Clinical Use of Ibuprofen is Associated with Slower FEV$_1$ Decline in Children with Cystic Fibrosis

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ONLINE DATA SUPPLEMENT

Additional Information Regarding the Longitudinal Statistical Model

Preliminary analyses found that the pattern of change in FEV_1 % predicted was not linear, and varied according to baseline age and FEV_1 % predicted. Thus, the basic model we fit allowed change in FEV_1 % predicted to be a quadratic function of time since baseline, stratified by age and level of FEV_1 % predicted into twelve strata formed by crossing 3 age strata (<8 yrs, 8-12 yrs, 13-17 yrs) with four strata of baseline FEV_1 % predicted (60-79%, 80-89%, 90-99%, ≥100%). Let $y^{(s)}_{ij(c)}$ be the change from baseline in FEV_1 % predicted at the jth follow-up time for the ith patient from center c in stratum s defined by baseline age and FEV_1 % predicted, and let $t_{ij(c)}$ be the time in years from baseline to the current year (here, an integer from 1 to 6), for i=1,…,n_c=number of patients in center c, j=1,…,$n_{i(c)}$=number of follow-up measurements for patient i in center c, c=1,…,C centers, and s=1,…12 strata. The basic longitudinal statistical model was a multilevel mixed model, written as:

$$y^{(s)}_{ij(c)} = (\beta^{(s)}_1 + b_{1c} + b_{1i(c)})t_{ij(c)} + (\beta^{(s)}_2 + b_{2c} + b_{2i(c)})t^2_{ij(c)} + \sum_{k=1}^{p} \theta_k X_{ik} t_{ij(c)} + b_{0c} + b_{0i(c)} + e_{ij(c)}.$$

Here, b_{0c}, b_{1c}, and b_{2c} are random intercept, slope, and quadratic terms for the cth center, assumed to be normally distributed with means of zero and 3x3 covariance matrix Σ_c. Similarly $b_{0i(c)}$, $b_{i1i(c)}$, and $b_{2i(c)}$, are random intercept, linear, and quadratic effects for the ith patient in the cth center, also assumed to be normally distributed with means of zero and a 3x3 covariance matrix Σ, where the center-specific and patient-specific terms are independent. The terms $\beta^{(s)}_1$ and $\beta^{(s)}_2$ are fixed effects representing linear and quadratic trends over time for the sth stratum of baseline age and FEV_1% predicted, s=1,…,12, $X_{ik(c)}$, k=1,…,p are measurements of p baseline covariates for the

i^{th} patient in the ith center, θ_k are fixed effects regression parameters, and the $e_{ij(c)}$ are residual random errors assumed to be independent of the other random effects with mean zero and variance σ^2. For example, if the kth covariate X_{ik} is a binary variable coded as 1 if the patient used ibuprofen and 0 if not, then the regression coefficient θ_k represents the mean difference in yearly rates of decline in FEV_1 % predicted in units of % predicted per year for a patient who is taking ibuprofen compared to a patient not taking ibuprofen, after controlling for the other variables in the model, which is the parameter of primary interest. Positive values for θ_k indicate a beneficial effect of ibuprofen in that those taking ibuprofen have less negative slopes over time in FEV_1 % predicted.