1. Introduction

Epidermolysis Bullosa (EB) is a group of genetically transmitted and chronic skin disorders without effective treatment. It affects 1 in 17,000 children and is characterized by spontaneous mucocutaneous blistering and ulcers caused by minor trauma. About 18 genes have been identified to be involved in EB’s etiology, encoding structural proteins and adhesive molecules of the epidermal basement membrane, resulting in over a thousand mutations that may occur de novo or follow a pattern autosomal dominant or recessive inheritance. The level of expression of these genes in the different skin layers and different types of mutations explain the phenotypic variability of the disease. So the pathophysiology consists in abnormal separation of skin layers due to genetic defects that alter one or more essential dermo-epidermal junction molecules.

There are three EB classic types ([Table 1]) which are differentiated by type of injury, histological characteristics, anatomical location, pattern of inheritance and gene mutation. The clinical presentation varies according to the type of disease.

2. Objectives

The aims of this study are:
- Present a review of Epidermolysis Bullosa’s research, understanding the rare disease’s context.
- Expose the protein, gene and cell therapies trials published, in order to discuss their treatment potential in humans.
- Understand the tissue regeneration and purpose a future strategy through 3D skin bioprinting.

3. Methodology

- Search articles in PubMed database published between 2008 and 2015 using the following terms: Epidermolysis Bullosa, rare diseases, orphan drugs, EB treatment, gene therapy for EB, cell therapy for EB, skin regeneration.
- Search scientific literature in conferences, Gene and Cell Therapy books and courses related with rare diseases.
- Consult reference web pages like CIBERER, EURORDIS, ORPHANET, UpToDate and GeneCraft.
- Contact to Marcolin del Rio, principal investigator for Epidermolysis Bullosa in CIBERER, and contact the association DEBRA in Spain.

4. Treatment Strategies for Epidermolysis Bullosa

1. Allogenic Fibroblasts. Intradermal injection leads to increased C7 expression in dermal-epidermal junction (ulcer’s healing). Limitations:
- C7 expression just for 28 days
- Multiple local injections (effectiveness?)

2. Allogenic Blood and Bone Marrow Cells. Increased fully functional lympho-haematopoietic system which develops different cellular shapes. Cellular capacity to secrete C7 in lesions. Long-term heal internal lesions. Security and effectiveness?

3. Mesenquimal Stem Cells. Currently the most important therapy for ulcer’s healing. Cells can be isolated from bone marrow or adipose tissue and their potential characteristics are:
- Anti-inflammatory
- Source of C7
- Pro-angiogenic
- Anti-microbial

4. Natural Therapy: revertant mosaicism. Second-site somatic mutation that corrects the inherited one and produce a normal patch skin (auto-corrected cells).

5. Induced Pluripotent Stem Cells (iPSC). De-differentiated keratinocytes and fibroblasts to create genetically corrected cells.

Systemic infusion of recombinant absent protein. There are good results in pre-clinical trials with murine model, that suggest it could be a possible treatment in humans.

1) Intradermal injections
2) Intravenous injections
Both are safety/effectiveness systems that improve the EB phenotype accelerating wound healing. However, necessary dosing levels has yet to be determined.

5. Conclusions

- Epidermolysis Bullosa is a complex rare disease with many clinical forms, that challenges the biomedical investigation.
- The patient’s associations role, like DEBRA, are very important as a support to these and for investing in research. It’s also important to have the world biobank where many EB samples can facilitate the study.
- The main treatment for EB is symptomatic and dealt with the care of wounds and blisters on a daily basis, as well as performing a small prophylaxis avoiding friction that can cause damage to the patient. Despite this, current research in this area is very active, which tries to develop new treatment strategies based on the therapies combination, and bioengineering.
- Although the best potential therapy would be gene therapy, currently there are more developed cell therapies, especially using mesenchymal stem cells and reversed epidermal stem cells.
- A possible hopeful future strategy could be the skin creation through 3D bioprinters.
- The main limitation in EB treatment’s research is the health care cost (orphan drugs), as this is a minority disease that affects relatively few patients. This is the principal weakness in biomedical research as it also involves an issue of ethics.

6. References