Beyond borrowed therapies: Ifetroban Fast Track designation in Duchenne muscular dystrophy cardiomyopathy

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Patients with Duchenne muscular dystrophy (DMD) face early death from heart failure and have advocated for effective treatments, as current therapies are borrowed from adult heart failure and do not target the cardiomyocyte-driven DMD pathology. Recently, the orphan drug ifetroban successfully completed phase II trial as a specific treatment for DMD cardiomyopathy (NCT03340675) and has been awarded Fast Track status by the Food and Drug Administration. This designation is a step toward a more flexible, patient-centered review process.

Keywords

Cardiomyopathies, clinical trial, drug approval, heart failure, ifetroban, muscular dystrophy, Duchenne, rare diseases, receptors, thromboxane

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Duchenne muscular dystrophy (DMD) is an X-linked myopathy resulting from inactivating dystrophin mutations that cause progressive muscle breakdown, affecting 1:5,000 live male births globally. Boys with DMD are typically diagnosed at ~4 years of age, lose ambulation as preteens and die of respiratory or heart failure by their third decade. With modern respiratory support, cardiac disease is the leading cause of death in DMD.[1] There are currently no Food and Drug Administration (FDA)-approved therapies to specifically target DMD cardiomyopathy; however, patient preference studies identify cardiac symptoms as a high-priority treatment target.[2] This remains a critical unmet medical need.

The dystrophin–glycoprotein complex structurally anchors the cytoskeleton to the extracellular matrix; when destabilized, the mechanical force of contraction causes repeated localized tears in the sarcolemma. This fragile, leaky membrane is the primary defect of dystrophinopathies, differentiating DMD cardiomyopathy from adult-onset heart failure. Membrane permeability, leaky calcium channels and decreased reuptake cause calcium overload with subsequent protease activation, mitochondrial dysfunction, oxidative stress and ultimately cardiomyocyte death with fibrofatty replacement.[1] Accumulated damage progresses into a dilated cardiomyopathy complicated by arrhythmia and ends in heart failure. The advance can be insidious, as fatigue and exercise intolerance are often unnoticed in a wheelchair-bound population; delayed treatment contributes to progression and decreased survival.[3,4] Yearly cardiac assessment, including electrocardiogram and imaging, is recommended beginning at diagnosis to identify and track cardiac involvement as early as possible.[3] The challenge is that available therapeutic interventions were not designed for a cardiomyocyte-initiated cardiomyopathy such as DMD.

Current guidelines suggest beginning first-line treatment by age 10 to reduce strain and remodeling.[3] DMD cardiomyopathy treatments are primarily borrowed from the 'four pillars' of adult heart failure therapy: (1) angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or the dual angiotensin receptor–neprilysin inhibitor, (2) mineralocorticoid receptor antagonists, (3) beta-blockers or (4) sodium–glucose cotransporter 2 inhibitors (SGLT2i).[5] Some of these, such as mineralocorticoid antagonists, interrupt systemic pathways downstream of damaged cardiomyocytes to decrease the progression of cardiac fibrosis, while the newer SGLT2i show great promise based on mortality benefits in other forms of heart failure, but the cardioprotective mechanism is still being fully elucidated.[1] All current therapies are more effective for prevention than for treatment and reduce hospitalization and mortality, although mortality remains.[1,4] More importantly, all current treatments were initially clinically developed in heart failure populations, which do not have the cardiomyocyte-centered process of membrane permeability, calcium overload, death and fibrosis that are the sequelae of DMD cardiomyopathy. The major potential therapeutics specific to DMD, including dystrophin restoration via genetic therapies, have not been fully evaluated for cardiac benefits in humans. These have promise because expression of limited or truncated dystrophin could essentially transform DMD into the much milder Becker muscular dystrophy (BMD) phenotype.[6] However,

cardiomyopathy is the leading cause of death in BMD, and female dystrophin mutation carriers also face significant risk.[7] Dystrophin replacement treatments still project eventual development of dilated cardiomyopathy and would require adjunct or primary therapeutics.

Enter ifetroban, a thromboxane–prostanoid receptor (TPr) antagonist and orphan drug from Cumberland Pharmaceuticals Inc. Ifetroban was originally developed as an antiplatelet agent, although the G protein-coupled TPr is also expressed in endothelial cells, immune cells, smooth muscle cells and cardiomyocytes for multisystem effects. Ifetroban blocks all ligands from activating the TPr, including thromboxane A2 and 15-F_{2t}-isoprostanes, oxidative stress byproducts elevated in DMD and BMD.[8] Systemic isoprostane or platelet-independent thromboxane levels have been associated with heart failure and cardiovascular mortality.[9–12] TPr activation increases intracellular calcium, causing vasoconstriction, arrhythmia, cardiomyocyte protease activation and death, with cardiac fibrosis, all of which contribute to DMD cardiomyopathy.[13,14] Ifetroban treatment in mouse models of muscular dystrophy improved survival and cardiac output in severe DMD models and improved ejection fraction, circulating natriuretic peptide and cardiac fibrosis in a less severe model of muscular dystrophy cardiomyopathy.[8] It normalized gene and protein expression in dystrophic hearts, recovering cardiac phenotype in mouse models.[8] Numerous early clinical trials of ifetroban and other TPr-specific antagonists have established drug safety in humans.[15] With an FDA Office of Orphan Products Development grant, Cumberland Pharmaceuticals Inc. recently conducted a double-blind phase II, placebo-controlled clinical trial over 10 sites nationwide (A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Study With an Open-Label Extension to Determine the Safety, Pharmacokinetics and Efficacy of Oral Ifetroban in Subjects With Duchenne Muscular Dystrophy [FIGHT-DMD]; ClinicalTrials.gov identifier: NCT03340675).[16] This 12-month trial tested two oral doses of ifetroban in patients with DMD with pre-existing cardiac involvement. Early results showed dose-dependent benefit, with the high-dose cohort demonstrating net improvement – not slower decline – in left ventricular ejection fraction (LVEF) and improved circulating natriuretic peptide.[17] An optional open-label extension with high-dose ifetroban was offered at the request of the DMD community. Every patient requested the extension; the earliest patients have now completed their fourth year on the drug.

This enthusiastic participation is characteristic of families affected by DMD, who are well-informed, organized advocates for congressionally appropriated funding for DMD as a rare disease. There is an acute sense in patients with DMD and families that time is running out.[18] They are as motivated to find effective treatment as would be expected of parents facing the loss of one or more sons to heart failure at a young age and of patients for whom each year is measured in decline. The DMD community is focused on accelerating responsible access to new therapies; the average time from drug patent to FDA approval is almost 14 years, half a DMD lifetime.[18,19] Formal recommendations to the FDA from Parent Project Muscular Dystrophy (PPMD) reflect the expressed risk/benefit preferences of patients and caretakers regarding DMD drugs: fast-tracked approval with a flexible review process, increased surrogate endpoints acceptable for use in clinical trials and adaptive approval.[20]

These recommendations can be met by the exercise of four existing FDA mechanisms developed for drugs targeting serious or life-threatening conditions. Priority Review expedites FDA review of the final application by four months if it demonstrates significant safety or effectiveness over existing therapeutics. Accelerated Approval allows approval based on a surrogate endpoint or an intermediate clinical trial endpoint 'reasonably likely to provide clinical benefit.' Breakthrough Therapy designation is granted if an early clinical trial demonstrates substantial improvement over available therapeutics, while the Fast Track designation accepts preclinical data and mechanistic rationale, beginning acceleration earlier in drug development to more quickly fill unmet serious medical needs. This permits shorter trials, giving patients access to earlier therapeutic benefit and the chance to avoid irreversible endpoints such as mortality.[19] These designations confer rolling review with more frequent meetings and written communication with the FDA; if clinical trial results are favorable, either designation can be converted to Accelerated Approval and/or Priority Review.[19] Based on the preclinical data, demonstrated safety and results of the clinical trial, the FDA recently awarded Fast Track designation to ifetroban.

This designation should expedite review of ifetroban and provide a flexible review process as suggested by PPMD.[18,20] More frequent FDA interaction and review of supportive data as they are submitted allows FDA to provide feedback on endpoints, biomarkers and concerns. This collaborative approach is helpful because the trial is the first successful phase II trial specific to DMD cardiomyopathy, and there is little precedent for successful surrogate or intermediate cardiac endpoints in the DMD population. The sum of preclinical data, mechanistic rationale and clinical trial results could eventually be used to grant Accelerated Approval, permitting a surrogate heart failure endpoint such as LVEF, which strongly predicts all-cause mortality in DMD, to be used for evaluation.[21] The alternative is requiring additional placebo-controlled trials to demonstrate long-term benefit on hospitalization or mortality; intermediate endpoints validated in adult heart failure trials, such as the 6-min walk test, primarily assess skeletal muscle function in patients with DMD. Evaluation of ifetroban as the first cardiac-specific DMD therapeutic should establish a framework for later evaluation of similarly targeted therapies. The DMD population has little appetite for long-term placebo-controlled studies, preferring an adaptive approval process that allows drug access with post-marketing safety and efficacy evaluation. They requested that patients' desire for swift access to potentially life-saving treatments be given greater weight than the need for near-certainty of efficacy.[20] Careful evaluation under the Fast Track designation is one step in this direction. ❑

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