Losartan as disease modulating therapy for Recessive Dystrophic Epidermolysis Bullosa (RDEB)

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SHORT PAPER

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Losartan as disease modulating therapy for recessive dystrophic epidermolysis bullosa

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Abstract

A 6-year-old child with recessive dystrophic epidermolysis bullosa, confirmed by history, clinical exam, and antigen mapping, was treated with losartan with reduction in the blistering and better quality of life.

KEYWORDS

epidermolysis bullosa, losartan, recessive dystrophic epidermolysis bullosa

1 | INTRODUCTION

Hallmarks of recessive dystrophic epidermolysis bullosa (RDEB) are unremitting blistering and chronic wounds leading to tissue fibrosis and scarring.[1] There is no cure for any of the subtypes of EB. Novel therapeutic approaches are therefore urgently required. In the present communication, we report a case of RDEB successfully treated with losartan (an angiotensin II receptor antagonist), leading to reduction of blistering and improved quality of life (QoL).

2 | CASE

A 6-year-old male child born from a consanguineous marriage, with RDEB confirmed by history, clinical exam (Figure 1A), and antigen mapping (Figure 2) presented for treatment. With the goal of selecting therapy that could improve wound healing, a literature search was done, leading to the choice of losartan, which has shown promise as an antifibrotic agent. Losartan was therefore started with a dose of 1 mg/kg orally once a day with necessary ethical and informed consent. The 25 mg tablets were crushed and powdered and added to 5 mL of cyproheptadine syrup and the child was given 2.5 mL of syrup daily, amounting to approximately 12 mg per losartan per dose. Within 2 weeks of starting the drug, there was a dramatic decrease in number of blisters with good wound healing (Figure 1B). This encouraged the continuation of treatment with losartan. The child was followed up monthly for a period of 7 months. There was reduction of blistering over the extremities and the trunk was almost lesion free at 7-month follow-up (Figure 1C). There was reduction in oral blistering with decreased sialorrhea. Due to the COVID-19 pandemic, child was not seen physically after that period.

3 | DISCUSSION

Search for the current strategies for molecular therapies for EB-revealed losartan as a promising antifbrotic drug in preclinical studies at Germany.[1]

TGF-b plays a role in inflammation and it can act in both pro- and anti-inflammatory manner. Losartan is known to inhibit excessive TGF-ß signaling in some, but not all, fibrotic diseases.[2] Recent investigations demonstrated that a parallel pathway, involving signaling through the anti-fibrotic AT-2 and MAS receptors, can be a target in RDEB.[2] In RDEB, losartan-mediated TGF-b inhibition (Figure 3) effectively lessens signs of tissue inflammation.[3]

At the EB World Congress, Dimitra Kiritsi, presented interim data on 18 patients in the trial (REFLECT—"Recessive dystrophic EB: Mechanisms of fibrosis and its prevention with losartan in vivo trial"), and opined that the losartan may be used for treating RDEB in the future.[4]

The precursor to the REFLECT trial was a study performed by Nyström et al[3] that has changed the concept of RDEB pathophysiology by demonstrating that it is a systemic and chronic inflammatory fibrotic disease. It also described evidence-based efficacy of losartan related to TGF-β-mediated dysregulation of inflammation and extracellular matrix remodeling.

In 2019, losartan was granted an orphan drug designation for the treatment of EB from both the Food and Drug Administration and the

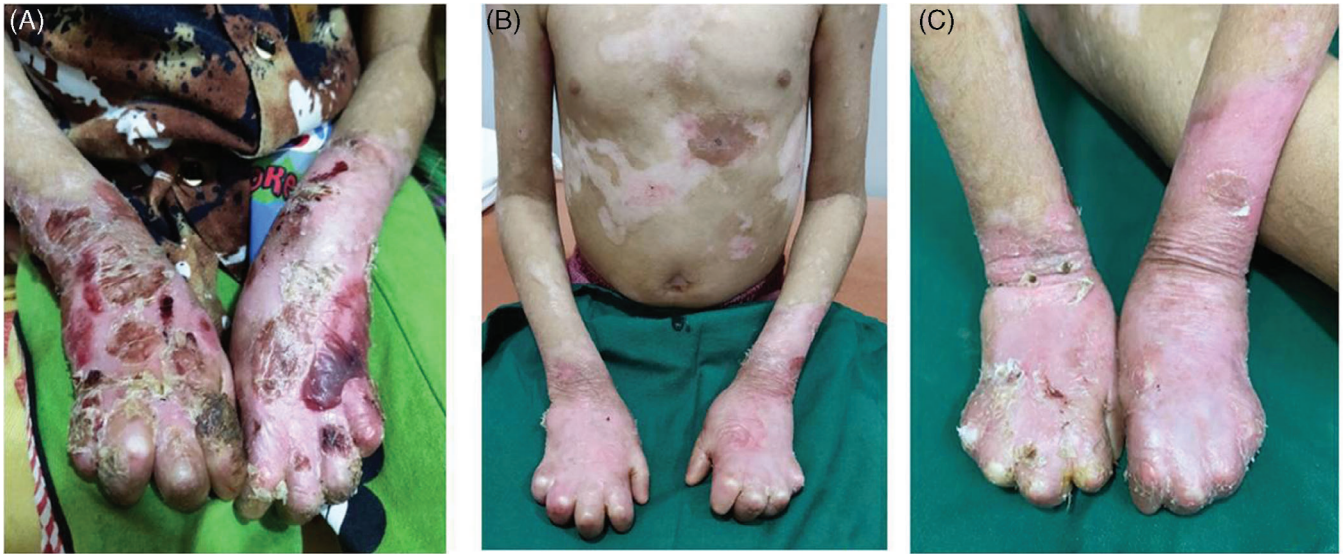

FIGURE 1 A, Base line image, B, image at 2 weeks, and C, 28 weeks after losartan with almost complete healing of the blisters

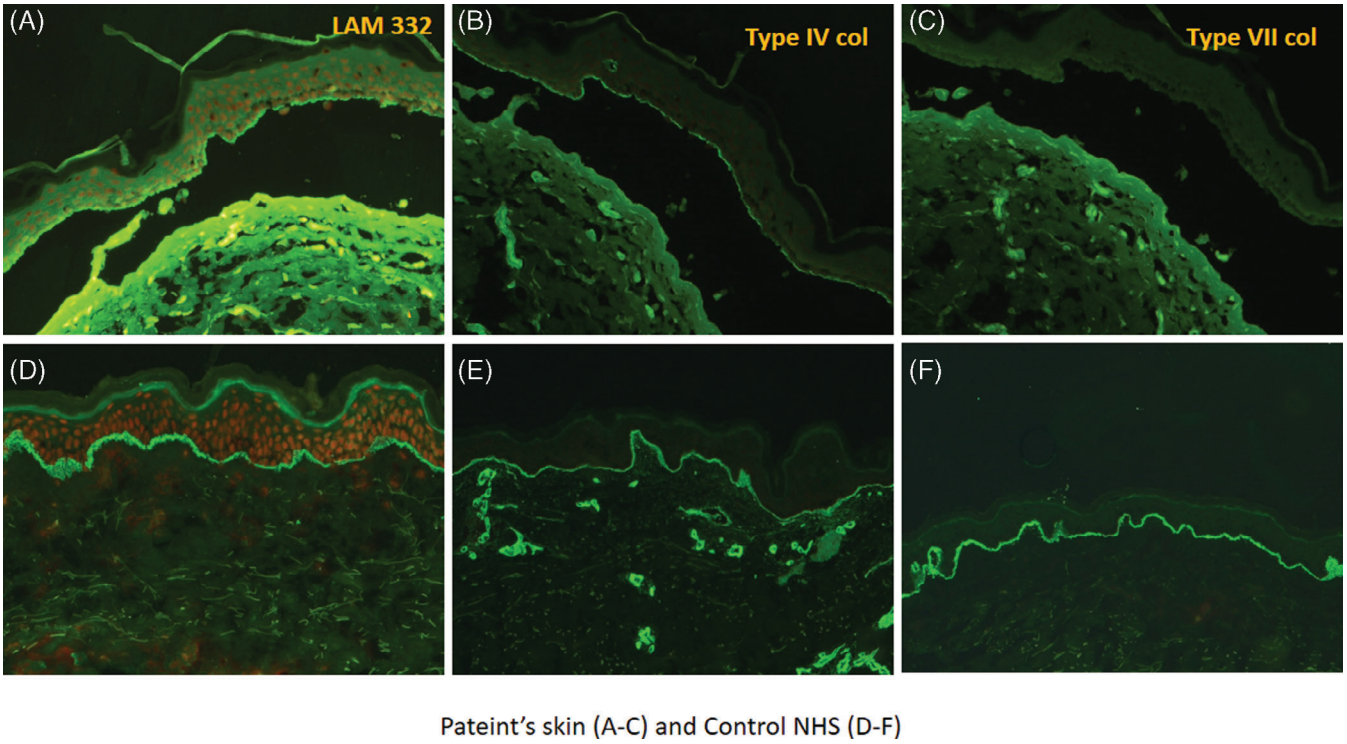

FIGURE 2 Frozen section of patient's skin and normal human skin as control. There is sub-epidermal split with complete absence of Type VII collagen with Type IV laminin 332 seen towards roof of the split. Features suggestive of RDEB

European Medicines Agency, but its use remains off label in children.[5] In normotensive subjects losartan has little or no effect on blood pressure unless the subjects are markedly salt depleted.[6] First-dose hypotension is uncommon with losartan. No clinically relevant adverse metabolic effects or laboratory abnormalities have been documented during losartan therapy, and renal function is preserved.[7] Given its long-term safe use in children and adults losartan seems an ideal repurposed drug for the first disease-modulating therapy of RDEB.[8] In the index case too, there were no significant side effects noted to losartan.

The reduction of blistering was by subjective assessment clinically and improved quality of life by history of reduction in salivation (Indirect indication of reduction in oral blisters) and improved nutritional status in the form of significant weight gain of almost 4 kg. QoLEB questionnaire developed by Frew et al[9] to assess the quality of life in EB children was not done.

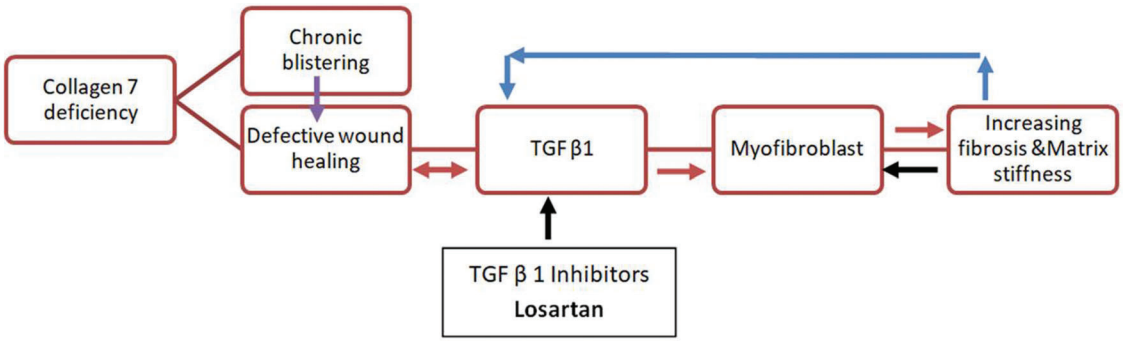

FIGURE 3 Mechanism of action of losartan in RDEB

Patients with RDEB will have statistically significant higher frequency of pruritus with itchiest type of wound in EB patients.[10] Hence, the losartan was dissolved in cyproheptadine for two way benefits in the index case. First to reduce the itching and second as five HT2 antagonists, cyproheptadine seems to be effective in inherited EB as pharmacological treatment.[11] The initial rapid response may be due to cyproheptadine reducing the EB associated itching and reduction of blisters.

The diagnosis was according to the clinical manifestation and antigen mapping result. The pathogenic mutation in the causative gene (COL7A1) was not done for want of facilities. If done it may be useful in establishing a genotype-phenotype correlation with the type of mutations and the patient's response to losartan.

In conclusion, a future role for losartan in treating RDEB awaits the results of randomized clinical trials to confirm benefits.

CONFLICT OF INTEREST

The author declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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