Duchenne muscular dystrophy is an inherited condition characterized by progressive muscle weakness, loss of ambulatory ability, and progressive decline in pulmonary function resulting in premature death. This X-linked disorder is caused by mutations in the dystrophin gene. The protein product of the dystrophin gene is located adjacent to the cell membrane, where it has a number of functions, including an important role in maintaining cell membrane stability. Although the protein is expressed in a variety of cell types, when mutated its most profound effects are in skeletal muscle cells. In myocytes, the mutant protein causes muscle cell death and subsequent replacement by fibrofatty tissue. Muscle cell death and replacement with fibrofatty tissue are responsible for an increase in muscle compartment size, leading to clinical pseudohypertrophy. The more proximal muscles are affected first, causing the characteristic weakness pattern and resulting in a positive Gower’s sign. Interestingly, high levels of muscle activity may hasten the myocyte cell’s death. As such, certain exercises could worsen strength.

With progressive muscle weakness, skeletal deformity occurs. Contracture of the tendo Achilles develops early. The etiology of the contracture is not completely clear, but it is possible that a cell-signaling function of dystrophin becomes disrupted by the mutation, enhancing fibrosis development. Over time, the muscle weakness results in affected boys being unable to walk and having to use full-time wheelchair use. Once in the wheelchair full time, almost all develop progressive spinal deformity. Only an unpredictable small proportion of boys with a stable or hyper-extend spine do not develop progressive scoliosis. The progressive spinal deformity is thought to be caused by overall muscle weakness, but replacement of muscle tissue with fibrofatty tissue could act to tether the spine and contribute to deformity progression. Muscle weakness also causes a progressive decline in pulmonary function, and with time cardiac function also becomes impaired. Affected boys ultimately die prematurely from the pulmonary and cardiac effects of the disease.

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The author did not receive any financial support for this study.

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Pharmacologic Treatment in the Absence of Effective Gene Therapy

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The spinal deformity in most patients is progressive, and untreated it results in substantial discomfort in later life in a subset of these boys. Because of the decline in pulmonary and cardiac function with time, surgery for the spine becomes potentially hazardous. Anesthetic and postoperative respiratory risks substantially increase when pulmonary function test values drop below 20% of predicted values. Current recommendations are for early surgery during the window of opportunity when respiratory function is satisfactory with onset of full-time wheelchair use. Spinal surgical stabilization is done for low-magnitude scoliosis (20–25 degrees) to take advantage of the maintained pulmonary function at that time and also since it is impossible in these early stages to predict who will develop progressive, symptomatic spinal deformity.

An ideal treatment of patients with Duchenne muscular dystrophy would be to replace the defective gene product. However, gene therapy approaches thus far have been unsuccessful for a variety of reasons, primarily due to the gene therapy product activating the immune system. In the absence of successful gene therapy, a variety of other approaches to impede the predictable, progressive decline in muscle strength have been attempted, the most successful of which to date has been use of steroids.

Steroids help stabilize cell membranes and decrease inflammation. As such, they have the potential to inhibit myocyte cell death and decrease some of the secondary effects associated with cell death. Although there were a number of early case series investigating steroid use in boys with Duchenne muscular dystrophy, a lack of appropriate control groups made the data generated difficult to interpret. This changed with the report of a prospective randomized trial showing that prednisone use slowed the rate of muscle weakening when instituted in boys who were still walking. Unfortunately, once the drug was stopped, the muscle weakness rapidly returned toward expected baseline. Since the steroid effect disappeared when the drugs was stopped, and the medication is associated with potential side effects, including weight gain, cataracts, osteopenia, and avascular necrosis, steroid use remained controversial.

Following the initial randomized trial, studies that examined the use of a variety of steroid medications, dosing regimens, and duration of therapy were reported. Several centers, including ours, investigated long-term steroid use, reasoning that since there was a rapid decline toward baseline muscle function following drug cessation, continuing therapy for a longer duration would result in longer-lasting effects.
these long-term steroid treatment studies, medications were started for boys who were still ambulatory and the medications were continued indefinitely. Although these trials did not use a randomized design, the natural history of progressive muscle weakness in Duchenne muscular dystrophy is quite predictable, and a major deviation from this relentless course is easy to detect.

We found that use of a relatively high daily dose of the steroid deflazacort resulted in long-term maintenance of pulmonary function. The age at which boys became full-time wheelchair users increased by several years over boys who did not use deflazacort. Similar findings have been reported from other centers. A recent comparative study examined the results from two centers using different dosing regimens and suggested that higher doses, administered daily, resulted in better maintenance of strength and prevention of skeletal deformity.

The implications of steroid treatment on the orthopaedic aspects of Duchenne muscular dystrophy are just beginning to be investigated. The most significant orthopaedic problem is the development of scoliosis. While preserving muscle strength might prevent spinal deformity development, osteopenia associated with steroid use could result in a more rapidly progressive deformity that would be difficult to surgically manage. We investigated a group of boys treated with daily high-dose deflazacort and found a substantially reduced rate of scoliosis compared with boys who elected not to take this medication. Eighty percent of untreated boys developed scoliosis of at least 20 degrees by age 18; fewer than 25% of the boys in the treatment group developed scoliosis. Similar findings were subsequently reported from other centers. Although steroid medications substantially alter the natural history of scoliosis development in these boys as teenagers, the longer-term implications remain unknown. It is possible that these boys will later develop progressive scoliosis requiring surgery at a time when operative intervention might be dangerous from anesthetic and postoperative respiratory standpoints. On the other hand, these boys might behave similar to patients with upper-cervical-level spinal-cord injury who develop a rapidly progressive scoliosis if the injury occurs while skeletally immature, but such deformity is rare after skeletal maturity. Perhaps if spinal deformity is prevented until skeletal maturity, a later progressive curve will not develop.

The complications reported with steroid use could result in a poor quality of life for boys with muscular dystrophy. Although weight gain associated with steroid use is a concern, this does not seem to be a significant problem. Surprisingly, late adolescent boys treated with steroids typically weigh less than boys not treated, possibly because they remain more physically active. Boys treated with steroids are slightly shorter than boys who are not treated; this is considered a result of long-term steroid effects on growth plate function.

Interestingly, this shorter stature may in part be responsible for the impressive pulmonary function results, as predicted values for pulmonary function are calculated based on height and the shorter stature results in the same raw pulmonary function data giving a higher percentage predicted value. Cataracts occur in a high proportion of boys using steroids, and their development seems dose-related. Despite the number of boys developing cataracts, eye involvement seems to be relatively mild, with no reports of a drop in visual acuity requiring ophthalmologic surgery. Avascular necrosis is reported with steroid use, but this side effect has not been reported in boys with Duchenne muscular dystrophy treated with steroids.

Boys using high-dose steroids predictably develop osteoporosis. Various series have reported different implications of this osteoporosis, with some showing a rather high incidence of vertebral stress fractures. In our series, we found symptomatic vertebral stress fractures to be relatively rare. Steroid-induced osteoporosis can be effectively managed using bisphosphonate therapy. Although results of bisphosphonate treatment specifically in Duchenne muscular dystrophy have not been reported, promising results have been presented in randomized trials related to other underlying disorders investigating steroid-induced osteoporosis treatment with bisphosphonates.

Successful pharmacologic therapy for Duchenne muscular dystrophy should result in affected boys living longer, higher-quality lives. Long-term steroid use improves pulmonary function, delays boys becoming full-time wheelchair users, and at least delays the development of scoliosis. Long-term effects on quality and length of life are not yet known. As the initial cohort of boys treated with long-term steroids reaches their late 20s, these issues can be addressed. In the meantime, current evidence raises the possibility that long-term use of steroids will result in improvement in quality and length of life in Duchenne muscular dystrophy patients. We believe that all boys with this disorder should be given the opportunity to start such medications early in their disease course, well before they reach the stage of full-time wheelchair use.

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