1- INTRODUCTION

Hemophilia is a hereditary coagulation disorder caused by lack of a coagulation factor. Patients have frequent bleeding that sometimes can cause death. The main forms of this disease are hemophilia A (deficiency of VIII factor) and hemophilia B (deficiency of FIX factor). Both of them have an X-linked inheritance.

The current treatment involves frequent intravenous injections of the clotting factor. But this approach has limitations (price, accessibility and development of inhibitors), so it’s important to develop a new treatment. This work presents gene therapy as an option to treat hemophilia.

2- OBJECTIVES

➢ To understand the clinical and genetic characteristics of hemophilia as a disease, as well as current treatments available.
➢ To consolidate the concept of gene therapy and its technical characteristics.
➢ To determine the evolution of the field of gene therapy for hemophilia in the last years: from the early clinical trials to the present.
➢ To establish whether gene therapy is an appropriate and beneficial treatment for hemophilia: determine the clinical hardships of the gene therapy.

3- METHODOLOGY

As a basis for the development of this work, many information sources such as reviews, scientific papers, theses, books and official websites were consulted. All the information was verified and filtered to obtain a well-structured study. Only those topics of greatest interest were selected. With all the gathered information, a written report and a poster were made.

4- CHARACTERISTICS OF THE VECTORS

<table>
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<tr>
<th>DNA</th>
<th>Retroviral</th>
<th>Lentiviral</th>
<th>Adenoviral</th>
<th>AAV</th>
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<td>Chromosome integration</td>
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<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>Quiescent cells transduction</td>
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<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<td>Immunogenicity</td>
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<td>Unlikely</td>
<td>Unlikely</td>
<td>Possible</td>
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<td>Safety concerns</td>
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<td>Possibility of insertional mutagenesis</td>
<td>Possibility of insertional mutagenesis</td>
<td>Toxicity</td>
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</table>

5- GENE THERAPY: CLINICAL AND PRECLINICAL TRIALS

**Ex vivo approach: transduction of fibroblasts with plasmid vectors (2001)**

**In vivo approach: transduction of the liver with AAV2 (2006)**

**Phase I/II Clinical trial**

Hemophilia B

Results:
- Transient hepatotoxicity.
- Moderate expression.
- Transient effect.

**Phase I Clinical trial**

Hemophilia A

Results:
- Safe and well tolerated.
- Transient effect.

**In vivo approach: transduction of the liver AAV8 (2011)**

**Phase I/II Clinical trial**

Hemophilia B

Results:
- Hepatotoxicity: resolved.
- Moderate expression.
- Long-term effect.

**Ex vivo approach: transduction of HSCs with lentiviral vectors (2014)**

**Phase I/II Clinical trial**

Hemophilia A

Results:
- Phenotype correction.
- Moderate expression.
- Promising approach.

**In vivo approach: transduction of the skeletal muscle with AAV2 (2003)**

**Phase I/II Clinical trial**

Hemophilia B

Results:
- Safe and well tolerated.
- Moderate expression.
- Long-term local effect.
- Multiple injections.

6- RELEVANT FACTS

✓ Currently the most promising approaches are the lentiviral and AAV vectors, based on the level of expression and immunogenicity. From now on the aim is to improve these vectors to obtain greater expression using lower doses to reduce the immune response.

✓ The liver is a promising target tissue due to its ability to induce immune tolerance, its high secretory capacity and its aptitude to create the endogenous post-translational modifications.

✓ One of the bottlenecks of gene therapy is the vector production.

✓ Gene therapy is a relatively new field so we have yet to see the long term effects.

7- DISCUSSION AND CONCLUSIONS

- The work presented in this poster is a general view about the evolution of gene therapy strategies to treat hemophilia. There exist multiple preclinical and clinical trials for this disease, but this work is centered in the most relevant ones.

- In conclusion, in this work all the objectives were met. A general knowledge about clinical and genetic characteristics, and treatments of hemophilia was reached. With the information sources consulted it was possible to determine the evolution of the trials used since the beginning to the present, and the feasibility and appropriateness of gene therapy as a treatment for hemophilia.

8- REFERENCES