

## REFERENCE

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# Angiotensin-converting-enzyme inhibitors versus steroids as first-line drug treatment in Duchenne muscular dystrophy

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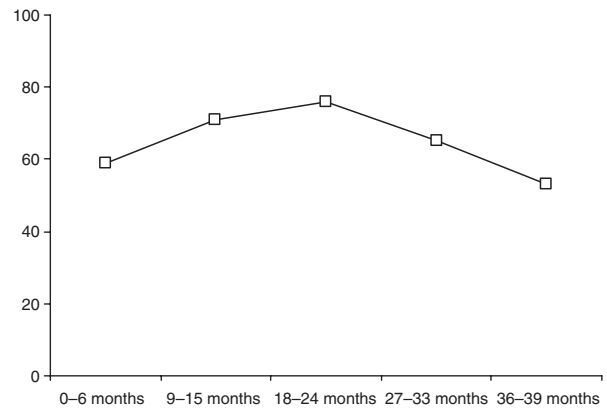
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SIR—We carefully read the editorial by Peter Baxter published in the April issue, as well as the original two-part paper by Bushby et al. in *Lancet Neurology* that extensively reviews the latest insights into the multidisciplinary management of people with Duchenne muscular dystrophy (DMD).<sup>1–3</sup> We found this article very interesting and helpful to any clinician interested in this pathology, and more generally, to any patient, family, physician, and patient support group involved with people with severe neuromuscular diseases. We also agree with the most controversial points raised in the editorial. Nevertheless, we would like to offer some additional remarks concerning the pharmacological treatment of DMD.

Five pages in the original article by Bushby et al. are devoted to steroid therapy. As others, we regularly use this treatment, which is well-tolerated at the beginning of medication and improves patient autonomy, including prolongation of time to loss of walking. Interestingly, using the same assessment tools, we found results very similar to those published by Vuillerot et al. (Fig. 1).<sup>4</sup> However, the long-term efficiency of corticotherapy is uncertain and is largely outweighed by side-effects in some patients. In non-ambulatory males, the effect on bone mineral density (with the risk of developing fractures and bone pain) and the propensity for excessive weight gain adversely increase the dependence, whilst the primary goal at that time (i.e. improvement in respiratory muscle strength and cardiac outcome) is not obvious. Moreover, some research



**Figure 1:** Mean changes in Motor Functional Measure (MFM) total score at baseline and over-time in 14 consecutive patients with dystrophinopathy (one female and 13 males; 6–17y) treated with steroids in Montpellier from 2004. The regimen of treatment was prednisone 1mg/kg on alternate days. As previously reported, steroid therapy improved muscle function for about 2 years, then followed by a gradual decline. The principal side effect was excessive weight gain. By comparison, it has been demonstrated that the natural evolution of the MFM score in people with Duchenne muscular dystrophy is in continuous and progressive decline with time.<sup>4</sup>

recently showed that mdx mice treated with corticoids have a highest risk of cardiomyopathy.<sup>5</sup>

On the other side, perindopril is not cited in the two-part article by Bushby et al. even though it is the first molecule (and the only one so far) that has demonstrated efficiency in improving life expectancy for males suffering from this devastating disease. Research primarily showed that early treatment with perindopril (i.e. introduced between the ages of 9y 6mo and 13y and before the occurrence of patent cardiomyopathy) delays the onset and progression of left ventricle dysfunction.<sup>6</sup> The benefits are even stronger with time since the mortality was five-fold lower in the early treatment group versus the delayed treatment group at the end of the 10-year follow-up period of this prospective pilot study ( $p=0.01$ ).<sup>7</sup> Perindopril is thus largely used in France and this medication is offered to virtually all males with DMD presenting normal left ventricular function at the age of 10. This medication is also very well-tolerated by patients.

Therefore we do not fully concur with the statements of the Bushby et al. papers that ‘... the pharmacological mainstay of neuromuscular management in DMD is the use of glucocorticoids,’ and ‘Recent evidence from clinical trials supports the treatment of cardiomyopathy associated with DMD before signs of abnormal functioning. Further studies are awaited to allow firm recommendations to be made.’ Instead, we believe that the current issue is: what is the optimal age to start angio-

tensin-converting-enzyme inhibitors? In vivo and in vitro studies support this hypothesis that this class of molecules not only acts on myocardium but also in increasing peripheral muscles function (including respiratory muscles) through their anti-inflammatory and anti-fibrotic properties. As both of these mechanisms are involved in the pathogenicity of dystrophin deficiency, therapeutic trials are currently under way to answer this important question.

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# Mechanical ventilation in children with severe neurological impairment

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SIR—We read with interest the paper by van Gestel et al.<sup>1</sup> and agree that the decision to intubate and initiate mechanical ventilation in children with severe neurological impairment can be very difficult.

In an audit at a tertiary care children’s hospital we reviewed children with neurological disorders who received long-term ventilation at home between August 2003 and October 2008 (Table I). Of the 21 children, 16 had progressive disease with a predominance of muscle disorder. All of them had respiratory failure and ventilation prolonged their lives. One child died after 5 years of ventilation while others were alive at the end of the audit period. They had been ventilated for mean of 2 years 5 months (range 6mo–5y). We have not evaluated the impact on quality of life or the economic burden of this intervention.

Two children had very severe neurological impairment at the start of ventilation (No. 9 and No. 14 in Table I). Their interaction with others was limited to an inconsistent smile. It was debatable whether they were suitable candidates for long-term ventilation.

Decision to offer mechanical ventilation including long-term ventilation in these children can cause medical, ethical, and legal dilemmas. We found the Royal College of Paediatrics and Child Health (UK) guidance<sup>2</sup> to be a valuable aid in this process. It outlines situations where it may be ethical and legal to consider withholding or withdrawal of life-sustaining medical treatment. When there is little or no prospect of meaningful interaction with others or the environment, life-prolonging treatment may not be in the child’s best interest.

We agree with the authors<sup>1</sup> that further prospective studies are required to guide clinicians through the decision-making process in this population.

This audit and publication were discussed with the hospital ethical committee who were satisfied that research ethical approval was not needed.