age_{0,i}^{\gamma}} * \eta_{1,i}$$

Slope:

$$\begin{cases} BL_i > 350 & slope = \theta_3 \\ BL_i \leq 350 & slope = \theta_4 \end{cases}$$

$$6MWT_i = BL_i + (slope + \eta_{2,i}) * t$$

Placebo Effect:

$$\begin{cases} If\ placebo\ unit; & PE = PEFF + \frac{\eta_{3,i}}{\sqrt{n}} \\ Else; & PE = 0 \end{cases}$$

Drug effect:

$$\begin{cases} If\ Ataluren\ unit; & DE = DOSE^{DEFF_1} \\ If\ Drisapersen\ Continuous\ unit; & DE = DOSE^{DEFF_2} \\ If\ Drisapersen\ Intermittent\ unit; & DE = (DOSE * 0.9)^{DEFF_2} \\ Else; & DE = 0 \end{cases}$$

$$\text{Total Effect} = \text{PE} + \text{DE}$$

$$Y_{i,j} = 6MWT_i + \text{Total Effect} + \frac{\epsilon_{i,j}}{\sqrt{n}}$$

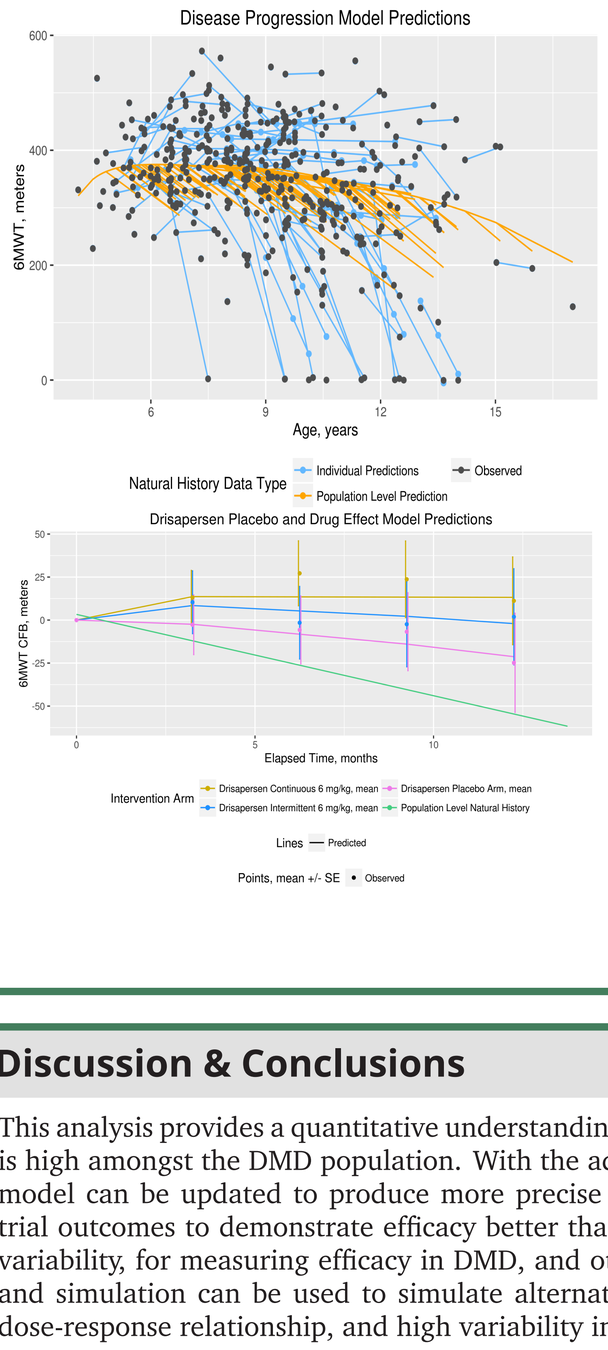

Figure 4: Individual (blue) and population level (orange) predictions of the 6MWT. The (orange) baseline population predicted 6MWT shows a maturational increase up to approximately age 6 years before declining as the disease progresses. Individual predictions show patients with a baseline 6MWT above 350 meters were predicted to have less decline in disease progression compared to those patients with a baseline less than or equal to 350 meters, matching the observed data.

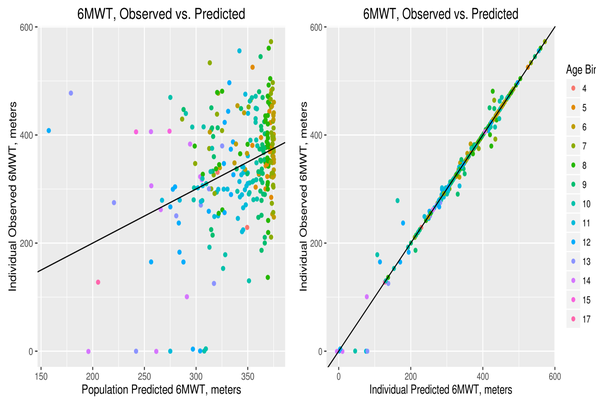

Figure 5: Left, Longitudinal disease progression model individual observed 6MWT versus population level predicted 6MWT with line of unity. Right, Longitudinal disease progression model individual observed 6MWT versus individual predicted 6MWT with line of unity. Using an exponential maturational piece, 6MWT across all ages (ranged from 4-17 years old, binned) was captured heterogeneously.

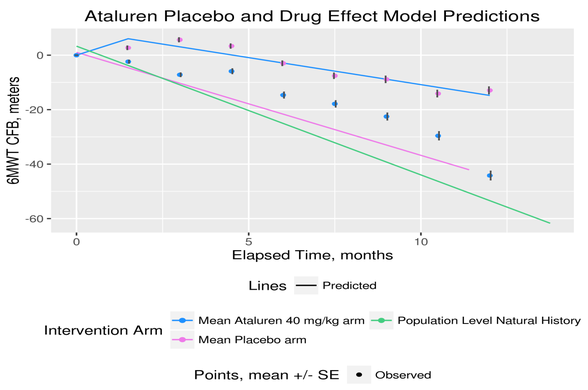

Figure 6: In yellow, the continuous (10 doses over 10 weeks) 6 mg/kg unit showed a significant drug effect with a >30 meter change from placebo (purple) at 1 year. In blue, the intermittent (9 doses over 10 weeks) arm did not show a significant drug effect compared to placebo. Both placebo and drug effect arms show higher 6MWT compared to the natural history population prediction (green). The placebo effect, PE, was estimated to be 3.80 +/-7.33m across all trials. PE was estimated with a high SE because of the variability in the placebo arm of ataluren. $DEFF_1$ was estimated to be 1.47 +/- 0.02. For the continuous drisapersen arm, this gives an estimated DE of 13.93(13.02, 14.90)m, and a drug effect on top of placebo effect of 10.13m. For the intermittent drispersen unit, the estimated DE is 11.93 (11.19,12.71)m with an effect on top of placebo of 8.13 m. $DEFF_1$ was well estimated with a RSE of 1.29%.

Figure 7: Individual level placebo data were combined with intervention arm metadata in MBMA to estimate the ataluren trial drug and placebo effects. The predicted and observed data show a significant difference between the placebo and treatment arm of over 30m. $DEFF_2$ was estimated to be 0.60 +/- 497 m. At a dose of 40 mg/kg, this gives a drug effect of 23.85 (-564.15, 611.85). The placebo effect, PE, was estimated to be 3.80 +/- 7.33m across all trials. This gives an estimated drug effect on top of placebo of 23.47, but the precision in the estimation of $DEFF_2$ was extremely poor. The %RSE was 83400%, so this drug effect can not be interpreted with confidence. There was not enough data to produce a confident estimation, especially with a sample size of 4 patients in the treatment arm and 2 patients in the placebo arm.

Discussion & Conclusions

This analysis provides a quantitative understanding of DMD disease progression using published,natural history 6MWT data. The variability in 6MWT is high amongst the DMD population. With the addition of more clinical trial data or the use of Bayesian estimation and simulation techniques, the model can be updated to produce more precise estimations of the placebo and drug effects. Alternative trial designs may enhance the clinical trial outcomes to demonstrate efficacy better than randomized placebo controlled trials. The 6MWT may not be the best endpoint, given its high variability, for measuring efficacy in DMD, and other clinical endpoints of muscle function may be better suited for DMD efficacy trials. Modeling and simulation can be used to simulate alternative designs when dealing with a small sample size, poorly understood disease mechanism and dose-response relationship, and high variability in clinical endpoints.

References

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