T.P.49
Low-dose steroid therapy for cardiomyopathy in Duchenne Muscular Dystrophy patients
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Steroid therapy in Duchenne Muscular Dystrophy (DMD) patients slows motor and respiratory function declines, while efficacy for cardiomyopathy is uncertain due to limited data. We reported the efficacy of long-term low-dose steroid therapy, at one-third the widely-used dose for DMD patients, in slowing respiratory failure and scoliosis progression without major side effects. Herein, we prospectively evaluated our low-dose steroid regimen for cardiomyopathy in DMD patients. Clinical longitudinal data were available for 12 steroid-treated (12–24, mean 18.9, years) and 14 non-steroid-treated (11–32, mean 19.6, years) non-ambulant DMD patients. Our regimen was started when patients recognized clear motor function declines. The initial dose was 0.5 mg/kg of prednisolone (PSL) every other day (0.25 mg/kg/day). Ages at ambulation loss, cardiomyopathy onset and starting NIV (non-invasive ventilation) were analyzed. The mean age at steroid therapy start was rather late, 9 (7–11) years. No apparent steroid side effects occurred. There was no statistically significant difference in loss of ambulation between the two groups. Among those over age 20 years, five of six non-treated patients needed NIV, before the middle teens in four, while only one of five steroid-treated patients started NIV. Respiratory decline tended to be slower in the steroid-treated group. Ten of 14 non-steroid-treated and five of 12 steroid-treated patients had cardiomyopathy, but the difference did not reach statistical significance. Steroid-treated patients tended to have less cardiomyopathy but most onsets were before the middle teen years. One patient with mild cardiomyopathy, detected before steroid therapy, showed rapid cardiomyopathy worsening within a few years while on PSL and died at age 12 years. Our results indicate that even low-dose steroids may slow respiratory failure and cardiomyopathy progression, but can cause severe cardiomyopathy at an early stage in some patients.

http://dx.doi:10.1016/j.nmd.2012.06.209

T.P.50
Outcomes associated with an Interdisciplinary Comprehensive Care program for DMD patients treated with long term glucocorticoids
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Glucocorticoid (GC) treatment is the recommended standard of care for patients with Duchenne muscular dystrophy (DMD). The benefit/risk ratio of GC treatment is influenced by adverse effects – cushingoid facies, weight gain, linear growth failure, osteoporosis, etc.; and can be maximized with mitigation of adverse effects. The multi-systemic problems of GC treated patients require a coordinated care approach to improve/stabilize/slow progression of motor function with GC, attain optimal nutritional status for age (low glycemic index diet and treatment of insulin resistance) and prevent contractures (daily home stretch program and night resting ankle braces). Objective: To evaluate the outcomes of integrative care for a cohort of GC treated DMD patients. Study design: Retrospective case series review. Patient characteristics: N = 130; mean age at last visit 9.5 y (±1.9), GC Daily GC (prednisone – 11; dexamethasone – 10); Prednisone change to dexamethasone – 9; mean start age of GC 5.0 y (2.6–8.0); daily start dose – 0.75 mg/kg prednisone or 0.9 mg/kg dexamethasone. Clinical motor outcomes: (1) Independent ambulators: 7–9 y – 96%; (n = 69); 10–12 y – 71% (n = 44); (2) Ability to climb steps: 7–9 y – 89%; 10–12 y – 62%; (3) Age for point of slope change for NSAA – 11 y (p = 0.02); timed Gowers 11 y (p = 0.01), timed 30 ft walk/run – no slope change found up to age 13; (4) Ankle Contractures: 7–9 y – 20.6%; 10–12 y – 43.2%. Growth outcomes at last visit: Height %: 7–9 y 9.4 ± 14.5; 10–12 y 9.0 ± 17.4; weight%: 7–9 y 47.7 ± 33.2; 10–12 y 52.4 ± 31.3; BMI% 7–9 y 81.3 ± 20.2; 10–12 y 82.4 ± 24.3. Bone health process outcomes: (1) Vitamin D sufficiency: 90% of patients (n = 120); mean 25 OH D – 36.9 ± 13.7 ng/ml; (2) % of patients with normal lumbar spine BMD z scores: 7–9 y 60%; 10–12 y 73%. Our review shows that an integrative care program for DMD patients on long term daily GC is effective in improving motor outcomes with an acceptable side effect profile.

http://dx.doi:10.1016/j.nmd.2012.06.210

T.P.51
Metformin reduces weight and BMI in Duchenne muscular dystrophy patients on long term glucocorticoid therapy
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Obesity is a significant problem in Duchenne muscular dystrophy (DMD) due to glucocorticoid (GC) therapy and motor decline. Excessive weight gain can further impair mobility, increase risk for diabetes and cardiopulmonary disease, and affect quality of life. Metformin improves weight and insulin resistance in obesity and type 2 diabetes. To determine if metformin reduces weight and BMI in DMD patients on long term GC who have excessive weight gain and insulin resistance. This was a retrospective case series of DMD boys on daily GC therapy who were treated with metformin for excessive weight gain and insulin resistance. Primary outcomes were rate of weight gain and BMI pre and post starting metformin. Weight and BMI measurements were collected 1 year prior, at initiation of metformin, and 6 and 12 months post. Generalized linear models for the vector of weight and BMI measurements over time were fit using generalized estimating equations. Forty-five DMD patients (mean age 12.7 ± 3.1 y) were studied. Patients had insulin resistance by glucose tolerance testing. Mean rate (±SE) of weight gain decreased from 7.5 ± 1.0 pre to –0.2 ± 1.7 kg/y (p < 0.001) post. In non-ambulatory boys (N = 29), rate of weight gain decreased from 8.3 ± 1.5 pre to –0.6 ± 2.5 kg/y post (p < 0.001). In ambulatory boys (N = 16), rate of weight gain decreased from 6.1 ± 0.7 pre to 1.0 ± 1.3 kg/y post (p < 0.001), and rate of BMI gain decreased from 2.8 ± 0.4 pre to 0.1 ± 0.7 kg/m²/y post (p < 0.001). Metformin reduced weight and BMI in DMD patients on daily GC therapy with excessive weight gain.

http://dx.doi:10.1016/j.nmd.2012.06.211

T.P.52
Pilot study of flavocoxid in ambulant DMD patients
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Muscle degeneration in Duchenne muscular dystrophy (DMD) is exacerbated by the endogenous inflammatory response and increased oxidative stress. A key role is played by nuclear factor (NF)-kappaB. We previously showed that flavocoxid, a flavonoid with antioxidant and anti-inflammatory properties, ameliorates muscle pathology and function in mdx mice. This effect seemed to be mediated by the inhibition of NF-kappaB, tumor necrosis factor-alpha, cyclooxygenase-2/5-lipoxigenase and MAPKs expression in muscle. Moreover, flavocoxid has been shown to decrement serum
levels of IL-1β and TNF-α in vivo studies. Primary end-point of this pilot study was to evaluate safety and tolerability of flavocoxid administered daily per os for one year in ambulant DMD patients. We also evaluated function, muscle strength and quality of life. The effects of flavocoxid on selected biomarkers was also assessed. We recruited 20 patients and herein present preliminary data on 15 patients who completed 9 months of treatment. We did not report any treatment-related adverse event and clinically meaningful change in laboratory findings. Serum expression analysis of inflammatory cytokines showed a significant reduction of TNF-α (p < 0.05) and a clear trend toward a decrement of IL-1β and MMP-9 and oxidative stress markers after 6 months of treatment. The results of the multidimensional clinical evaluation were variable and showed an overall stabilization of clinical course, even in patients showing deterioration in the year before baseline. We demonstrated that flavocoxid at this dosage is safe and able to exert its biological effects on inflammatory pathways relevant to DMD pathogenesis.

http://dx.doi:10.1016/j.nmd.2012.06.212

T.P.53
Effect of perindopril orodispersible on muscular function in early stage of Duchenne Muscular Dystrophy
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Two years randomised study, versus placebo. Phase III, multi-centric, double-blind, 40 DMD children corticoid free were randomized to receive either placebo either perindopril, 0.150 mg/d for 2 years. The main criteria: 6 mm walking test (6MWT) was assessed every 6 months as well as the 3 mn stair climbing test (3MST), the muscular testing (MT) and the tolerance. The main objective was the effect of perindopril on peripheral muscular function. At inclusion, mean age: 5.31 ± 1.19 years, weight: 18.90 ± 3.25 kg and height: 109.3 ± 8.3 cm. No difference between groups was noted in demographic data, vital signs, 6MWT (319.4 ± 78.3 ms), 3MST (69.7 ± 33.4) and MT global score (3.9 ± 0.6). 6MWT: the mean decrease was smaller in the perindopril group (–44.9 ± 132.7 m) (median = –43 m) as compared to the placebo group (–84.1 ± 134.3 m) (median = –63 m), (NS). 3MST: mean decrease: were –15.7 ± 34.6 stairs in the perindopril group (median = –13.0) versus –27.4 ± 41.8 stairs (median = –41.0) in the placebo group (NS). The mean global score of MT tended to remain stable from baseline to the last post-baseline value in both, but the mean global score for lower limb remained stable in the perindopril group (–0.1 ± 0.9) whereas it tended to decrease in the placebo group (–0.8 ± 0.8) and was close to the statistical significance (p = 0.063). Adverse events were in accordance with the safety profile of the perindopril and the age of children. In summary, results of this study performed in DMD children (2.5–7 years) suggested that perindopril arginine salt, at a dose of 0.150 mg/kg/day during 2 years, preserve the peripheral muscular function as compared to placebo, assessed by the 6MWT, the 3MST and the MT global score.

http://dx.doi:10.1016/j.nmd.2012.06.214

T.P.55
Allele-specific knockdown to mutant mRNA retrieves cellular function in fibroblasts with point-mutated Ulrich CMD
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Ulrich congenital muscular dystrophy (UCMD) is an inherited muscle disorder characterized clinically by muscle weakness, distal joint hypermobility, and proximal joint contractures. Sporadic/dominant and recessive mutations in the three collagen VI genes, COL6A1, COL6A2, and COL6A3, are reported to be causative. In the sporadic/dominant form, heterozygous point mutations causing glycine substitution in the triple helical domain have been identified. In this study, we examined the effects of mutant allele mRNA-specific knockdown using siRNAs that target point mutations in COL6A1 on the phenotype of UCMD fibroblasts. We designed several siRNAs for COL6A1 point mutation with/without a mismatched base and measured gene-knockdown effect and specificity of those siRNAs on normal and mutant human COL6A1 cDNA. The selected siRNAs were introduced into patient’s fibroblasts, and then the cell-associated collagen VI expression and the ability for cell–substrate attachment were evaluated. Two siRNAs were selected out in transfection experiments. Both worked well on the recovery of extracellular localization of collagen VI surrounding fibroblasts, while on cell attachment assay, none of them showed remarkable recovery of cell-attachment. These results suggest that allele-specific knockdown of the mutant mRNA can potentially be considered a therapeutic strategy in UCMD due to COL6A1 point mutations.

http://dx.doi:10.1016/j.nmd.2012.06.215