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# NEWS

## Safety and tolerability of edasalonexent in pediatric patients with DMD


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Physicians have few options for the treatment of Duchenne muscular dystrophy (DMD). Deflazacort and prednisone are limited in some cases by side effects, and eteplirsen is approved for a subset of DMD patients with specific pathogenic variants in the *DMD* gene. The orally administered drug edasalonexent is a small-molecule compound whose components, salicylic acid and docosahexaenoic acid (DHA), act by inhibiting NF-κB, reducing the catabolism of muscle proteins and modulating inflammatory pathways. In a recent article in the *Journal of Neuromuscular Diseases* (https://doi.org/10.3233/JND-180341), Finanger et al. describe a 1-week, open-label, phase 1 study that assessed the safety, tolerability, pharmacokinetics, and pharmacodynamics of edasalonexent in children with DMD. Seventeen males were enrolled; all participants were ambulatory, harbored a pathogenic variant associated with DMD, and lacked prior exposure to glucocorticoids. The mean age of participants was 5.5 years (range ≥4 to <8 years). Fifteen participants (88%) were white and not Hispanic or Latino. Participants were randomized to three cohorts. On each of study days 2 through 6, cohort 1 received two 17 mg/kg doses of edasalonexent, cohort 2 received two 33 mg/kg doses, and cohort 3 received three 33 mg/kg doses. On study days 1 and 7, cohorts 1, 2, and 3 received single doses of 17, 33, and 67 mg/kg, respectively. For each cohort, participants were randomized to take edasalonexent on days 1 and 7 with either a low-fat meal on day 1 and a high-fat meal on day 7 or vice versa. On all other study days, participants took the drug with high-fat meals. All participants completed the study without dose reductions, interruptions, or discontinuations of treatment. On days 1 and 7, median time to peak plasma concentration, pooled for low- and high-fat groups, was 1.5 to 2.1 hours across all cohorts except for cohort 1 on day 1, for which median time to peak plasma concentration was 6.1 hours. Exposure, measured from pooled day 1 and 7 data, rose approximately proportional to dose across the three cohorts when edasalonexent was taken with a high-fat meal. On day 7, the expression of genes regulated by NF-κB was inhibited significantly for cohorts 2 and 3, compared with day 1. Thirty adverse events (AEs) were reported in 12 patients (70%); 27 AEs were mild and 3 were moderate in severity. Gastrointestinal AEs comprised 17 of the reported events. No serious AEs occurred. The authors conclude that edasalonexent is well tolerated and that it inhibits NF-κB signaling. They suggest that further studies are warranted. *—Raye Alford, News Editor*

## Investigating biological pathways involved in waist-to-hip ratios


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The waist-to-hip ratio (WHR), which is used to assess central body fat distribution, is associated with cardiometabolic disease risk. The relationship between WHR and metabolic outcomes has been supported by genome-wide association studies (GWAS). As reported in a recent article in *Nature Genetics* (https://doi.org/10.1038/s41588-018-0334-2), Justice et al. conducted a large-scale examination of exome array data to identify coding variants associated with central obesity and to characterize the implicated genes and biological pathways. The research team undertook a two-stage fixed-effects meta-analysis of associations between body mass index–adjusted WHR and DNA variants. In stage 1, 228,985 variants were assessed in 344,369 individuals of African, European, Hispanic or Latino, and South and East Asian ancestry. In stage 2, 70 variants that had been identified in stage 1 were evaluated in 132,177 individuals of largely European ancestry, from the UK Biobank and deCODE cohorts. This two-stage process revealed statistically significant associations for 48 coding variants in 43 genes; 16 variants were classified as novel because they occurred more than one megabase from single-nucleotide polymorphisms (SNPs) previously associated with WHR. Sex-stratified analyses and separate meta-analysis of European-only data identified an additional 8 variants, 7 of which were novel. Of the 56 total variants identified in 51 genes, 19 variants demonstrated sex-specific effects, 43 were common variants, 13 were low-frequency or rare variants, and 11 low-frequency or rare variants were computed to have a stronger effect relative to previously identified common variants. Conditional analyses, to identify independent signals and new associations, resulted in 24 variants of which 15 were common variants and 9 were low-frequency or rare variants. Pathway analysis revealed associations between the identified variants and lipid metabolism, adiponectin, glucose homeostasis, insulin resistance, and adipocyte and skeletal biology. Associations were also found with total body fat and truncal fat percentage. *Drosophila* knockdown experiments with orthologs of two genes identified in this study, *DNAH10* and *PLXND1*, revealed associations with lipid metabolism. Among the genes identified in this study, the authors assert that *ACVR1C*, *ANGPTL4*, *DAGLB*, *DNAH10*, *IZUMO1*, *MGA*, *MLXIPL*, and *RASIP1* are involved in lipid metabolism and homeostasis. They conclude that lipid metabolism is an important factor in the distribution of body fat and that analysis of low-frequency or rare variants can provide valuable insights because of the potentially large effect size of such variants. They assert that their findings suggest new therapeutic targets and note that not all variants found were associated with expected effects, necessitating consideration of downstream effects of variants in the selection of potential therapeutic targets. *—Raye Alford, News Editor*