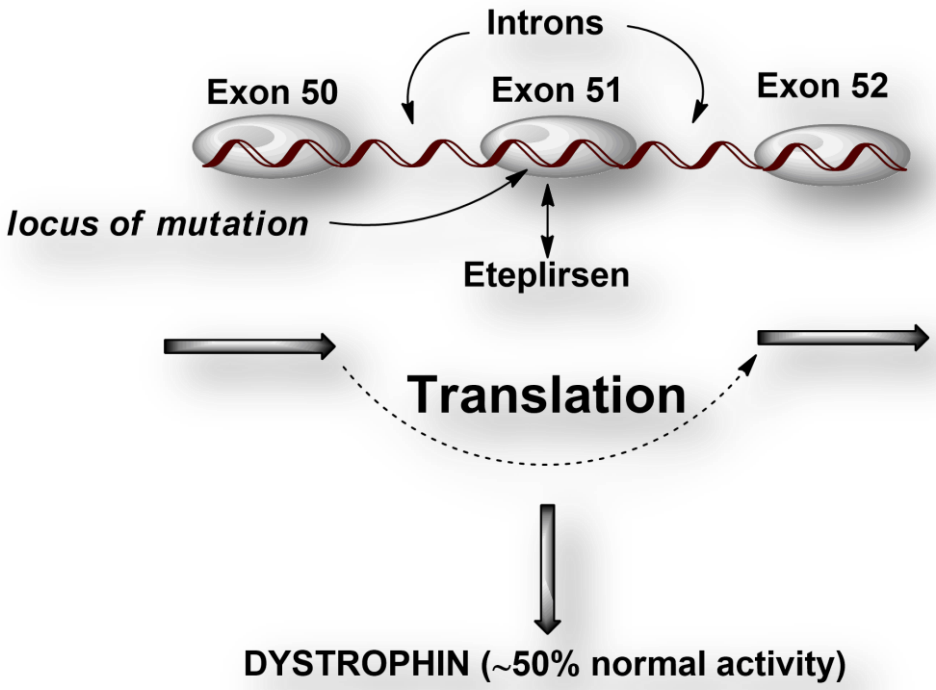

The approval by the US Food and Drug Administration (FDA) of Eteplirsen, a drug for the treatment of Duchenne muscular dystrophy, the most common of childhood muscular dystrophies, is a clear example of the influence of lobbyists on the political decisions made on medical issues. The worldwide incidence of Duchenne muscular dystrophy is estimated at 1 out of 3,600 births. Being a sex-linked genetic disorder (a mutation of the X chromosome), virtually all patients are boys (X*Y); girls suffer a less severe form, or are asymptomatic (X*X). Women are carriers of this genetic alteration, although the emergence of cases where there has been no family history (spontaneous mutations) are relatively frequent.

The eponym of the disease derives from Guillaume-Benjamin-Amand Duchenne (1806-1875), considered the founder of neurology in France. He described various muscle diseases which immortalized his name, such as Duchenne muscular dystrophy, Duchenne-Aran muscular dystrophy and Duchenne-Erb palsy. The very first muscle biopsy is among his achievements. His research into the electro-physiology of muscle activity laid the groundwork for further progress.

Steroids (corticosteroids) are used to decelerate the progression of the disease by virtue of their anti-inflammatory properties, but these drugs have many side effects which limit both the dose that can be administered and the duration of treatment.

Eteplirsen is marketed by Sarepta Therapeutics under the trade name of Exondys 51®. It is indicated for approximately 13% of all patients with Duchenne Muscular Dystrophy, who are affected by a specific mutation of exon 51, found in raw RNA (where introns have yet to be removed), the final stage before translate to protein.

A clinical study of Eteplirsen was led by Dr. Jerry R. Mendell, director of gene therapy for Muscular Nationwide Children's Hospital in Columbus, Ohio, USA. The study was carried out on only 12 patients; 4 of them were treated with the highest dose, four with a placebo, and the remaining 4 received suboptimal doses.

Exondys 51® was authorized by Fast Track Designation [1], although the manufacturer, Sarepta Therapeutics, committed itself to performing a clinical trial [2] in order to confirm their preliminary results. The study, which the FDA used as a basis to authorize the drug, involved only 12 boys, with neither a control nor placebo group. The endpoint measured the number of additional metres that patients were able to walk over a 6- minute period. After four years of weekly infusions of Eteplirsen, they were able to walk an average of 162 meters further than a group of patients from Belgium and Italy, whose detailed clinical histories were used as a "control group". Moreover, 10 of the 12 participants in the clinical trial were still able to walk after four years of treatment as opposed to one out of thirteen in the "control group". Those who were critical of the approval of Eteplirsen stated that the results were based on too low a number of patients to be considered statistically significant. Furthermore, the observed differences in the ability to walk are within the range of the natural variability usually associated with the illness. Moreover, the increase in the amount of dystrophin (the protein lacking in these patients) is about 1% [3]; an insufficient value to demonstrate a significant clinical improvement.

For the reasons stated in the previous paragraph, many independent experts believe that there is no clinical evidence to justify the authorization of the medicine.

In the United States, associations of relatives of patients with Duchenne muscular dystrophy have been organized in lobbies. They have managed to mobilize some members of US Congress to write letters to the Food and Drug Administration pushing for the approval of the drug.

The final FDA decision has been delayed many months. A committee led, by Dr. Robert M. Califf, announced the final decision after a members' vote: seven votes in favour of approval, three against, and three abstentions.

The immediate economic repercussion was a significant increase in the share price of Sarepta Therapeutics on Wall Street.

Sarepta Therapeutics changed its name recently from AVI BioPharma, in an attempt to change its prolonged misfortune.

The preclinical designation of Eteplirsen was AVI4658.

However, the approval of Eteplirsen could affect the prestige of the FDA, who made the decision under political pressure without conclusive evidence regarding the efficacy and safety of Eteplirsen.

Diana Zuckerman, President of the National Centre for Health Research, in Washington, said the FDA has created a dangerous precedent by authorizing a drug without having been contrasted against other drugs for the same indication, or even a placebo.

Dystrophin is a cytoplasmic protein found in muscle cells which allows the dissipation of the contractile force during muscle cell contraction.

Duchenne muscular dystrophy is a recessive genetic disorder linked to the short arm of the X chromosome (Xp21 loci), which affects about 1 out of 3.500 births. Children with this disorder suffer progressive muscle weakness leading to death in late adolescence or early adulthood.

The genetic basis is a mutation of the gene encoding dystrophin. This gene, one of the longest, known as *dmd* (Duchenne Muscular Dystrophy), contains 79 exons. The mutation of exons 47 or 48 causes the synthesis of a shortened version of dystrophin, which retains of its activity, and is responsible for Becker dystrophy, a less severe type than Duchenne Muscular Dystrophy. However, another mutation, in the exons 50 and 51 of the *dmd* gene makes dystrophin synthesis unfeasible. The lack of this protein leads to Duchenne Muscular Dystrophy, the most serious version of all muscular dystrophies.

The gene associated with Duchenne Muscular Dystrophy was identified [(5)] in 1989. Dystrophin is found in the sarcolemma, in both skeletal and smooth muscle, and also located in the heart muscle, the central and peripheral system, and the retina. The lack of dystrophin (as in Duchenne Muscular Dystrophy) or the existence of partially functional dystrophin (as in Becker Muscular Dystrophy) leads to a progressive deterioration of muscle function, the most serious, and ultimately fatal consequence of these disorders.

Becker Muscular Dystrophy is milder because a partially functional version is synthesized. The life expectancy of patients with Becker Dystrophy is superior, in terms of decades, to that of patients with Duchenne Dystrophy, in which there is no synthesis of dystrophin at all.

Duchenne muscular dystrophy is a rare genetic alteration affecting boys. Sufferers are unable to produce a muscle protein called dystrophin, which acts as a buffer against the impacts of everyday life. Children show symptoms when they start to walk, at about two or three years of age. The disease progresses in such a way that boys at the age of 10 require a wheelchair, and usually die within their second or third decade of life.

The drug, now approved, Eteplirsen (Exondys 51®), is based on the technology of Exon Skipping [(4)]. Conceptually, the drug allows the ribosome machinery to "skip" the defective exon, and the synthesis of dystrophin is uninterrupted. This synthetized dystrophin, although defective, maintains about half of its normal activity. Eteplirsen is specific for a type of mutation located at gene 51 position (hence the registered name Exondys 51®) affects approximately 13% of patients with Duchenne muscular dystrophy. Using Exon Skipping technology, others drugs are being developed for other specific mutations.

Eteplirsen mutes part of the gene which encodes the synthesis of dystrophin known as exon 51, which contains a mutation that disrupts the synthesis of dystrophin in some patients. During transcription, if this exon is circumvented, muscle cells can produce a dystrophin which, although imperfect, maintains some residual physiological activity (~ 50%), and therefore alleviates the symptoms of patients with Duchenne muscular dystrophy.

The cost of treatment with Exondys 51® is $300,000 annually. As said before, Exondys 51® has been authorized through an accelerated procedure because of

the absence of other pharmacological alternatives. However, the FDA obliges the manufacturer (Sarepta Therapeutics, based in Cambridge, Massachusetts) to conduct clinical studies to support the very limited preliminary conclusions regarding the effectiveness of the drug. The FDA reserves the right to withdraw the drug if the results of the prospective clinical trial do not confirm the results of the pivotal study mentioned earlier. Sarepta Therapeutics argues that a clinical trial with a placebo group would not meet the appropriate ethical standards because this would deprive a number of children of the benefits of the drug. In a premarket study involving 12 children, the clinical histories of Belgian and Italian children were taken as a "placebo group". In addition, the patients' families would not accept that their children participate in the clinical trial of an already approved drug where they might be included in a placebo group.

However, Janet Woodcock, Director of the Centre for Drug Evaluation and Research at the FDA, stressed the need for a post-marketing confirmatory clinical study.

When it comes to drugs for rare diseases, the FDA, based on a legislative amendment in 2012, is increasingly taking into account the views of patients, and assessing the benefits the drug would lend their quality of life, not just the impersonal statistical findings of clinical studies.

Sarepta Therapeutics received an additional priority authorization conceded to laboratories which develop drugs for uncommon paediatric diseases. This is the seventh rare paediatric disease that benefits from this special programme aimed at the urgent approval of medicinal products.

Bibliography

1.- López-Tricas, JM. Approval of New Drugs. [PENDIENTE DE COMPLETAR LA REFERENCIA CUANDO SE PUBLIQUE, POSIBLEMENTE EN EL NÚMERO DE SEPTIEMBRE-OCTUBRE 2016].
2.- Anonymous. Efficacy Study of AVI-4658 to Induce Dystrophin Expression in Selected Duchenne Muscular Dystrophy Patients. In: https://clinicaltrials.gov/ct2/show/NCT01396239?term=%22Eteplirsen%22+AND+%22Sarepta+Therapeutics%22&rank=4. In: www.ClinicalTrials.gov. Consult: September 2016.
3.- Anonymous. Efficacy, Safety, and Tolerability Rollover Study of Eteplirsen in Subjects with Duchenne Muscular Dystrophy. In: https://clinicaltrials.gov/ct2/show/NCT01540409?term=%22Eteplirsen%22+AND+%22Sarepta+Therapeutics%22&rank=6. In: www.ClinicalTrials.gov. Consult: September 2016.
4.- López-Tricas, JM. Exon Skipping, a New Pharmacological Strategy for Duchenne Muscular Dystrophy. In: http://www.info-farmacia.com/medico-farmaceuticos/revisiones-farmaceuticas/exon-skipping-new-pharmacological-strategy-for-duchenne-muscualr-d. In: www.info-farmacia.com. Consult: September 2016.
5.- Aartsma-Rus A, Bremmer-Bout M, Janson A, den Dunnen J, van Ommen G, and van Deutekom J. Targeted exón skipping as a potential gene correction therapy for Duchenne muscular dystrophy. Neuromuscul Disord. 2002; **12**: 571-577.

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