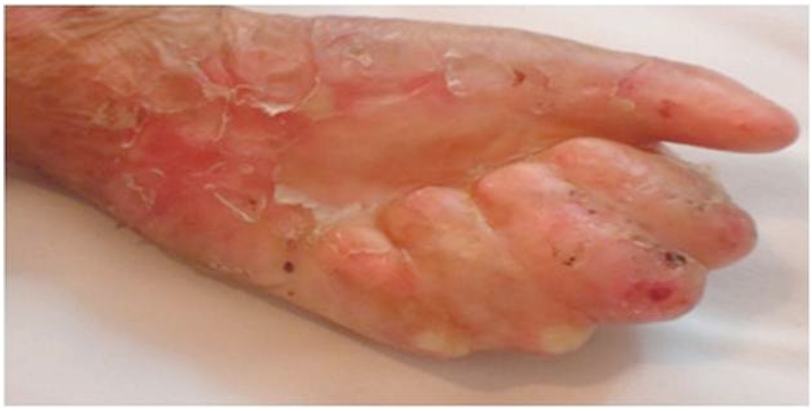
Interesting Case Series

A rapid response to matrix therapy with RGTA® in severe epidermolysis bullosa

Al Malaq, Ali*; Barritault Denis**

* King Faisal Specialist Hospital and Research Center, Riyadh KSA, ** University Paris Est-Creteil and OTR3 4 rue Française Paris 75001 France
Corresponding author: Denis Barritault barritault@u-pec.fr tel+33664100550



This 12 year old child has pseudo-syndactyly of the hand which is almost always associated with epidermolysis bullosa, Hallopeau-Siemens type.

Next

QUESTIONS

1. **What is the pathophysiology of epidermolysis bullosa?**
2. **What are the complications of epidermolysis bullosa?**
3. **What are the conventional treatments of epidermolysis bullosa?**
4. **Can matrix therapy be a solution to close skin ulcers in epidermolysis bullosa?**

Back Next

DISCUSSION

Introduction:

Hereditary epidermolysis bullosa (EB) is a group of rare connective tissue diseases characterized by recurrent blister formation in the skin and mucosal membranes in response to mechanical trauma. It is inherited in either an autosomal dominant or recessive manner with an overall incidence and prevalence of about 1/20,000 live births and 1/125,000 respectively[1]. Patients require extensive, time consuming and painful daily wound care to protect the denuded skin. Treatments of epidermolysis bullosa remain mainly at preventing complications from blistering. There is currently no curative treatment, only DNA-based prenatal testing in families at genetic risk and several ongoing trials based on cell and/or growth factor therapies.

This twelve year patient has a recessive dystrophic epidermolysis bullosa, Hallopeau-Siemens type, with a chronic non-healing painful lower extremity ulcers that healed within four weeks after a twice weekly topical application of a Matrix Therapy solution of RGTA® (OTR3, Paris, France).

Case Description:

A twelve year old child with a Hallopeau-Siemens type of epidermolysis bullosa and suffering from none healing leg ulcers for four years was treated at the clinician's initiative after approval of the parents, with a solution of RGTA® (figure 1). The treatment consisted of topical application of a cotton gauze impregnated with the solution to the wound bed twice weekly for five minutes per application, combined with a daily none adhesive dressing change (without compound). Significant pain relief was obtained within five minutes after the first administration of the product. Although intense pain recurred by the next day, it was not as severe as described prior to the treatment. Similar pain relief was observed following each application. After one week (two applications), pain was reduced by 80%, then subsequently disappeared. Skin color changed (Figure 2B) with a decrease in inflammation with subsequent granulation and healing (Figure 2C). After two weeks of RGTA® application, the wound area was reduced (Figure 2D) until complete closure at four weeks with no oozing (Figure 2F). There was no recurrence during an observation period of two years.

Discussion:

1) What is the pathophysiology of epidermolysis bullosa?

The skin is made of three layers: the epidermis, the dermis and then the hypodermis. In healthy individuals, anchoring proteins, such as collagens and laminins, are important for the maintenance, the hook of the basement membrane zone underlying the epithelium and for preventing the layers from moving independently. In EB patients, the epidermis and dermis have altered or lack some of these anchoring proteins that hold them together. As a result, the skin is extremely fragile and minor mechanical action, like rubbing, pressure or friction, can separate the layers of the skin and form blisters and painful sores, comparable to second or third-degree burns. This lack of anchoring proteins is known to arise from mutations in at least 15 genes, leading to a broad spectrum of diseases: EB Simplex (EBS) involving keratin V and XIV, Junctional EB (JEB) involving laminin-5, alpha-6 beta-4 integrin and BPAG2, Dystrophic EB (DEB) characterized by mutations in collagen VII gene, and Kindler syndrome (KS) involving KIND1[1].

2) What are the complications of epidermolysis bullosa?

Epidermolysis bullosa is commonly observed in children from all ethnic origins, with no gender prediction. Its severity ranges from mild, with localized blistering of the hands and feet, to generalized blistering of the skin, sometimes up to 75%, as well as of the oral cavity and injury to many internal organs, which can lead to death between the 20th to 30th years. As a result of chronic blistering of the skin,

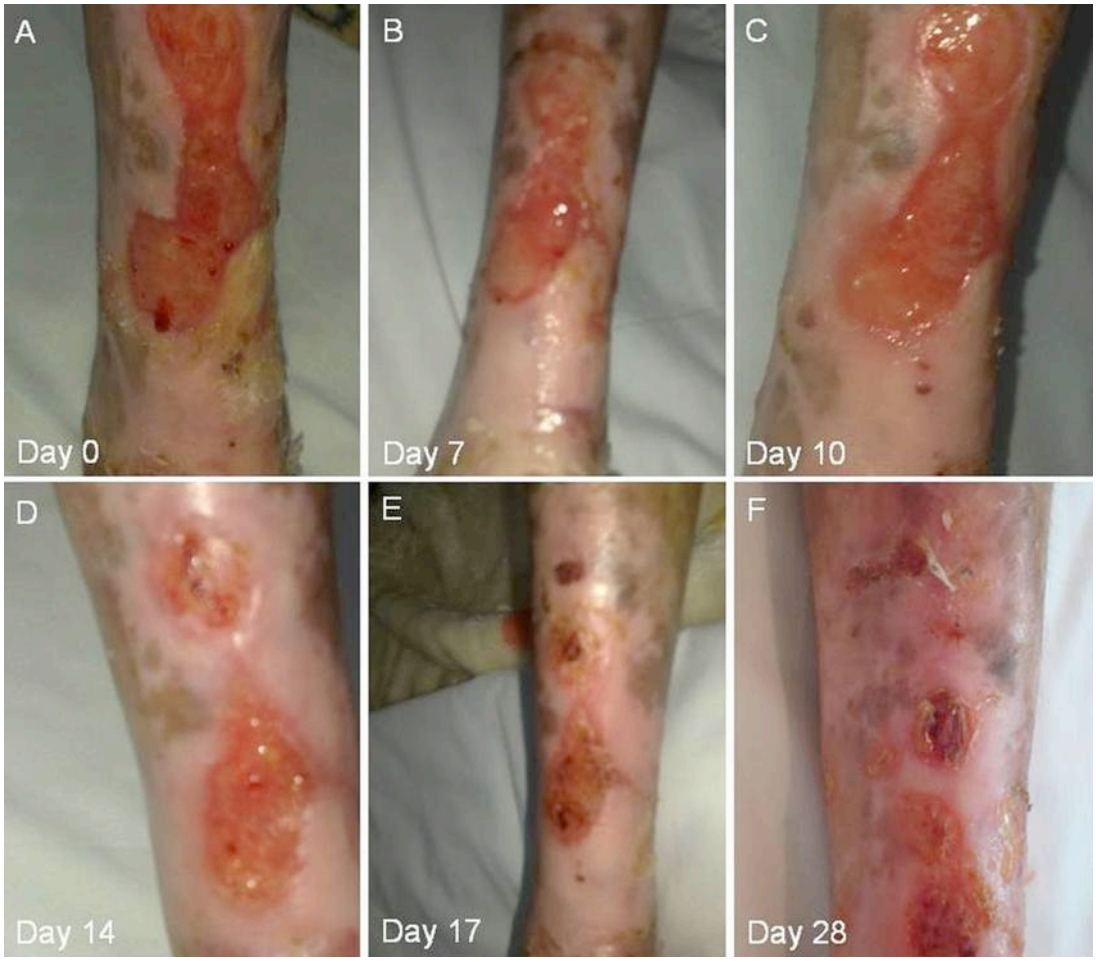
these patients suffer from anemia, life threatening infection and chronic infection, including sepsis, and in the most severe cases from the loss of function in the hands and feet by pseudo-syndactyly and musculoskeletal contractures or dystrophy. The mucosae can also be affected, leading to eye disorders, periodontal diseases, esophageal and gastrointestinal strictures, possibly causing feeding difficulties, severe malnutrition and then growth retardation.
As there is no real way to prevent damage from occurring, as it is very aggressive for most of the children who exhibit signs of the disease, their condition can get progressively worse as it increasingly damages their body tissue over time. This can lead to the development of skin cancers in the recessive forms of EB, as a result of the chronic damage done to the skin[2].

3) What are the conventional treatments of epidermolysis bullosa?

There is currently no satisfactory method for the treatment of epidermolysis bullosa.
EB patients must maintain a high standard of personal hygiene and skincare in order to avoid blisters formation and infections. They are dealing with daily dressing changes, including cleansing wounds and removing dead skin, local anti-biotherapy, application of fresh dressings... which can be painful and can take several hours.
Researchers are currently focusing their effort on developing products to help blisters heal by engineered skin grafting and to reverse the phenotype of EB patients by gene therapy.

4) Can matrix therapy be a solution to close skin ulcers in epidermolysis bullosa?

RGTA® is the acronym of ReGeneraTing Agent and a new therapeutic class of product, known as Matrix Therapy, with a unique mode of action. RGTA® is 1-6 alpha poly-glucose with substituted carboxymethyl and sulfated groups chain with relative mean Mr 80 000D. It is engineered to mimic and replace the destroyed heparan sulfate in the wounded tissue serving as both a matrix element bridging matrix proteins of the extracellular scaffold and storage-protection of bioactive peptides including cytokines and growth factors from degradation[3]. It appears that when introduced to the bed of the chronic wound it restructures the scaffold organization of matrix proteins and allows the newly synthetized cytokines, chemokines and growth factors secreted by the cells surrounding the wound to create a cellular micro-environment capable of supporting healing[3]. The wound bed resumes an organization that resembles the original healthy tissue, leading to a healing process reminding of a regeneration as documented in many preclinical studies[3] including skin[4,5,6,7,8,9], and mucosa[10,11].
Several thousand patients have been successfully treated with no reported adverse effects. A growing body of evidence is accruing to support the efficacy and safety of this new approach documented by case reports and trials[12]. Pain killing activity was also reported[13] in another similar product developed to treat persistent corneal epithelial defects and ulcers[14, 15]. It would also be interesting to investigate the effect of RGTA® therapy on various forms of epidermolysis bullosa as the mode of action would not depend on it and to investigate the effect on the complications such as anemia, feeding difficulties, eye disorders…
The promising beneficial actions of Matrix Therapy were the stimulus to use this in the treatment of this patient. This case demonstrates the potential use of Matrix Therapy for this debilitating disease.
Controlled trials will be performed.



Leg skin color changes and wound area reduction until complete closure during RGTA® treatment of a patient with epidermolysis bullosa

REFERENCES

1. Fine JD, Inherited epidermolysis bullosa. Orphanet J Rare Dis. 2010 May 1
2. Fine JD, Hintner H, Life with epidermolysis bullosa. Eds. 2009
3. Van Neck J, Tuk B, Barritault D and Tong M. Heparan Sulfate Proteoglycan Mimetics Promote Tissue Regeneration: An Overview, Tissue Regeneration - From Basic Biology to Clinical Application. *InTech,, Prof. Jamie Davies (Ed.), ISBN: 978-953-51-0387-5*
4. Barbier-Chassefiere V, Garcia-Filipe S, Yue XL, et al. Matrix therapy in regenerative medicine, a new approach to chronic wound healing. *J Biomed Mater Res A 2009; 90(3): 641-7*.
5. Garcia-Filipe S, Barbier-Chassefiere V, Alexakis C, Huet E, Ledoux D, Kerros ME, et al. RGTA OTR4120, a heparan sulfate mimetic, is a possible long-term active agent to heal burned skin. *J Biomed Mater Res A. 2007 Jan;80(1):75-84*.
6. Tong M, Zbinden MM, Hekking IJ, Vermeij M, Barritault D, van Neck JW. RGTA OTR

4120, a heparan sulfate proteoglycan mimetic, increases wound breaking strength and vasodilatory capability in healing rat full-thickness excisional wounds. *Wound Repair Regen. 2008 Mar-Apr;16(2):294-9*.

7. Tong M, Tuk B, Hekking IM, Vermeij M, Barritault D, van Neck JW. Stimulated neovascularization, inflammation resolution and collagen maturation in healing rat cutaneous wounds by a heparan sulfate glycosaminoglycan mimetic, OTR4120. *Wound Repair Regen. 2009 Nov-Dec;17(6):840-52*.
8. Tong M, Tuk B, Hekking IM, Pleumeekers MM, Boldewijn MB, Hovius SE, et al. Heparan sulfate glycosaminoglycan mimetic improves pressure ulcer healing in a rat model of cutaneous ischemia-reperfusion injury. *Wound Repair Regen. 2011 Jul-Aug;19(4):505-14*.
9. Tong M, Tuk B, Shang P, Hekking IM, Fijneman EMG, Diabetes-Impaired Wound Healing Is Improved by Matrix Therapy with Heparan Sulfate Glycosaminoglycan Mimetic OTR4120 in Rats. *Diabetes, 2012, in press*
10. Morvan FO, Baroukh B, Ledoux D, Caruelle JP, Barritault D, Godeau G, et al. An engineered biopolymer prevents mucositis induced by 5-fluorouracil in hamsters. *Am J Pathol. 2004 Feb;164(2):739-46*.
11. Mangoni M, Yue X, Morin C, Violot D, Frascogna V, Tao Y, et al. Differential effect triggered by a heparan mimetic of the RGTA family preventing oral mucositis without tumor protection. *Int J Radiat Oncol Biol Phys. 2009 Jul 15;74(4):1242-50*.
12. Desgranges P, Louissaint T, Allaire E, et al. First Clinical Pilot Study of Matrix Protection Therapy in Vascular Disease with Regenerating agent technology. *Journal of Wound Technology 2011 ; 13: 44-48*.
13. Groah SL, Libin A, Spungen M, et al. Regenerating matrix-based therapy for chronic wound healing: a prospective within-subject pilot study. *Int Wound J 2011; 8(1): 85-95*.
14. Chebbi CK, Kichenin K, Amar N, et al. Pilot study of a new matrix therapy agent (RGTA® OTR4120) in treatment-resistant corneal ulcers and corneal dystrophy. *J Fr Ophtalmol 2008; 31(5): 465-71*.
15. De Monchy I, Labbé A, Pogorzalek N, Gendron G, M'Garrech M, Kaswin G, et al. Management of herpes zoster neurotrophic ulcer using a new matrix therapy agent (RGTA): A case report. J Fr Ophtalmol. 2012 Mar;35(3):187.e1-6. Epub 2011 Oct 19

Back