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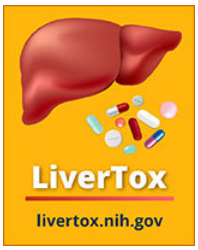


Eteplirsen

Updated: February 27, 2020.

OVERVIEW

Introduction

Eteplirsen is synthetic antisense oligonucleotide designed to cause skipping of abnormal exons during synthesis of the dystrophin gene and that is used to treat Duchenne muscular dystrophy. Clinical experience with eteplirsen has been limited, but it has not been linked to serum enzyme elevations or to instances of acute liver injury with symptoms and jaundice.

Background

Eteplirsen (e" tep lir' sen) is a synthetic antisense oligonucleotide designed to cause exon 51 skipping in the processing of mRNA for the dystrophin gene, which encodes an essential protein for muscle integrity. Patients with Duchenne muscular dystrophy typically have deletion mutations in exons [43 to 55] of the dystrophin gene, which disrupt the open-reading frame and the normal synthesis of the protein. Without dystrophin, muscle fibers become damaged during contraction resulting in inflammation and eventually replacement of muscle by fibrous and adipose tissue. Duchenne muscular dystrophy is an X-linked recessive disease that generally becomes clinically apparent by the age of 2 or 3 years, resulting in gradual loss of muscle and progressive disability often leading to loss of ambulation by age 10, ventilatory failure in early adulthood, and death in the 20s or 30s. In cell culture, antisense molecules were designed that allowed for skipping of the abnormal exon 51 found in 10% to 12% of patients with Duchenne muscular dystrophy and that replaced the defective dystrophin gene with a truncated but functional dystrophin molecule. In animal models, eteplirsen led to increases in truncated muscle dystrophin. In small clinical trials, eteplirsen was found to increase levels of dystrophin protein in muscle, on the basis of which it was approved for use in patients with Duchenne muscular dystrophy with a confirmed mutation in the dystrophin gene amenable to exon 51 skipping. Eteplirsen is available in solution in single dose vials of 100 mg or 500 mg (50 mg/mL). The recommended regimen is 30 mg per kg body weight once weekly by intravenous infusion. Side effects of eteplirsen include headache, fever, falls, abdominal pain, cough and nausea. Injection site reactions and hypersensitivity reactions including rash, pruritus, urticaria and skin exfoliation have occurred. Because eteplirsen is infused weekly, most patients have indwelling venous access catheters placed, which may pose a risk for complications of infection and septicemia.

Hepatotoxicity

Duchenne muscular dystrophy is a rare disease, affecting ~1:5000 newborn boys, and those with deletion mutants in exon 51 account for only 13% of patients with the disease. Because the pivotal trials of eteplirsen were conducted in small numbers of patients, the full spectrum of adverse events and hepatotoxicity may not be fully known. Nevertheless, serum aminotransferase elevations were not described in the registration trials of

eteplirsen and there were reportedly no discontinuations because of adverse events. Thus, eteplirsen has not been linked to instances of acute hepatitis or jaundice, but it has had limited clinical use.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

How eteplirsen might cause liver injury is not known. One possibility is that exon skipping may cause disruption of translation of other genes. It is metabolized by intracellular nucleases and has little effect on cytochrome P450 enzyme activities.

Outcome and Management

Eteplirsen therapy has not been associated with hepatic injury, either in the form of minor serum enzyme elevations or clinically apparent liver injury. Monitoring of liver tests during therapy is not recommended.

Drug Class: Genetic Disorder Agents

Other Therapeutic siRNA and Antisense Agents: Givosiran, Golodirsen, Patisiran

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Eteplirsen – Exondys 51®

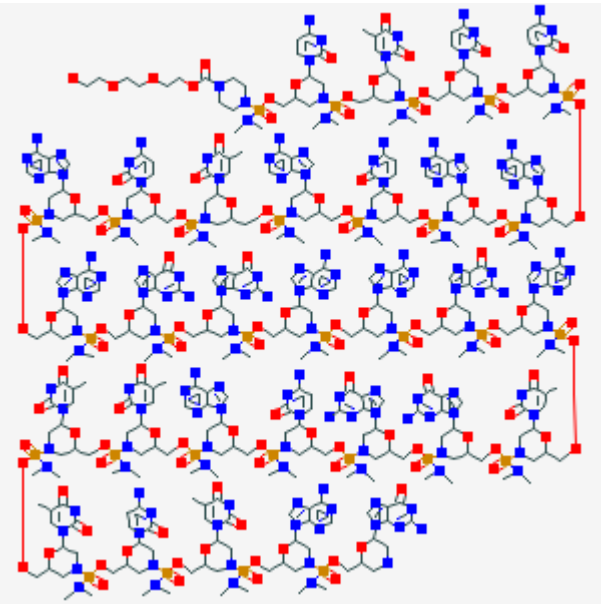
DRUG CLASS

Genetic Disorder Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Eteplirsen	1173755-55-9	C364-H569-N177-O122-P30	

ANNOTATED BIBLIOGRAPHY

References updated: 27 February 2020

Abbreviations: siRNA, small interfering RNA.

Mendell JR, Rodino-Klapac LR, Sahenk Z, Roush K, Bird L, Lowes LP, Alfano L, et al; Eteplirsen Study Group. Eteplirsen for the treatment of Duchenne muscular dystrophy. Ann Neurol. 2013;74(5):637–47. PubMed PMID: 23907995.

(In a small randomized controlled trial, 12 boys with Duchenne muscular dystrophy and mutations in exon 51 of the dystrophin gene were treated with eteplirsen [30 or 50 mg/kg intravenously] or placebo once weekly for 24 weeks, after which the placebo recipients received eteplirsen; muscle biopsies taken before and at 24 and 48 weeks showed increases in dystrophin with treatment and there were no treatment related side effects and no change in liver chemistries).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology. 2015;148:1340–52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, no cases were attributed to RNAi or antisense therapies or medications for muscular dystrophy).

Mendell JR, Goemans N, Lowes LP, Alfano LN, Berry K, Shao J, Kaye EM, et al; Eteplirsen Study Group and Telethon Foundation DMD Italian Network. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. Ann Neurol. 2016;79:257–71. PubMed PMID: 26573217.

(Follow up study of 12 patients with Duchenne muscular dystrophy treated with eteplirsen for up to 36 months [Mendell 2013] found improvements in pulmonary function tests and 6 minute walk tests in eteplirsen treated compared to historical untreated controls; therapy was well tolerated and "there was no signs of symptoms of hepatic toxicity").

FDA. Summary Review and Evaluation. Eteplirsen. 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf

(The FDA clinical review of eteplirsen for efficacy and safety found only marginal evidence of benefit and no major safety issues, although the number of patients treated with eteplirsen that could be evaluated were few; there were no liver related serious adverse events or discontinuations and no mention of ALT elevations during therapy).

Syed YY. Eteplirsen: First global approval. Drugs. 2016;76:1699–704. PubMed PMID: 27807823.

(Review of the mechanism of action, history of development, clinical efficacy and safety of eteplirsen shortly after its approval as therapy of Duchenne muscular dystrophy in patients with confirmed mutation in exon 51 of the dystrophin gene, the approval being based upon increased dystrophin levels in muscle biopsies and not upon clinical benefit; there were no discontinuations for adverse events and "no clinically relevant effects" on liver function).

Eteplirsen (Exondys 51) for Duchenne muscular dystrophy. Med Lett Drugs Ther. 2016;58(1507):145–6. PubMed PMID: 27805575.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of eteplirsen shortly after its approval in the US as therapy of Duchenne muscular dystrophy mentions that there was no evidence of clinical benefit of therapy and that the minimal increases in dystrophin levels in muscle were of uncertain clinical relevance; no mention of ALT elevations or hepatotoxicity).

Kesselheim AS, Avorn J. Approving a problematic muscular dystrophy drug: implications for FDA policy. JAMA. 2016;316:2357–8. PubMed PMID: 27775756.

(Commentary on the approval of eteplirsen by the FDA pointing out the lack of rigor in the clinical studies on its effects and the use of a surrogate marker to assess efficacy that has never been shown to reflect or predict clinical improvement).

Chi X, Gatti P, Papoian T. Safety of antisense oligonucleotide and siRNA-based therapeutics. Drug Discov Today. 2017;22:823–33. PubMed PMID: 28159625.

(Oligonucleotide and siRNA based treatments are currently being evaluated in several diseases and have been found to have unexpected toxicities including antisense thrombocytopenia [mipomersen, drisapersen] and peripheral neuropathy [revusiran]; no discussion of hepatotoxicity).

Messina S, Vita GL. Clinical management of Duchenne muscular dystrophy: the state of the art. Neurol Sci. 2018;39:1837–45. PubMed PMID: 30218397.

(Review of current optimal clinical management of Duchenne muscular dystrophy focusing upon standard respiratory, cardiovascular, orthopedic and nutritional support as well as recent innovative approaches to therapy including exon skipping and premature stop codon suppression).

Aartsma-Rus A, Arechavala-Gomeza V. Why dystrophin quantification is key in the eteplirsen saga. Nat Rev Neurol. 2018;14:454–6. PubMed PMID: 29967362.

(Editorial discussing eteplirsen which was approved based upon its effects in increasing dystrophin levels in muscle rather than a clinical effect on preventing progression of disease mentions the challenges of accurate measurement of dystrophin levels and the limited amount of uncontrolled clinical data on the effects of eteplirsen therapy on ambulation and muscle strength).

Charleston JS, Schnell FJ, Dworzak J, Donoghue C, Lewis S, Chen L, Young GD, et al. Eteplirsen treatment for Duchenne muscular dystrophy: Exon skipping and dystrophin production. Neurology. 2018;90:e2146–e2154. PubMed PMID: 29752304.

(Reanalysis of the muscle biopsies from the initial trial of eteplirsen in 12 patients with Duchenne muscular dystrophy found increased levels of dystrophin after 24, 48 and 180 weeks of treatment by RT-PCR, Western blot, immunohistochemistry and immune fluorescence using untreated controls to estimate baseline levels of the protein).

Verhaart IEC, Aartsma-Rus A. Therapeutic developments for Duchenne muscular dystrophy. Nat Rev Neurol. 2019;15:373–86. PubMed PMID: 31147635.

(Review of the pathogenesis, clinical features and natural history of Duchenne muscular dystrophy and recent innovative approaches to treating the underlying genetic defect; this X-linked recessive disorder affects approximately 1 in 5000 boys and is associated with progressive loss of muscle function, presenting clinically by 2-3 years of age and leading to disability in childhood with loss of ambulation by age 12, ventilatory failure by age 20 and death during the 3rd or 4th decade of life; innovative approaches include exon skipping, genome editing, stop codon readthrough, stem cell therapy, and amelioration of secondary pathology with antiinflammatory agents and antioxidants).

Alfano LN, Charleston JS, Connolly AM, Cripe L, Donoghue C, Dracker R, Dworzak J, et al. Long-term treatment with eteplirsen in nonambulatory patients with Duchenne muscular dystrophy. Medicine (Baltimore). 2019;98:e15858. PubMed PMID: 31261494.

(Detailed description of 2 of the initial 12 patients receiving eteplirsen for Duchenne muscular dystrophy who had rapid loss of ambulation but were continued on treatment and who remained relatively stable thereafter; in long term follow up there were no serious hepatic adverse events and no mention of ALT elevations in the listing of side effects).

Khan N, Eliopoulos H, Han L, Kinane TB, Lowes LP, Mendell JR, Gordish-Dressman H, et al; Eteplirsen Investigators and the CINRG DNHS Investigators. Eteplirsen treatment attenuates respiratory decline in ambulatory and non-ambulatory patients with Duchenne muscular dystrophy. J Neuromuscul Dis. 2019;6:213–25. PubMed PMID: 30856119.

(Among 74 patients with Duchenne muscular dystrophy treated with eteplirsen and corticosteroids in 3 prospective trials, the average yearly decline in forced vital capacity was less [-2.2% to -3.8%] than in a matched, untreated control group [-6.0%]).

Levin AA. Treating disease at the RNA level with oligonucleotides. N Engl J Med. 2019;380:57–70. PubMed PMID: 30601736.

(Review of the mechanism of action, current status and future promise of RNA based therapies that use synthetic oligonucleotides to modulate RNA function and have been applied to diseases ranging from hemophilia, amyloidosis, muscular dystrophy and hyperlipidemia).

Aartsma-Rus A, Goemans N. A sequel to the eteplirsen saga: eteplirsen is approved in the United States but was not approved in Europe. Nucleic Acid Ther. 2019;29:13–5. PubMed PMID: 30526286.

(Editorial discussing eteplirsen which was approved for use in Duchenne muscular dystrophy in the US but not in Europe, while atauren, another mutation specific therapy, was approved in the US but not in Europe).

Setten RL, Rossi JJ, Han SP. The current state and future directions of RNAi-based therapeutics. Nat Rev Drug Discov. 2019;18:421–6. PubMed PMID: 30846871.

(Extensive review of gene silencing using RNA interference pathways and the potential of RNAi therapeutics which has promise in many genetic and acquired diseases including transthyretin amyloidosis [transthyretin], HIV infection [CCR5], HBV [HBV mRNA], alpha-1-antitrypsin deficiency [zz A1AT], hypercholesterolemia [PCSK9]).

Verhaart IEC, Aartsma-Rus A. Therapeutic developments for Duchenne muscular dystrophy. Nat Rev Neurol. 2019;15:373–6. PubMed PMID: 31147635.

(Review of mechanisms, challenges, and clinical efficacy of new molecular approaches to therapy of muscular dystrophy including gene therapy with viral vectors, exon skipping using antisense oligonucleotides [casimersen, eteplirsen, drisapersen, golodirsen], stop coding readthrough [ataluren], gene addition, CRISPR-Cas9 genome editing, and myoblast transplantation).

Aartsma-Rus A, Corey DR. The 10th oligonucleotide therapy approved: golodirsen for Duchenne muscular dystrophy. Nucleic Acid Ther. 2020 Feb 11. [Epub ahead of print].

(Review of the efficacy and safety of 10 oligonucleotide therapies approved in the US or Europe, including specific discussions of formvirsen, mipomersen, eteplirsen, nusinersen, patisiran, givosiran and golodirsen).