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Review of the Latest Methods in the Treatment of Epidermolysis Bullosa and Other Chronic Wounds, Development of Innovative Advanced Therapy Medicinal Product

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Abstract

Epidermolisis Bullossa (EB) is classified as genodermatosis, a hereditary genetic skin disorder that causes severe, chronic skin blisters with painful and life-threatening complications. Currently, there is no effective therapy or cure for EB. Over the past decade, however, a number of important advances have been made that bring the clinic closer to new methods of treatment, including gene therapy, protein replacement therapy, cell therapy (allogeneic fibroblasts, Mesenchymal Stromal Cells (MSCs), bone marrow stem cells transplant, culture/vaccination of revertant mosaic keratinocytes, gene editing/engineering and the clinical application of inducible pluripotent stem cells. Tissue engineering scientists are still trying to develop structures that mimic the structure and natural healing process to promote skin reconstruction in the event of incurable injuries.

Although the cure for EB remains elusive, recent animal model data and preliminary human clinical trials have raised the expectations of patients, clinicians and researchers whereby modifying the disease and improving life quality are attainable goals. In addition, the lessons learned from the treatment of EB may have a significant impact on improving the treatment of other genetic diseases.

Keywords: Biological dressing; Human skin allograft; Allogenic human skin equivalent; Epidermolysis Bullosa

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Abbreviations

ATMP: Advanced Therapy Medicinal Product; EB: Epidermolysis Bullosa

Introduction

Epidermolysis Bullosa (EB) is a group of autosomal dominant and recessive disorders in which injury leads to blistering and skin erosion Fine et al. [1]. Several different subtypes have been described in which the underlying molecular pathology includes mutations in at least 10 different genes encoding structural proteins within the Dermo-Epidermal Junctions (DEJ) or primary epidermal keratinocytes [2]. One of the most severe clinical forms of EB is the Recessive Dystrophic EB (RDEB). This condition is characterized by widespread fragility of the skin and mucous membranes.

Usually, wounds and blisters are followed by scarring and an increased incidence of squamous cell carcinoma, which constitutes the main cause of death in young adults with RDEB [3]. The persons affected thereby also suffer from many non-skin complications; including chronic anemia and osteopenia, tactile hallucination [4]. RDEB is caused by loss of function mutations in the type VII collagen gene, COL7A1 [5].

Currently, there is no causal cure for EB - phenytoin, psoralen plus UVA photochemotherapy, tetracycline, systemic glucocorticoids and antimalarial drugs [6-9] have not been very effective and EB therapy consists primarily in local wound healing and avoiding injury. Surgical treatment consists of skin transplants, repairing glove deformities, splinting and dealing with visceral complications (e.g., jejunostomy tubes, esophageal dilation). Other important complementary therapies include physiotherapy, genetic counseling, aggressive infection treatment, nutritional supplementation and

regular monitoring of malignant skin tumors. Skin and wound care in EB is specific to both the type of EB and individual wounds of each child. The availability of dressings and personal preferences are also of great importance when choosing materials. An ideal dressing is yet to be developed, although many suitable dressings are currently available. It is difficult for wounds to heal and chronic wounds often occur. Factors that adversely affect healing include anemia, malnutrition, infection and itching [10-26]. Parallel advances in gene and stem cell therapy are approaching combinatorial therapies that promise clinically significant and lifelong improvement. Recent studies using hematopoietic stem cells and mesenchymal stromal cells, or stem cells in the treatment of EB have the potential to treat the most severe cases permanently and effectively. In addition, advances in the use of gene therapy and gene editing techniques, combined with the development of induced pluripotent stem cells from patients with EB, allow for autologous therapies derived from a renewable cell population which are patient specific.

The low success rate of conventional wound management methods necessitates the production of skin substitutes, including a layer of keratinocytes inoculated on a biocompatible carrier. This can help to create a microenvironment suitable for both fibroblasts and epithelial cells in repairing the wound and reducing the undesirable results of the above-mentioned methods [27-30]. A multidisciplinary field called tissue engineering was created through the collaboration between biomedical and biomaterials engineers, cell and molecule scientists as well as clinicians in order to develop viable and advanced medical devices to restore the normal functions of damaged tissue. Thanks to this interdisciplinary field, many bioengineered skin substitutes have been developed with possibility of being used as an appropriate dressing over a damaged area to treat healing-resistant wounds that can be as effective as or can even surpass conventional wound healing methods Larouche et al. [31-34].

In this article, we describe new methods of treating genodermatoses on the example of EB and conduct a discussion of their advantages and limitations as effective therapies.

Materials and Methods

Dressings and new methods of wound care

The recently developed innovative dressing materials involve bioelectric dressings, double-layered silk gelatin, and dressings with new ointments, including Triterpene [35-50]. In recent studies surveying the opinions of specialists on healing burns, an "ideal" burn wound dressing was described as having non-adhesive, absorbent properties and antimicrobial activity [51]. Goertz et al. [39] describe a solidifying gel that dissolves depending on temperature, providing an interface that is more friendly for patients with superficial wounds. In particular, their new gel is liquid at room temperature and hardens to a gel consistency at normal body temperature or above it, which causes less pain and leads to better results with regard to staining, leakage and odor, compared to silver sulfadiazine gauze. Another promising dressing recently described in non-human studies includes a gelling dendrite dressing based on hydrogel, having three-stage bonds which are able to dissolve on demand [52-54]. The possibility of applying the gel, which solidifies in a few minutes, simplifies the process of applying the dressing significantly. *In vivo* model studies have shown that these gels ensure effective hemostasis and prevent infection while providing a moist wound-healing environment. In addition, an important feature is the ability of clinicians to dissolve the dressing on demand for atraumatic removal of the dressing. Antibacterial gel dressings based on chitosan (Opticell Ag+) have recently been introduced, which provide a moist, adaptable, highly absorbable dressing with antimicrobial effect to reduce dressing changes and alleviate pain. [55]. Catrix powder (bovine cartilage powder; Cranage Healthcare International) is a medically recommended alternative, and early studies suggested faster healing of blisters after Catrix application. Children often suffer from recurring infections and the author managed to reduce bacterial growth by using clothes containing silver thread. Honey is available in the form of impregnated dressings and ointments and is effective both in the treatment of chronic wounds and in reducing biological load. Cutimed Sorbact (BSN) dressings remove bacteria in the process of hydrophobic interaction; the dressings are coated with a fatty acid derivative which attracts bacteria to the dressing, where they are bound. Preliminary studies showed that this dressing is effective for wound healing in people with chronic EB-related wounds. Dressings containing polyhexanide (PHMB), such as Suprasorb X1 PHMB (Activa Healthcare, Lohmann & Rauscher, UK), provide antimicrobial treatment for critically colonized and infected wounds and are recommended for long-term application. The polymer membrane dressing (PolyMem, Ferris, OH, USA) contains a cleaning agent (surfactant) which also reduces the biological load and allows the healing of resistant wounds. Polymeric membrane dressings have the advantage of being "self-contained" without the need for a non-adherent primary or secondary dressing to protect or manage exudation. The frequency of dressing changes depends on personal choice, available time and level of exudation. Infected or critically colonized wounds require more frequent dressing changes. The use of honey products and polymeric dressings on the membrane initially increases the exudation, so before starting, one must establish the commitment to daily dressing changes.

Ibuprofen-soaked (Biatain-Ibu) dressings have proved to be helpful for some wounds, although they are not licensed for children aged under [12-15]. Topical hydrogel morphine is also effective. Other dressings with analgesic properties include biosynthetic cellulose, such as Suprasorb X, which has an additional cooling effect and is helpful in reducing pain associated with blisters and wounds [56-60].

Autogenic skin transplantation

Skin transplantation is an old technique which was rediscovered during the First and Second World Wars as the main way to heal wounds. During these years, Padget and Hood invented a dermatome, an indispensable device used to this today to collect large portions of skin. In 1929, Brown developed a split-thickness skin transplantation technique, distinguishing between full-thickness, medium-thickness and epidermal transplants.

Classification of skin transplants

Skin grafts can be categorized by graft thickness, geometry, and source. Depending on the thickness of the grafts, a distinction is made between Split thickness Skin Grafts (SSG) and Full Thickness Skin Grafts (FTSG).

Split thickness skin grafts consist of epidermis and some layers of dermis. In the context of SSG, different types of skin grafts can be identified: thin SSG (0 mm to 2 mm), medium SSG (0 mm to 4 mm) and thick SSG (0 mm to 6 mm).

Full-thickness skin grafts consist of epidermis, dermis and various layers of subcutaneous tissue. The amount of dermis plays the key role in determining the mechanical, functional, and aesthetic and transplant trophic properties. In fact, a thicker transplant

has better mechanical, functional and aesthetic properties, but neovascularization and revascularization occur with some difficulties and last for at least 5 days. SSGs are characterized by a poor cosmetic effect, which is why they are often used only for functional repair. In addition, SSGs contain fewer tissues which require revascularization after implantation; therefore thin grafts can be used to treat wounds with reduced blood supply [61-64].

Repeated inflammation and scarring leads to pseudo syndactyly (covering of the fingers and toes in the cocoon of the epidermis - deformation of the "glove") and contraction of the fingers [65].

The method of supplying and covering skin defects varies depending on the centers and the experience of the surgeons; it may be performed by using FTSG or SSG. However, there is little evidence in the literature of the superiority of one over the other, and long-term results may vary slightly. There are several factors to consider: availability of donor sites and their potential to heal; delaying the onset of contraction; the likelihood of a transplant; and patient selection.

FTSG should delay contraction recurrences compared to SSG [66-69]. However, the use of FTSG is often worse than applying SSG, leading to potential scar formation. In addition, the site where skin has been collected heals much worse in patients with EB, limiting the surface of the skin that can act as a source and increases the likelihood of scar contraction at the site of collection; according to one of the authors, the collection site of a donor with EB was not cured after 21 years. The epithelium usually separates from the dermis during the procedure. In the case of SSG, which the authors collect by hand with a knife, it can be perforated 1:1.5 to increase the coverage area. The application of dermatome to collect the skin is not recommended, because the machine damages surrounding tissues, which leads to wounds and blisters.

Problems can be minimized by collecting only the epithelium as a "split" graft. Not only is healing faster, but the epithelium can be collected from any place where there is no damaged skin and blisters with purulent substance. Recurrent contracture is more common in this technique within 6 months, but healing at the donor site is more predictable and usually occurs within 2 weeks. The authors have used this technique several times [70-73].

Tissue engineered skin substitutes

Tissue engineering is rapidly moving from basic research to commercial applications. Many skin substitutes have been produced by *in vitro* methods. They are available in various forms, mainly classified into epidermal, dermal and dermo-epidermal or composite skin analogues, which may consist of cell-based or cell-free scaffolds [74-77].

Biocompatibility, biodegradability, non-carcinogenic cross-linking, cost-effectiveness, no risk of infectious diseases and prevention of stimulation of recipient's immune system are factors, which are to be considered in order to create safe and high-quality engineering requirements for the skin [78-81]. The main approach in the engineering of skin substitutes is the culture of primary skin cells, such as stem cells, fibroblasts, keratinocytes, melanocytes and Langerhans cells in a natural or biosynthetic scaffold mimicking the Three-Dimensional (3D) structure of normal cells [82,83].

Although there is a wide range of tissue engineering products available on the market, almost none of them can meet all the requirements set for real skin, including deep skin processes, appropriate vascularization and normal pigmentation [74,82].

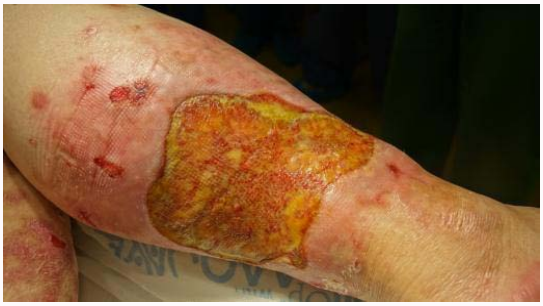

Figure 1: Day 0, admission, 15 cm × 15 cm, fibrin-covered ulceration, located on the posterolateral surface of the patient's right leg accompanied with multiple post ulcerative trophic lesions on the distal segment of the left leg, isolated bullae, multiple dispersed erosions covered with erythematous skin.

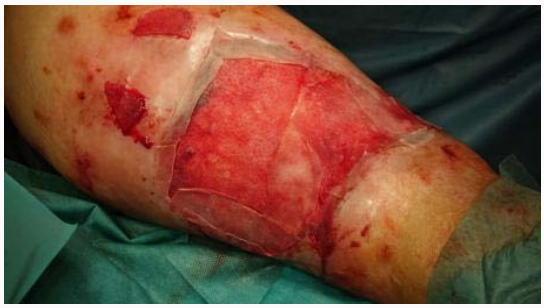

Figure 2: Day 0, procedure, wound covered with prepared graft.

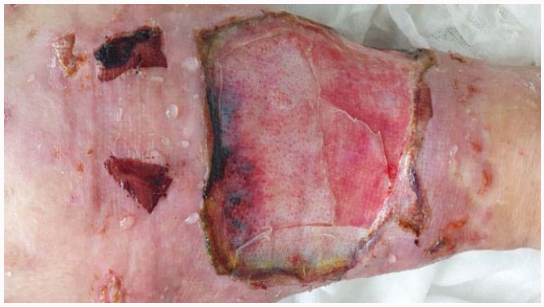

Figure 3: Day 5, first dressing change.

The first product that has transferred the potential of tissue engineering to applications in EB is an autologous Cultured Epidermal Substitute (CES). The pioneering work by Rhein Wald and Green demonstrated that it is possible to grow epidermal keratinocytes as layered sheets from a single cell suspension [84-87], and the multilayer sheets obtained in this way were shown to be very effective in healing burns and wounds in EB [88-90].

Along with the acceptable concept of demand for skin components, several types of two-layer skin substitutes consisting of both epidermal and dermal components have been developed. Bell et al. developed a Cultured Skin Substitute (CSS), the equivalent of live skin, which consists of collagen gel with fibroblasts covered with keratinocytes [91-94]. Boyce and Hansbrough developed CSS consisting of collagen/GAG with fibroblasts deposited by keratinocytes [95]. Kuroyanagi et al. also developed a cultured skin substitute consisting of a spongy collagen matrix with fibroblasts applied over keratinocytes [96]. These two-layer skin substitutes are

designed to be a permanent cover for full-thickness skin defects.

Biobrane

Biobrane is a synthetic two-layer substitute of skin which serves as a skin substitute. It consists mainly of type I swine collagen around a 3D nylon filament and a layer of ultra-thin semi-permeable silicone film as an epidermal layer which controls the loss of skin fluid [81,97-98]. Jutkiewicz et al. [73] published the first report on the use of Biobrane for postoperative hand care within the group of patients suffering from RDEB.

Apligraf

Apligraf is a two-layer skin substitute composed of dermis and epidermis equivalents. The epidermis and skin layers contain appropriately cultured keratinocytes and fibroblasts obtained from a newborns foreskin. Also, bovine type I collagen is present in the skin layer which promotes growth and differentiation of cells [97-101]. It has a positive influence on wound healing, providing ECM components, essential growth factors and cytokines. A decrease in immune system stimulation in the recipient's body has been reported because Apligraf does not contain antigen-presenting cells, such as macrophages and dendritic cells. There have been no reports of the rejection of bovine collagen or alloantigen's expressed on keratinocytes or fibroblasts [102-105]. However, Apligraf has a short shelf life and its use is associated with high costs [106]. A positive effect of applying this dressing in EB wound care has been documented [107,108].

OrCel™

OrCel™ is a two-layer composite consisting of a Type I bovine collagen matrix into which cultured neonatal keratinocytes and foreskin fibroblasts were implanted to form the dermis [109,110]. Its scaffolding is thicker than Apligraf , and the patient's cells penetrate this 3D scaffold after transplantation. OrCel™ is used in RDEB [78]. In addition, it stimulates wound healing by cytokines and growth factors such as TGFα, Fibroblast Growth Factor-1 (FGF-1), Keratinocyte-1 Growth Factor (KGF-1), which are released at the affected site [81,111]. However, bovine collagen increases the risk of transplant rejection and disease transmission [106].

ATMP (Advanced therapy medicinal products)

Despite all efforts, each of the available skin substitutes has disadvantages and is unable to reproduce the function and structure of real skin [81].

Research is currently under way on launching the ATMP, which are based on our clinical and preclinical observations showing prolonged viability of acellular human skin grafts with multipotent stem cells. This was confirmed with histological and electron-microscopic evaluation of biopsies, which demonstrated host-cell infiltration and neovascularization of the biological dressing. Moreover, the dressings were characterized by low immunogenicity, as confirmed by histology exam and T-cell proliferation assays *in vitro*. Our study was divided into 2 stages. The first stage involved preclinical assessment and *in vitro* studies regarding the safety and efficacy of the biological dressing in the form of an allogenic graft of human skin equivalent. The next stage comprised analyses of the response to treatment and clinical outcome *in vivo*. The clinical procedure was performed in a 51-year-old woman with dystrophic EB and the study had been approved by the Bioethics Committee at Warsaw Medical University (KB/2019 14.01.2019; KB/177/2015).

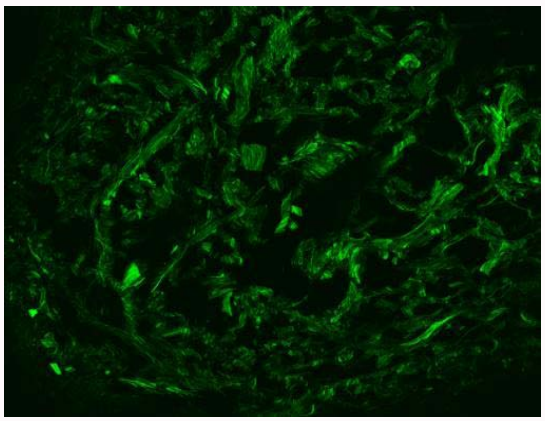

Figure 4: Laser scanning confocal microscopic study using- second harmonic Generation technique" reveals the structure of collagen fibrils in ADM after decellularization and X-ray radiation 35 kG (Bar = 50 mikron).

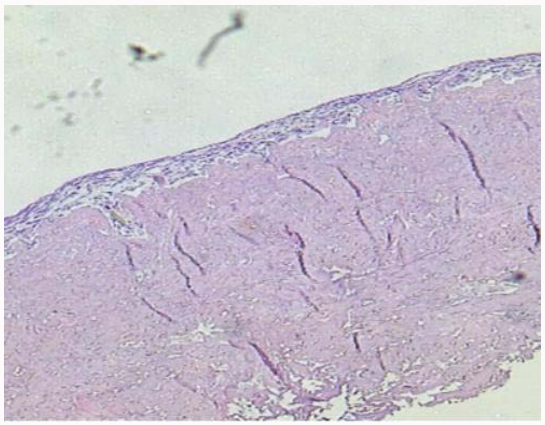

Figure 5: Hematoxylin and eosin stain of scaffold populated with mesenchymal cells from Wharton's jelly. After 72 h of culture MSC create a multilayer structure on the scaffold resembling human epithelium.

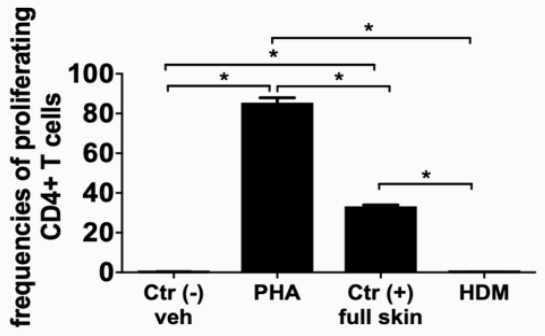

Figure 6: Frequencies of proliferating CD4+ T cells.

Our data indicate that grafting as a potential new medicinal product was safe and effective in patients with rare diseases, such as EB, and may be used for stem cells to create new Advanced Therapy Medicinal Products. During a 200-day follow-up, we proved the safety of using human scaffolds (allogeneic graft) by observing no apparent infection or necrosis. Instead, we noted fewer required dressing changes, promoted wound healing, pain reduction, and an overall improvement in the quality of life in patients with EB [112,113] (Figures 1-6).

In 29.09.2020 the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products issued a decision (Nr UR/DBL/D/237/2020) on the authorization of a clinical trial. "The development of innovative advanced therapy medicinal product (biological dressing of the human race) in the treatment of epidermolysis bullosa and other chronic wounds" with the protocol number Bioopa DBL.474.317.2020.

Gene engineering

Until recently, EB treatment consisted only in applying symptomatic treatment. With the development of genetics, new and exciting therapies are being proposed to address the cause of skin fragility in these patients, including the replacement of an abnormal protein (e.g., collagen VII in RDB) and bone marrow transplantation)

Recent studies suggest that the delivery of allogeneic fibroblasts to the skin of patients with RDEB may be beneficial in improving skin adhesion and increasing the deposition of type VII collagen on the dermo-epidermal junction [114]. There is promising data from patients treated with RDEB with immuno-myeloablative chemotherapy and allogeneic stem cell transplantation, which results in better wound healing, reduced blistering and increased collagen VII deposition on the dermo-epidermal junction.

Viral vectors are the most common form of gene therapy for treating genetic disorders. Retroviral, lentiviral and adenoviral vectors have been developed for RDEB gene therapy. Retroviral vectors have been used for transduction of fibroblasts, which were then evaluated and used for injection into a mouse model of RDEB. Transduced fibroblasts have been shown to express functional C7, embed it as mature anchor fibrils, and ensure improvement based on both *in vitro* and *in vivo* evaluation [115].

The first application of gene therapy in RDEB patients was a retroviral vector used for transduction of keratinocytes containing full-length human COL7A1 [116]. Transduced keratinocytes were then cultured in a GMP device to generate corrected epidermal sheets for autologous therapy. These external autologous transplants were tolerated for 12 months with positive results. Adenoviral vectors were used similarly to correct RDEB cells, both fibroblasts and keratinocytes, and then to determine the iPSC line for future therapeutic application [117]. Improved iPSC it was then used to differentiate into keratinocytes that were able to express C7 and transform into layered layers both *in vitro* and *in vivo*. Lentiviral vectors have also been developed for C7 gene therapy [118]. Recently, a lentiviral vector containing the codon-optimized COL7A1 gene was developed and used to correct RDEB fibroblasts [119]. Corrected fibroblasts have been shown to express full-length functional C7 *in vitro* and embed C7 in DEJ in skin grafts in immunodeficient mice. These approaches may be useful in developing the combinatorial therapies needed to address the systemic problems of this disease.

Although encouraging, more research is needed to determine the long-term safety and effectiveness of this modality. Until then, the goals of treatment are to optimize wound healing and minimize disability caused by blisters.

Discussion

Despite the tremendous progress that has been made over the past few decades in understanding molecular genetics and the underlying pathological mechanisms of this group of diseases, there is still no cure.

There have been many preclinical attempts to develop new treatments for EB. The goal of these approaches to therapy was to correct the primary genetic defect at the level of DNA, mRNA or protein using induced Pluripotent Stem cell (iPS) or keratinocyte-based gene correction, the use of protein therapies for antisense oligonucleotides, and the use of medications which trigger Premature Termination Codon reading (PTC). Another line of potential treatment strategies includes disease-modifying therapies that ensure relieving the symptoms and deal with inflammatory and fibrotic processes responsible for specific EB phenotypes. Although such reports are promising, any potentially effective EB therapies are currently at preclinical stage and are not yet available on the market. Thus the search for new methods of treatment is still very important.

Since the complex EB phenotype triggers a cascade of secondary pathological consequences, successful treatment will likely require combinatorial strategies. Although there is promise in HCT applied to treat EB, it is a procedure with inherent risk, including transplant failure, graft versus host disease, transiently compromised immune system, and side effects resulting from the chemotherapy regimen [120,121]. Although the use of HCT for EB treatment is associated with an inherent risk and not all treated patients have shown significant improvement, the potential for HCT or other stem cell therapy is promising and should be continued and improved. The study of the biological mechanisms revealed by stem cell therapies such as HCT and gene therapy will be valuable in guiding our future approaches. The subset or subsets of cells derived from an HCT transplant which are effective in producing C7 and mediating wound healing have not been sufficiently characterized, although some studies have given some insight into which cells may be responsible [122,123]. Identifying these subgroups may help modify the transplant protocol or increase therapy in a way that promotes greater C7 production in patients who do not respond well to HCT.

In addition, wound healing is a complex process and it is unclear whether there are many types of cells, which are responsible for important processes needed for sufficient long-term improvement of EB skin, i.e. wound healing, C7 production, reproduced epithelium and long-DEJ thermal stability [124-126]. There may certainly be immune cells which are important in the early stages of wound healing and extracellular matrix production but do not contribute to long-term skin populations [127-129]. On the contrary, there may be some subsets of stem cells, such as MSCs or blood-derived stem cells, which contribute to the cellular compartments of wounded skin by differentiation or trans-differentiation but which require specific conditions and time to yield significant therapeutic effects beyond the initial waves of differentiated immune cells [130-132]. It is necessary to analyze these aspects carefully in order to understand the complexity of using stem cell therapy in the treatment of EB. Additional therapies such as the therapy of anti-fibrotic or anti-inflammatory drugs, C7 protein therapy, and treatment with methods other than non-stem cell therapy, like genetically modified cells treatment.

In conclusion, recent data on animal models and preliminary clinical trials have aroused significant hopes for the development of new and effective EB therapies. Although the promise of a cure is still elusive, it is clear that several diseases modifying therapies are emerging, and with further refinement and additional clinical testing, translational research in EB is significant and is gradually changing life for the better. The lessons learned from EB treatment may have a significant impact on improving the management of other forms of

EB and other genetic diseases.

The concept of treating inherited disorders of connective tissue with BMT is not new. In fact, "the history of EB" is somewhat analogous to research conducted approximately two decades ago on osteogenesis imperfecta, a genetic disorder manifested as excessive bone fragility with cracking as a result of the defects of type I collagen gene. A series of experiments conducted with using allogeneic bone marrow cells of children with severe osteogenesis defect were carried out as a result of encouraging preclinical trials [133]. Preliminary observations indicated a significant improvement in the mineral content of the body and microscopic bone structure, which was associated with reduced frequency of fractures and accelerated growth.

However, the observed clinical improvement was not maintained over time within the group of all patients, which raised questions about the regenerative capacity of mesenchymal progenitor cells derived from the donor, and the lack of persistent donor osteogenesis was considered to be a reflection of an internal program or signaling exogenous environment which suppressed the ability to differentiate transmitted stem cells [134].

According to the latest applications of different types of stem cells containing embryonic, prenatal and adult stem cells, endothelial cells and melanocytes parallel to the significant improvement in the engineering of biocompatible materials such as collagen, HA, elastin, PLA, PLGA and PEG, there is now hope for effective treatment of incurable wounds. Recent achievements will lead to the production of skin substitutes displaying the basic qualities of natural skin, including sweat glands and hair bulbs, as well as even pigmentation and healing of scars in the future [135]. However, further research and efforts are crucial for creating truly natural skin-mimicking substitutes. There has been significant progress towards treating patients with EB through different approaches. On the other hand, it is clear that the current approaches are not yet a cure for this destructive disease, and the risks of some of these procedures should be considered in the context of potential benefits. Advanced and innovative strategies with improved safety profiles, which are currently being developed, are clearly required for the successful treatment of this group of currently incurable diseases.

Future prospects

The future of skin regeneration and wound healing lies in the fields of tissue engineering and regenerative medicine. In order to obtain a perfect skin substitute, one should consider a variety of features, such as better vascularity, through the application of bioreactors to support vascular formation, longer life and integration with the tissue of the host. Scaffold polymers, growth factors and all of the cell lines should ideally mimic the skin's natural structure and function in the most efficient way. To this end, new cells such as melanocytes and hair follicles should be added to scaffoldings produced in the 3D technology. Microfluidic dermal printing and automatic tissue paper printing are new techniques which revolutionize tissue engineering strategies. Skin substitutes are currently attracting a lot of attention, and much experimental research is required to improve the safety and effectiveness of stem cells and engineering materials in order to meet the demand for high-quality and profitable products which are manufactured according to standard protocols [74,76,83,136].

In addition, progress is being made, but there is much to be done to achieve a cure for EB. Future approaches should be forward thinking. For example, in regard to gene therapy, it may be safer and more beneficial in the long term to fix the gene on the inside than to provide an artificial, outside source of cells. From a stem cell aspect, giving stem cells that provide therapeutic benefit internally, such as hematopoietic stem cells, may provide a more systemic benefit than treatment with other cellular options. While difficult, fixing the inside- both the genetic component and the cellular component of EB- may be the best approach toward lasting benefits on the outside.

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