UNIVERSITY OF MINNESOTA ROCHESTER

Exondys 51 (Eteplirsen)

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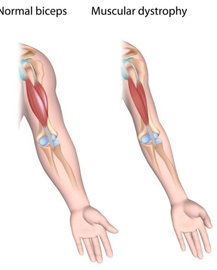
Introduction

- Exondys 51 is a drug used to treat Duchenne muscular dystrophy (DMD).
  - DMD is a fatal disorder characterized by decreased levels of dystrophin, a protein that stabilizes muscle fibers.
  - Exondys 51 utilizes exon skipping and essentially ignores exon 51, the mutated portion of the gene (Lim, Maruyama, & Yokota, 2017).
- After following the FDA drug approval process through various trials, ethical concerns were raised regarding the use of children in clinical trials, the percent increase of dystrophin fibers and whether it was sufficient, and the high cost of the drug.

Keywords: Exondys 51, exon skipping, exon 51, dystrophin, Duchenne muscular dystrophy



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Pre-Clinicals

- Suzani et al. (2010) findings
  - The experiment that was carried out was an observational study.
  - The trial was focused on the safety of Exondys 51 in cynomolgus monkeys.
    - They monitored the vital signs of the monkeys throughout the study to make sure that Exondys 51 had no adverse effects.
    - They used aberration tests which confirmed that the drug had no mutagenic effects on the chromosomes.

Discussion and Conclusions

- Exondys 51 has been proven to be safe and effective.
  - The drug had no adverse effects on the health of cynomolgus monkeys as well as no effect on the chromosomes (Suzani et al., 2010).
  - Exondys 51 does not cause dangerous side effects in humans (Kinali et al., 2009).
  - There were no adverse effects, no impact on organ functions, and there was improvement in the patients' dystrophin levels regardless the dosage amount during the phase II trial (Cirak et al., 2011).
- The drug was approved by the FDA before a phase III trial was conducted to test its safety and efficacy on a larger number of humans. Further research is required to determine if Exondys 51 is safe and effective on a larger scale.

Clinicals

- Kinali et al. (2009) findings
  - All seven patients injected with Exondys 51 showed no immune response or other harmful effects.
  - Patients injected with a lower dose (0.09 milligrams in 900 microliters saline) did not show an increase in dystrophin levels. However, patients injected with a higher dose (0.9 milligrams in 900 microliters of saline) expressed an increase of dystrophin. This indicates that there is a minimum dosage for the drug to be effective.
  - This study did not test subjects for increased muscle function.

- Cirak et al. (2011) findings
  - Of the 19 patients afflicted with Duchenne muscular dystrophy, 17 of them had up to a 7.5% increase in dystrophin fibers within their muscle after being treated with Exondys 51, shown below in Figure 1.

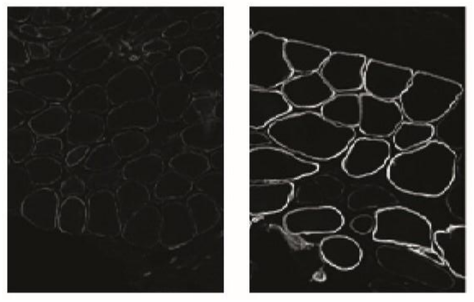

Figure 1: This image of a muscle biopsy shows the increase in dystrophin levels during pre-treatment (left) and post-treatment (right) in one of the patients treated with Exondys 51.

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Abstract

The safety and efficacy of the drug Exondys 51 were assessed to determine if it is a suitable treatment for those afflicted with Duchenne muscular dystrophy (DMD), a fatal disease that reduces dystrophin production in young boys. During both the preclinical and clinical trials, ethical concerns were raised regarding the use of children as participants in the studies, if the percent increase in dystrophin levels was sufficient, and the cost of the drug that only prolongs this fatal disease. Throughout the study, researchers used methods such as testing for side effects in cynomolgus monkeys, administering various dosage amounts to subjects, and taking muscle biopsies to compare the dystrophin levels in the muscle before and after treatment. The results from all of the performed trials showed no signs of adverse effects in either the monkeys or the human participants. Researchers found Exondys 51 to be effective as it increased dystrophin levels, but also safe as they had closely monitored the subjects' vital organ functions. Even though this drug was proved to be both safe and effective, ethical concerns remain. Exondys 51 would be deemed ethical if there are guidelines in place for the use of children as participants in a study, and if the increase in dystrophin levels was sufficient enough to justify the high cost of a treatment that did not complete all clinical trials, nor cure DMD.