

Duchenne muscular dystrophy: an important negative trial



Duchenne muscular dystrophy is a relentlessly progressive X-linked disease. If untreated, boys develop symptoms of weakness before age 5 years, become wheelchair dependent by age 8–10 years, and develop respiratory muscle failure by age 14–18 years. Corticosteroids are of major benefit because they improve muscle strength,^{1,2} increase muscle mass,³ and slow the progression of the disease for 18 months^{1,2} and probably for much longer.² The side-effects of corticosteroids and their incomplete therapeutic benefit have prompted a search for drugs that would have a so-called steroid-sparing effect, permitting use of a lower steroid dose. The possibility that such drugs could even potentiate steroid benefit has further encouraged this search. The immunosuppressant azathioprine had no clinical benefit alone or with steroids,⁴ but two open studies of ciclosporin were interpreted as showing benefit.^{5,6}

The multicentre, randomised trial reported by Kirschner and colleagues⁷ in this issue of *The Lancet Neurology* shows definitively that ciclosporin A is safe but of no benefit either alone or in combination with steroids for patients with Duchenne muscular dystrophy. The trial studied well defined patients, and with 76 assigned to placebo and 77 assigned to ciclosporin A it was adequately powered for the primary outcome variable (manual muscle testing), a measure validated in previous clinical trials.^{1,2} The only major criticism of the study is that the dose used was lower than in the two previous studies.^{5,6} However, the dose used (3.5–4.0 mg/kg bodyweight) is the maximum safe dose for children and is of benefit in other disorders.

Although the study by Kirschner and colleagues might be seen as reporting a negative result, it has great importance in two regards. First, as treatment strategies are pursued to restore dystrophin, the missing gene product in the disorder, immunosuppression is needed to prevent immune-mediated rejection. Ciclosporin A has been widely used in other settings for such immunosuppression and it is of crucial importance to have defined its safety and its lack of effect on muscle strength. This large study provides solid data to this effect.

Second, the lack of benefit of ciclosporin A in Duchenne muscular dystrophy either alone or with steroids drives another nail in the coffin of the logical

hypothesis that prednisone benefits patients with this disorder by immunosuppression. There are inflammatory, cytotoxic lymphocytes in biopsied muscle of boys with Duchenne muscular dystrophy, and prednisone decreases their number.⁸ However, azathioprine, which is also of no clinical benefit, produces a similar decrease in the number of cytotoxic lymphocytes, suggesting that immunosuppression is not pertinent to the benefit of steroids.⁹

If ciclosporin and azathioprine are of no benefit, what then is the mechanism of the dramatic, albeit incomplete, benefit of prednisone? Prednisone does not increase levels of dystrophin, nor does it abolish muscle necrosis,^{8,9} but in studies of boys with Duchenne muscular dystrophy it does increase muscle mass rapidly by as much as 20%.³ It does not increase muscle protein synthesis but decreases muscle protein degradation.³ The basis for this slowing of degradation is unknown. Although the present study and earlier work^{8,9} argue against an immune basis for the steroid response, the matter is not settled.

This study by Kirschner and colleagues provides additional interesting information. An intermittent corticosteroid regimen (0.75 mg prednisone/kg bodyweight for 10 days on and then 10 days off) was studied; there was no concurrent placebo control for this phase of the study, but benefit was noted. However, the improvement and subsequent lengthy plateau in strength seen with daily prednisone^{1,2} was not uniformly recorded. The relative risk versus benefit of various steroid regimens remains unknown.¹⁰ It is of great importance to define the best regimen of corticosteroids for Duchenne muscular dystrophy as well as to standardise the best strategies for the prevention of their side-effects.⁵ Advances in dealing with the complications of Duchenne muscular dystrophy caused by corticosteroids are already improving the prognosis of this disease.^{11,12}

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