Gene therapy for Duchenne muscular dystrophy: balancing good science, marginal efficacy, high emotions and excessive cost

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Duchenne muscular dystrophy (DMD), the most common form of all muscular dystrophies, is an X-linked disorder affecting approximately one in 5000 newborn boys.[1] Patients experience difficulty in ambulation which steadily progresses to wheelchair confinement by the age of 12 and death between 25–30 years of age due to respiratory muscle weakness or cardiomyopathy. DMD is caused by mutations in the dystrophin gene, with 65% being deletions (the rest duplications or point mutations) that disrupt the open-reading frame of dystrophin mRNA, preventing the expression of a functional protein.[1,2] Lack of dystrophin, a structural sarcolemmal protein that stabilizes the muscle fibre, causes muscle fibre degeneration, inflammation and fibrosis, clinically manifested as muscle weakness.[2]

The ideal therapy is obviously the induction of sustainable dystrophin expression in all affected muscles by applying genetic-based strategies; more than 30% of new dystrophin is needed, however, needed to be clinically meaningful.[1,3–5] Unfortunately, in spite of experimental gene therapies in animal models and excellent basic studies, no gene therapy has been successful in DMD. The scene may be changing as one such agent, eteplirsen, offers a glimmer of hope, although blunted by unprecedented controversy between investigators, the FDA's scientific advisers, industry and the FDA's leadership,[6] generating a polarized environment. In this current inflammatory climate, a balanced commentary on eteplirsen and all gene-therapy-based efforts is timely, as chronologically outlined below.

Gene therapy replacing the dystrophin gene

This is a monumental task because dystrophin is big (2.2 Mb) and the cDNA long (11 kb), necessitating delivery of a short gene, labelled mini-dystrophin, that mimics the milder Becker's muscular dystrophy (BMD) phenotype, using adeno-associated virus (AAV) vectors.[4] The results have been disappointing because AAV vectors have limited packaging capacity and the injected capsid proteins were immunogenic, causing T cell-mediated cytotoxicity against the vectors and the dystrophin protein.[3–5]

Stop-codon read-through

About 10% of DMD have a nonsense mutation, where a stop codon is prematurely inserted in the mRNA, preventing the gene from being fully translated into dystrophin.[1,5] Agents, such as the aminoglycoside antibiotic gentamicin, that suppress nonsense mutations have failed. Ataluren, a similarly acting oral agent, increased dystrophin production by 11%, but three phase II–III trials were ineffective.[5–7]

Exon skipping

In the allelic, more benign BMD, dystrophin mutations do not disrupt the open-reading frame, and a smaller, partially functional dystrophin is produced.[1–6,8] Because the deletions in DMD exons cause non-functional dystrophin, skipping the exons adjacent to the deletions can theoretically lead to a semi-functional shortened protein mimicking the BMD phenotype.[4–8] *In vivo*, such exon skipping is achieved with antisense oligonucleotides that produce dystrophin by restoring the open-reading frame.[4–8] Although the majority of the deletions are found non-randomly throughout middle exons of the gene,[3] 13% of DMD patients harbour a mutation suitable for skipping exon 51.[6–8] On this basis, two exon 51-skipping agents, *drisapersen*, a 2′-O-methyl-phosphorothioate antisense oligonucleotide, and *eteplirsen*, a phosphorodiamidate morpholino oligomer, were trialled, targeting increased dystrophin.

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The first trial, using intramuscular drisapersen, increased sarcolemmal dystrophin in 64–97% of examined myofibres; subsequent phase II/III clinical trials using systemic drisapersen delivery did not demonstrate significant improvements in the 6 minute walk test (MWT) after 48 weeks.[5,7–9] A longer-term trial of 188 weeks also did not produce meaningful gains.[7–9] The FDA concluded that drisapersen was not effective, and terminated future trials.

Eteplirsen (EXONDYS 51™; Sarepta Therapeutics) increased dystrophin expression after one intramuscular injection, but also after weekly intravenous infusions in a 12-week phase II trial.[10,11] In a seminal 12-patient, semi-controlled study, four patients were randomized to weekly intravenous infusions of 30 mg/kg eteplirsen, four to 50 mg/kg and four to placebo.[12] After 24 weeks, all patients, including the four placebo-treated patients, received open-labelled eteplirsen for another 24 weeks. An increased percentage of dystrophin-positive fibres to 23% of normal was noted in the 30 mg/kg group; at week 48, the dystrophin expression increased to 52% in the 30 mg/kg group and 43% in the 50 mg/kg group.[12] Eight ambulation-evaluable eteplirsen-treated patients experienced a 75-metre benefit, compared to four placebo-delayed patients.[12] A follow-up, open-labelled, 36-month extension phase of the same patients showed a statistically significant advantage of 151 m ($p < 0.01$) on the 6MWT, compared to 13 historically matched controls from Italy and Belgium, with 2/12 (16.7%) losing ambulation in 3 years compared to 6/13 (46.2%) of the controls.[13] Based on the surrogate endpoint of increased dystrophin, the FDA approved EXONDYS 51™ on September 2016, under the accelerated approval pathway, as 'being reasonably likely to predict clinical benefit'. The approval was conditional on completing an uncontrolled efficacy trial by 2021; if this fails, the drug's approval may be withdrawn.[14,15]

The FDA's decision was: (a) historic, as eteplirsen is the first-ever FDA-approved medication for DMD; (b) surprising, because approval was based not on clinical efficacy but on the surrogate biomarker of dystrophin increase in amounts not necessarily clinically meaningful; and (c) controversial, because it was approved when the FDA's senior leadership overruled the recommendations of their own scientific staff and FDA-appointed external advisers who opposed approval.[14–16] The controversy continued afterwards, when FDA scientists required retraction of Mendel's paper after inspecting his facility and independently concluding that the 48-week data were erroneous and misleading.[14–18] They highlighted various methodological concerns about the quantification of immunohistochemically assessed dystrophin, on which approval was granted, citing support of re-analysis data by independent assessors.[14–18] The FDA requested a fourth biopsy for quantitative western-blot analysis, which was performed in 11 patients receiving open-label eteplirsen for 36–40 months. A mean dystrophin increase of 0.9% was observed, compared to 0.08% in untreated patients, reflecting an increased dystrophin intensity in positive fibres from 9.4% to 22.6%, which was still of uncertain significance.[14–16,18] Mendel fought back, standing by his work and concluding that eteplirsen meaningfully increased dystrophin expression.[17] What did we learn from the eteplirsen controversy and the FDA's decision?

First, the FDA's leadership can overrule their own scientists and their externally appointed independent committees, who found the results unconvincing or marginally effective, even causing resignation of the division chief. Second, the FDA leadership may – to their credit – show flexibility when dealing with a devastating childhood disease like DMD, where vigorous controlled studies may not be practical; whether good-quality science presented by high-integrity investigators such as Mendel's group, or the emotionally charged environment of lobbying families, advocacy groups and industry had any impact, remains unclear. It is likely that in the absence of effective therapies, FDA leaders foresaw a glimmer of hope, likened to the 'beginning of the end' for a disease like DMD. Although such flexibility is highly commendable, its merit remains uncertain in view of continuing criticisms from the scientific communities[14,18] because: (1) approval was based on a small sample size of 12 patients; (2) post-hoc calculations of the 6MWT were based on an open-label study and compared to historical cohorts from other countries, raising reliability concerns; and (3) western-blot analysis of 13 new patients from an ongoing eteplirsen study revealed minor dystrophin increases, from 0.16% to 0.44% after 48 weeks, still considered of uncertain clinical significance.[14–16,18]

The most troubling issue, however, may not be eteplirsen's approval process and the use of a doubtful biomarker instead of clinical efficacy,

but rather the drug's excessive cost. Immediately following approval, the *Wall Street Journal* wrote: 'FDA approved EXONDYS 51, even though it has not completed late-stage clinical trials to prove effectiveness, at $300,000 annually.'[19] The recent editorial in the *New England Journal of Medicine* puts the cost at US$57,600/month, and doubting whether the small dystrophin increases could affect clinical progression; some national insurers had already declined covering the drug as it was considered 'experimental'.[20] Will the approval of eteplirsen become frustrating to patients' families fighting insurance providers for an astronomically expensive drug? Will the process become disappointing when it is realized that the most anticipated benefit is the possibility for delayed progression and hope for future-generation drugs? What about the underinsured and patients in other parts of the world who may place themselves under extreme financial burdens, desperately believing that eteplirsen will save their boys' lives? Will the manufacturer's brochure clarify these questions? In the meantime, all clinicians caring for DMD patients should educate the families correctly, not raising unreasonable hopes but also not disappointing them.

The moral issues surrounding cost in DMD is exemplified by another drug, deflazacort, approved immediately after eteplirsen. Deflazacort, a glucocosteroid of the oxazoline class, was shown in a phase III study completed 22 years ago to be as effective in DMD as prednisone, but with lesser complications.[21] These old data, published after Marathon Pharmaceuticals acquired the rights to the drug, led to FDA approval. Companies cheaply acquiring older drugs that have lost their patent protection is not new. What is new is the excessive cost: prednisone costs a few dollars per month, while deflazacort, currently available in Europe, Asia and South America, costs about US$1,000/year; US patients buy it online for about $1,500–2,000/year.[5,19] After FDA approval, EMFLAZA™ (the approved name of deflazacort) will be available to US patients for $89,000/year.[22] Such prohibitive cost for an old corticosteroid that sells for 50–70 times less in the rest of the world has generated an outcry, reaching the US senate.[22]

Notwithstanding all the above, DMD patients and their families deserve better therapies. The systemic delivery of exon-skipping agents might be 'the end of the beginning' for such a devastating disease as newer gene therapies are coming to the fore. The excellent basic science and the progress in applying gene therapies are paying off; eteplirsen is a minor but important baby-step, enough to say that when it comes to gene therapies in DMD, 'the future is not what it used to be'. Time will tell, however, whether eteplirsen is not an expensive placebo and whether the FDA made a wise move looking positively at the future.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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