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The clinical efficacy and safety of anti-IgE therapy in recessive dystrophic epidermolysis bullosa

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KEY WORDS: Recessive dystrophic epidermolysis bullosa; anti-IgE; Omalizumab; biologics; wound healing.

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ETHICS APPROVAL: The study was carried out in accordance with the declaration of Helsinki and approved by the Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine. Written informed consent, including consent for photography, was received from participants prior to inclusion in the study.

DATA AVAILABILITY STATEMENT: Data supporting the findings from this study are available from the corresponding author on request.

CONFLICT OF INTEREST: None.

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ABSTRACT

The treatment of recessive dystrophic epidermolysis bullosa (RDEB) remains challenging. Elevated IgE levels have previously been reported in several RDEB patients. In this prospective, single-centre, open intervention study, elevated IgE levels were seen in 11 out of 12 patients with intense pruritus, and the patients with elevated IgE levels received anti-IgE therapy every 4 weeks for at least 3 cycles. Compared with the baseline, 10 patients with RDEB had good clinical outcomes with enhanced wound healing, a reduction in Birmingham (epidermolysis bullosa) EB severity score by 15%, a reduction in affected body surface area by 23.3%, amelioration of skin inflammation, and an increase in type VII collagen deposition by 13.1-fold. All the patients had a good tolerance to anti-IgE therapy. Furthermore, patients with higher IgE levels tended to have higher disease severity and more favourable clinical outcomes. Our report also suggested the potential role of IgE in the pathogenesis of inflammatory conditions associated with RDEB. (ChiCTR1900021437)

1. INTRODUCTION

Recessive dystrophic epidermolysis bullosa (RDEB) is caused by mutations in the *COL7A1* gene that encodes type VII collagen (C7), which is the main component of anchoring fibril proteins that localize to the basement membrane zone (BMZ) ^{1 2}.

From birth, children with RDEB have painful erosions and blisters on skin and mucous membranes, and later in the disease course, mitten deformities, oesophageal strictures, and aggressive squamous cell carcinoma may occur³. Currently, no therapeutic strategies are consistently effective for RDEB, and in some cases, they have been associated with serious adverse consequences^{4,5}.

In several reports, elevated IgE levels have been found in dystrophic epidermolysis bullosa patients^{6,7}. In this report, elevated IgE levels were found in 11 out of 12 RDEB patients with intense pruritus. Omalizumab is an anti-IgE monoclonal antibody, suggesting that it may possibly benefit RDEB patients with elevated IgE levels⁸. Herein, we evaluated 12 cases of RDEB to investigate the use of anti-IgE therapy to promote RDEB for the first time (Fig. 1).

2. MATERIALS AND METHODS

2.1 Patients

We recruited RDEB patients from December 2018 to June 2019 (Fig. 1).

For subcutaneous treatment, intact skin test sites were injected subcutaneously with 150 mg of Omalizumab per site every 4 weeks for at least 3 cycles. The initial Omalizumab dosage in our patients was determined according to the dosage used for the treatment of asthma.

The patients in this study were not immobilized and were allowed to perform normal routine activities throughout the study. The primary end points were assessed by the Birmingham EB severity (BEBS) score and affected body surface area (BSA) (max

score=100) at each visit. Secondary end points were the visual analogue scale (VAS) pruritus score, dermatology life quality index (DLQI) score at each visit and IgE levels in the skin at baseline or at the end of the fourth cycle ⁹.

2.2 Analysis of total serum IgE

The total serum concentration of IgE antibodies was measured by using an N Latex IgE Mono Kit (OQTG15, Siemens, Germany) via the BN II System according to the manufacturer's instructions. Two millilitres of blood was diluted 1:20 for serologic testing. Each serum sample was assayed twice, and the mean IgE level was used for the analysis.

2.3 Skin IgE detection

Samples were fixed with 4% paraformaldehyde, permeabilized and blocked in immunol staining blocking buffer (Beyotime, China) for 1 h at room temperature. Samples were incubated with anti-IgE antibody (Abcam, ab75673) at 4 °C. The samples were then incubated with an anti-rabbit secondary antibody for 1 h and DAPI for 5 min. A Leica DMIRE2 digital scanning confocal microscope (Leica Microsystems, Germany) was used to detect fluorescence and obtain images. The filters used were appropriate for the detection of Alexa Fluor 488 and Alexa Fluor 405. Images were processed using ImageJ, Photoshop CS5 and Adobe Illustrator software. The absolute number of dermal cells positive for IgE in each microscope field was calculated by randomly selecting 5 fields under a 200x field of view and calculating the average value.

2.5 Statistics

The SEM was calculated for each sample. To compare the differences before and after treatment, we used parametric tests in GraphPad 6.0. Spearman's rank order correlation coefficient was used to assess the degree of the relationship between variables. $p < 0.05$ was considered significant. For more detailed descriptions of the methods, see the Methods in the Supplement.

3. RESULTS

3.1 Patients

Among the 12 enrolled RDEB patients¹⁰, (4 intermediate RDEB, 6 severe RDEB and 2 pruriginosa RDEB), 11 patients with elevated skin IgE levels received anti-IgE therapy (median age 27.727 years old, range 8 – 45 years old), and 1 patient terminated treatment after three cycles of anti-IgE therapy because of a poor response (Fig. 1, Suppl. Tables 1 and 2). Interestingly, higher disease activity generally correlated with higher inflammatory infiltration and IgE counts in the skin in this RDEB cohort (Fig. 2A). We also found a positive correlation between serum and skin IgE levels ($r=0.8964$, $p<0.0001$) (Fig. 2B).

3.2 Anti-IgE therapy improved wound healing

Clinical improvement was observed within the first month following anti-IgE therapy in all patients. Compared with the baseline, 10 out of 11 patients with RDEB had good clinical outcomes, with enhanced wound healing, especially for chronic open wounds that had not healed for more than 6 months in patients 3, 5, and 7, and reduced disease severity (the BEBS score was reduced by 15%, $p<0.0005$; BSA was

reduced by 23.3%, $p<0.01$) at the end of the last cycle (Fig. 2C, Suppl. Fig. 1, and Suppl. Table 3). Furthermore, RDEB patients who had higher disease severity tended to respond more favourably, although the difference in BEBS score was not statistically significant due to the small sample size (Fig. 2D).

Two pruriginosa RDEB patients revealed progressive improvement after anti-IgE therapy, with flattening of plaques and dramatic improvement in bullae mainly over the elbows, knees and shins (Suppl. Fig. 1A) ⁸.

Anti-IgE therapy was well tolerated, with no reports of increased blistering. After a 2-month follow-up period, no obvious clinical relapses had occurred.

3.3 Anti-IgE therapy ameliorated skin inflammation

Compared with the baseline, 10 out of 11 patients with RDEB had good responses in amelioration of skin inflammation, with relief of pruritus by 42% ($p<0.0001$) and decreased DLQI values ($p<0.0001$) at the end of the last cycle (Fig. 3A and Suppl. Table 3). Fully differentiated epidermis with spinous and granular layers, decreased dermal inflammatory infiltration, and IgE levels decreased to 3% were observed at the end of the fourth cycle compared to those at baseline (Suppl. Figs. 2 and 3A, Fig. 3B-C). Generally, higher IgE levels in the skin correlated with a better clinical response, although the score was not statistically significant due to the small sample size (Suppl. Fig. 3B).

3.4 Anti-IgE therapy increased C7 levels at the BMZ

C7 levels increased 13.1-fold at the BMZ at 4 months compared to those at baseline, although the responses were variable in different patients (Fig. 3D, Suppl. Fig. 4).

4. DISCUSSION

In this study, we found a significant clinical improvement in RDEB patients with anti-IgE therapy. These results indicate that anti-IgE therapy promoted wound healing by decreasing IgE levels, ameliorating skin inflammation, inhibiting collagen degradation, and further increasing collagen expression in the BMZ.

In the RDEB group, we generally found a positive correlation between disease activity and IgE levels at baseline; furthermore, anti-IgE therapy could effectively reduce skin IgE levels and disease severity, indicating that IgE plays a role in skin inflammation, such as erythema, inflammatory cell infiltration and pruritus, in patients with RDEB¹¹. Furthermore, we observed a positive correlation between serum IgE levels and skin IgE levels, indicating that we can refer to the serum IgE level to some extent to determine whether the patient is suitable for anti-IgE treatment and to predict the treatment effect.

Inflammatory conditions, such as IL-1 β , IL-2, IL-6, IL-10, TNF- β and IFN- γ levels, were elevated in RDEB¹²⁻¹⁵. Anti-inflammatory therapy, such as corticosteroids and methotrexate, thalidomide and dupilumab, have been found to alleviate inflammatory conditions of the disease¹⁵⁻¹⁷. In the RDEB group, markedly decreased inflammatory cell infiltration, decreased erythema and pruritus, improved wound closure and increased C7 levels were also observed after anti-IgE therapy, indicating that anti-inflammatory therapy may decrease disease severity by inhibiting the degradation of C7. Omalizumab blocks IgE from binding and activating the Fc ϵ RI on mast cells

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and basophils and has been hypothesized to have significant immunomodulatory activity beyond its role in immediate hypersensitivity¹⁸. Patient 9 terminated treatment due to a poor response. Although his IgE level was relatively high, it may be due to relatively mild inflammatory conditions in the skin.

A correlation exists between the amount of C7 present at the BMZ and the severity of the disease, so the goal of RDEB therapy is to generate sufficient levels of C7 at the BMZ¹². In this study, we observed increased C7 levels at the BMZ and decreased disease severity, which indicates that Omalizumab-induced C7 was partially functional in these patients. In contrast to localized gene therapy, such as gene-corrected autologous cell therapy or local injection of gentamicin, anti-IgE therapy can improve wound healing throughout the body without obvious side effects⁵
¹⁷.

There are several limitations to this study. First, this study included a small sample size and lacked a control group. Second, our patients were not completely symptom-free with the prolonged use of medication, which might be linked to enhanced drug clearance or different drug pharmacokinetics. Furthermore, mediators other than IgE may also play a role in regulating RDEB disease activity.

5. CONCLUSION

To the best of our knowledge, we have reported the first study to treat RDEB patients with Omalizumab. Our report also suggested the potential role of IgE in the pathogenesis of RDEB. Given its safety and efficacy, anti-IgE therapy was helpful in

severe RDEB patients with high IgE levels, and there may be less injury to the skin that could delay adverse events.

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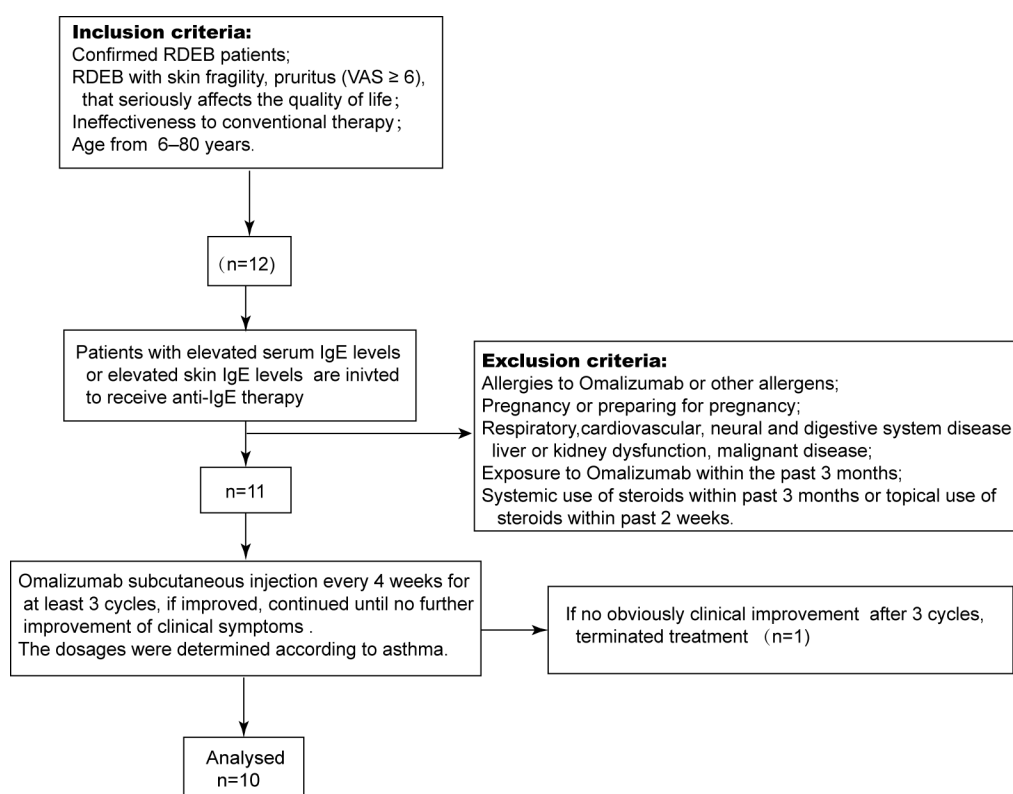
7. FIGURE LEGENDS

Figure 1. Patient enrolment and treatment. Flow chart summarizing the enrolment of patients with RDEB and completion of the trial.

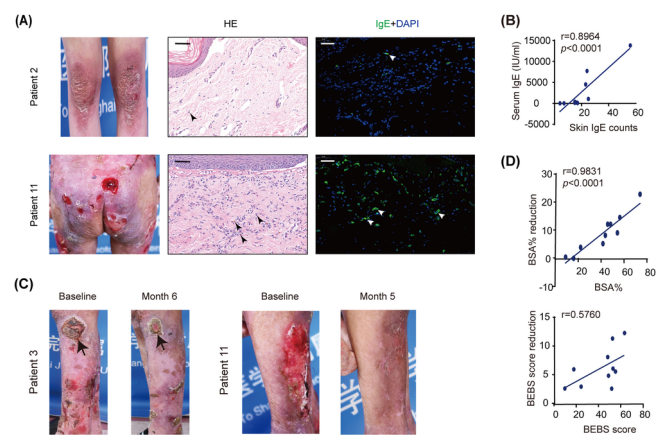
Figure 2. Higher inflammatory conditions are generally associated with higher disease severity and better clinical response with anti-IgE therapy. **(A)** A generally positive correlation between disease activity and dermal inflammatory infiltration and dermal IgE counts. Bars, 50 μm. **(B)** Positive correlation between skin IgE levels and serum IgE levels ($r=0.8964$, $p<0.0001$). **(C)** Patient evaluation at baseline and at the end of the last cycle, which revealed decreased new blister formation, enhanced wound healing, especially for chronic wounds (black arrowhead), and large resolution of inflammatory plaques, leaving post-inflammatory hypo- and hyperpigmentation. **(D)** Patients with RDEB who had a higher BEBS score or BSA tended to respond more favourably than patients who had a lower BEBS score or BSA ($r=0.9831$, $p<0.0001$ for BSA; $r=0.5760$, $p>0.05$ for BEBS score).

Figure 3. Anti-IgE therapy efficiently decreased skin inflammatory conditions and increased type VII collagen (C7) levels at the basement membrane zone (BMZ). **(A)**

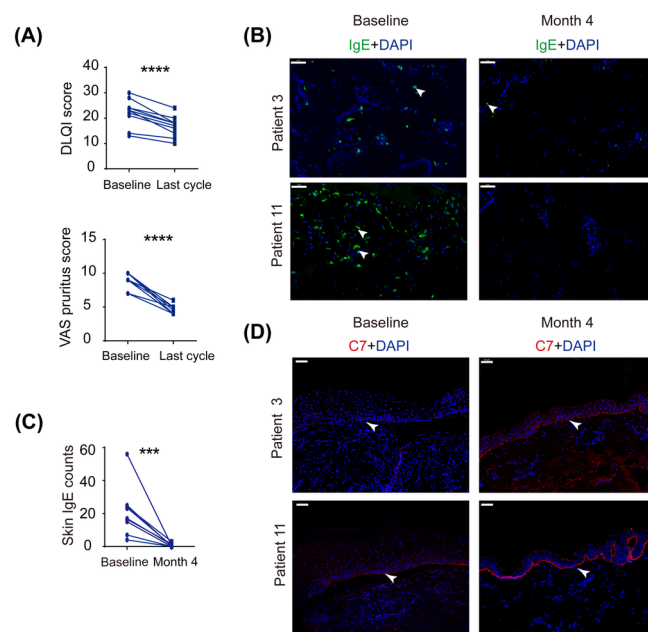
Patient evaluations at baseline and at the end of the last cycle revealed increased quality of life (decreased DLQI score and VAS pruritus score). **** $p<0.0001$. **(B-C)** Apparently reduced IgE (green, white arrowhead) expression at month 4 compared to that at baseline. Biopsies obtained at month 4 showed only weak IgE expression at the dermis. Bars, 50 μm . *** $p<0.001$. **(D)** Increased C7 levels at the BMZ were observed in skin biopsies at 4 months compared to those at baseline. Bars, 50 μm .



CGE_14062_jdv fig 1.tif



CGE_14062_clini fig 2.tif



CGE_14062_clini fig 3.tif

Supplementary Materials for

The clinical efficacy and safety of anti-IgE therapy in recessive dystrophic epidermolysis bullosa

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1. MATERIALS

1.1 Patients

The inclusion criteria for this study were as follows: (a) confirmed RDEB patients: clinical diagnosis of RDEB with *COL7A1* mutations; (b) RDEB with skin fragility, pruritus (Visual Analog Scale pruritus score, VAS pruritus score ≥ 6), that seriously affects the quality of life; (c) elevated serum IgE levels (> 100 IU/ml) (normal range: 0-100 IU/ml) or elevated skin IgE levels (normal controls: negative staining); (d) ineffectiveness to conventional therapy; and (e) 6–80 years of age.

Exclusion criteria were as follows: (a) allergic to Omalizumab or other allergens; (b) pregnancy or preparing for pregnancy; (c) respiratory and cardiovascular system disease, liver or kidney dysfunction, or malignant disease; (d) exposure to Omalizumab within the past 3 months; or (e) systemic use of steroids within the past 3 months or topical use of steroids within the past 2 weeks.

The withdrawal criteria were as follows: withdrawal from the clinical trial was

indicated after 3 cycles without significant clinical improvement according to the Birmingham EB Severity (BEBS) score, or VAS pruritus score.

The termination criteria were as follows: the clinical trial was terminated if clinical symptoms did not improve further according to the BEBS score or VAS pruritus score for 3 consecutive cycles.

1.2 Safety assessment

The primary safety outcomes were headache, fever, abdominal pain and allergic reaction. To prevent possible side effects, participants were observed carefully for 2 hours after the first three treatments. Secondary outcomes included, liver and kidney function tests and histopathological examination at baseline and at the end of the fourth cycle.

1.3 Histology

Skin biopsy specimens at baseline were obtained at perilesional sites approximately 1 mm away from a lesion, from which 5 mm punch biopsies were obtained. Biopsies after 4 cycles were obtained adjacent to the first biopsy sites and processed in an identical fashion.

2. RESULTS

2.1 Table S1. Baseline characteristics.

Pat No./sex/age	RDEB subtype	COL7A1 mutations	Protein change	Serum IgE [†]	Skin IgE [‡]	Extracutaneous clinical feature
1/14y/M	Pruriginosa	c.8627G>T c.7598delT	p.C2876F p.G2533fs	11.5	4	Nail dystrophy, occasional oral and corneal erosions.
2/7y/F	Intermediate	c.712delC c.846+2T>C	p.L238fs splice site	1.4	7	Nail loss, frequent oral erosions, persistent dysphagia, contractures and webbing of fingers, mild malnutrition.
3/26y/F	Severe	c.2722C>T c.3723+5G>A	p.Q908X splice site	772 0	24	Nail loss, frequent oral erosions, severe dysphagia, severe malnutrition, pseudosyndactyly, alopecia.
4/7y/F	Severe	c.3624_3634del c.7106-2A>G	p.S1209fs splice site	193	16. 5	Nail loss, occasional hoarseness, pseudosyndactyly, severe dysphagia, mild malnutrition.
5/37y/F	Severe	c.7234C>T c.846+2T>C	p.R2412X splice site	78.9	17	Nail loss, frequent hoarseness, frequent oral and corneal erosions, microstomia, alopecia, pseudosyndactyly, severe dysphagia.
6/32y/F	Severe	c.3625_3635del c.6187C>T	p.S1209fs p.R2063W	131	15	Nail loss, pseudosyndactyly, severe dysphagia, alopecia, moderate malnutrition.
7/35y/F	Intermediate	c.130G>A c.6836C>A	p.D44N p.S2279X	374	15	Nail loss, frequent oral erosions, difficulty in swallow, keratitis, contractures and webbing of fingers, moderate malnutrition.
8/35y/M	Pruriginosa	c.7265G>A c.7485G>A	p.G2422E splice site	1050	25	Nail dystrophy, occasional oral erosions, occasional dysphagia.
9/43y/M	Intermediate	c.7549G>A c.4089delT	p.G2517S p.L1363f	842	20	Microstomia, difficulty in swallow, contractures and webbing of fingers, nail loss, moderate malnutrition.

s						
10/16y/ M	Severe	c.5942delA c.8569G>T	p.K1981 fs p.G2857 X	4530	23	Nail loss, mild dysphagia, contractures and webbing of fingers, nail dystrophy, moderate malnutrition.
11/9y/ M	Severe	c.3625_3635 del c.3625_3635 del	p.S1209f s p.S1209f s	1380	56 0	Nail loss, severe dysphagia, severe malnutrition, keratitis, pseudosyndactyly.

y, years. M, male. F, female. RDEB; Recessive dystrophic epidermolysis bullosa.

†Serum IgE normal range, 0-100 IU/ml. ‡Calculate the absolute number of positive dermal IgE cells in each microscope field by randomly selecting 5 fields under the 200x field of view and calculating the average value. The dermal IgE staining of 3 normal controls was negative.

2.2 Table S2. Omalizumab treatment of RDEB patients

Pat.no	Regimen	Response
1	300 mg SC q4 wk for 6 mo.	After OMZ administration, relief of new blister formation and pruritus, prurigo flattened.
2	150 mg SC q4 wk for 6 mo.	Mild relief of new blister formation and pruritus and enhanced wound healing upon anti-IgE therapy according to patient's reports; 3 % reduction in BEBS score.
3	300 mg SC q4 wk for 6 mo; Mupirocin ointment.	24 hours after OMZ therapy, relief of pruritus; relief of erythema and blister after 1wk; During the clinical trial her BSA declined from 73.5 to 50. Partial healing of chronic wounds;
4	150 mg SC q4 wk for 2 mo; q6 wk for 1 mo; q4 wk for 3 mo.	1 mo after OMZ therapy, clinical improvement was observed; D/c'ed because of finger surgery. Relapse with increased erythema area and new blister formation. OMZ restarted and titrated to effect.
5	150 mg SC q4 wk for 6 mo	Decrease in area of erythema and pruritus and enhanced chronic wound healing within the first mo. Decreased 8.5 in BSA score.

6	300 mg SC q4 wk for 6 mo	Decreased 5.5 in BSA score and blister formation and pruritus, enhanced wound healing.
7	300 mg SC q4 wk for 6 mo	Decrease in area of erythema and pruritus and enhanced wound healing especially for chronic wound healing. 9.5 reduction of BSA score.
8	300 mg SC q4 wk for 4 mo	Progressive improvement with flattening of plaques and with redness, scales, crusts and lichenification mainly over elbows, knees and shins.
9	300 mg SC q4 wk for 3 mo	1 mo after OMZ therapy, slightly decrease of erythema and new blister formation. D/c'ed because of poor response to OMZ after 3 cycles.
10	150 mg SC q4 wk for 5 mo	Decreased 12.5 of BSA score and pruritus and enhanced walking ability after OMZ therapy.
11	150 mg SC q4 wk for 5 mo	Enhanced wound healing and walking ability, decreased 12.5 of BSA score and pruritus improved after OMZ therapy.

OMZ, Omalizumab; q, every; SC, subcutaneous injection. BEBS, Birmingham EB Severity; BSA, affected body surface area (max score=100). D/c'ed, discontinued.

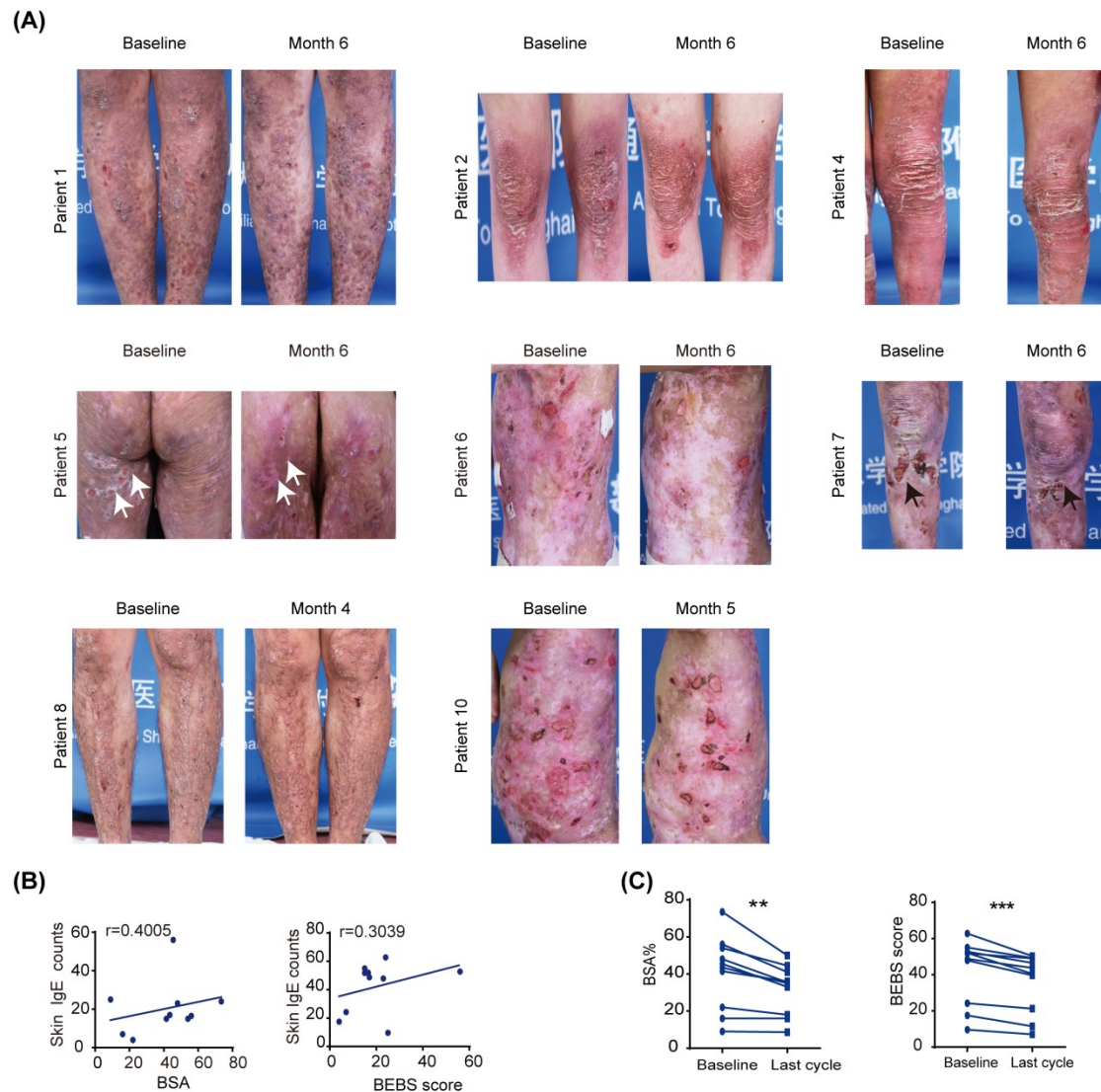
2.3 Table S3. Clinical assessment before and after anti-IgE treatment in the 11 study patients

Subject No.		Pat.1	Pat.2	Pat.3	Pat.4	Pat. 5	Pat.6	Pat.7	Pat.8	Pat.9	Pat.10	Pat.11
BEBS	Baseline	17.5	24.25	62.8	52	48.8	51.75	55	9.63	34.8	47.88	52.75
	After ^{&}	11.5	21.25	50.3	40.5	43.8	49	49.25	7	-	39.63	46.5
BSA	Baseline	22	16	73.5	56	43.5	41.5	54	9	21.5	48	45.5
	After	18	16	50	41	35	36	44.5	8.63	-	35.5	33
VAS	Baseline	7	7	10	9	10	9	9	7	6	9	10
	After	4	5	4	4	5	5	6	5	-	5	4.5
DLQI	Baseline	14	21	30	23	23	24	22	13	18	24	28
	After	12	16	24	18	14	20	17	10	-	18	18

After[&], at the end of last cycle. BEBS score, Birmingham EB Severity score. BSA affected body surface area (max score=100), Area of damaged skin, including erosions, blisters, scabs, erythema, atrophic scars not hyperpigmentation or

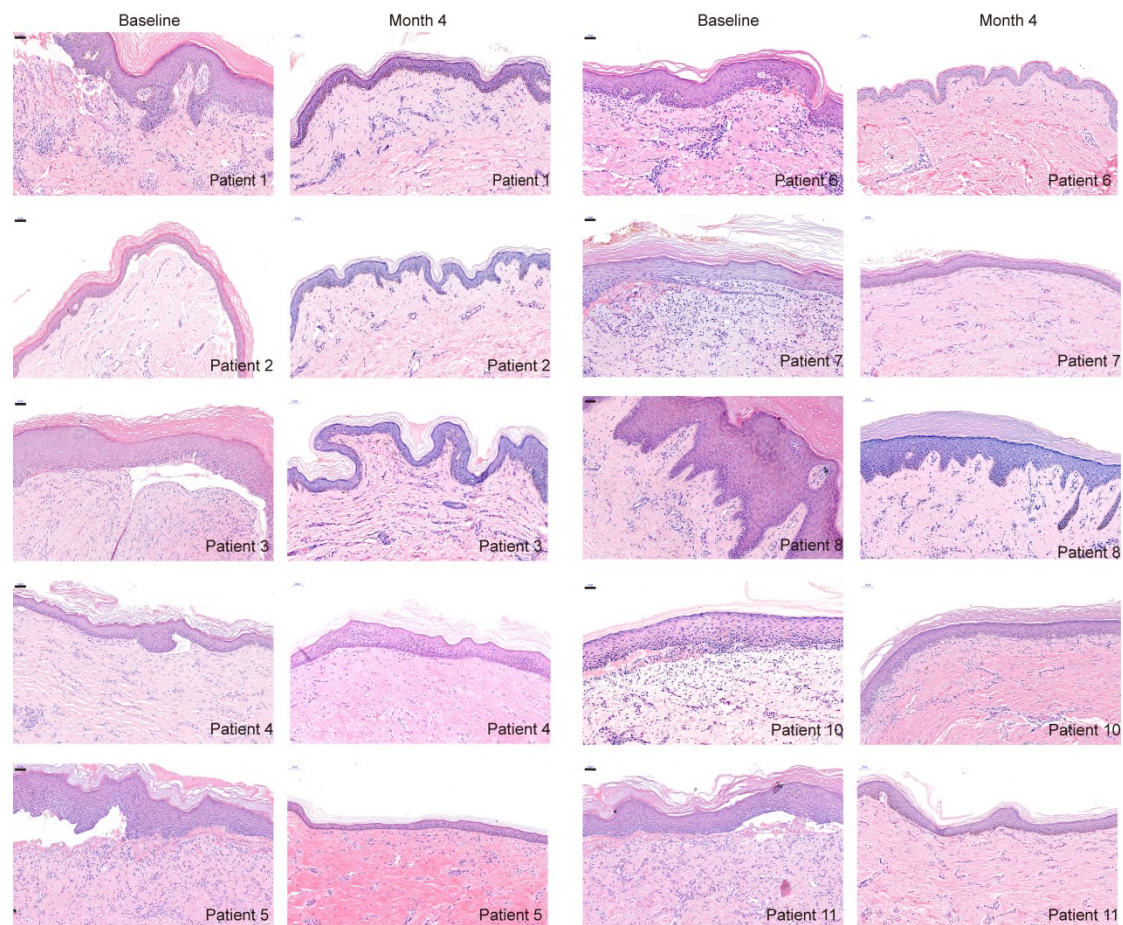
depigmentation. VAS pruritus score, Visual Analogue Scale score in pruritus. DLQI score, Dermatology Life Quality Index score. For the DLQI, each response is scored from 0 to 3, with a maximum score of 30, and higher scores indicate greater impairment of the patient's quality of life.

3. FIGURE

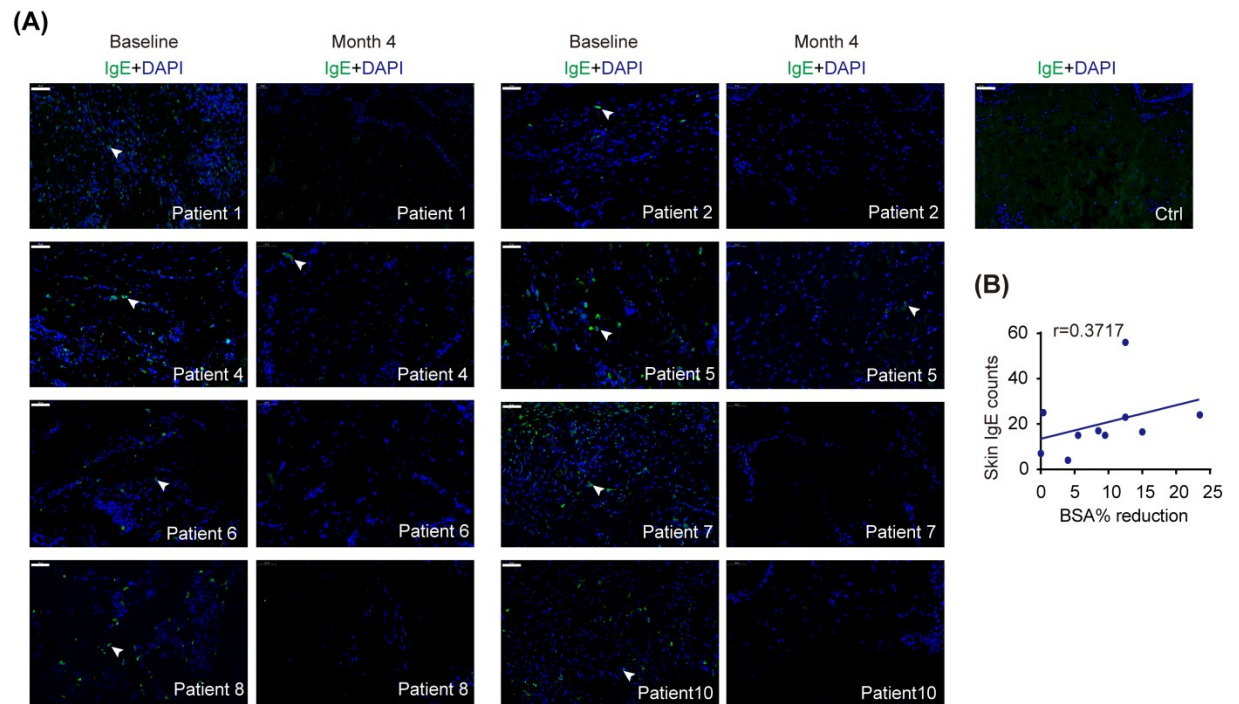


Supplementary Figure 1. Clinical findings of patients with RDEB treated with Omalizumab. (A) Patients evaluation at baseline and at the end of last cycle, which revealed decreased new blister formation, enhanced wound healing, and large resolution of inflammatory plaques, leaving post-inflammatory hypo- and hyperpigmentation. Pruriginosa RDEB 1 and 8 exhibited with flattening of plaques, reduced erythema, scales, crusts and lichenification over the extremities. Patient 2 also exhibited improvement of wound healing and decreased new blister formation, though no obviously changes in affected area. Patient 4 and 10 inflammatory erythematous plaques have significantly resolved, and improvement of wound healing. Chronic wounds (black arrowhead) also exhibited significant improvement in wound healing in patient 7. (B) A generally positive correlation between disease

activity (affected body surface area, BSA and Birmingham EB Severity score, BEBS score) and skin IgE levels ($r=0.4005$, $p>0.05$ for BSA, $r=0.3039$, $p>0.05$ for BEBS score). (C) Patients evaluation at baseline and at the end of last cycle, which revealed decreased disease severity (BSA, BEBS score). $**p<0.01$, $***p<0.001$.

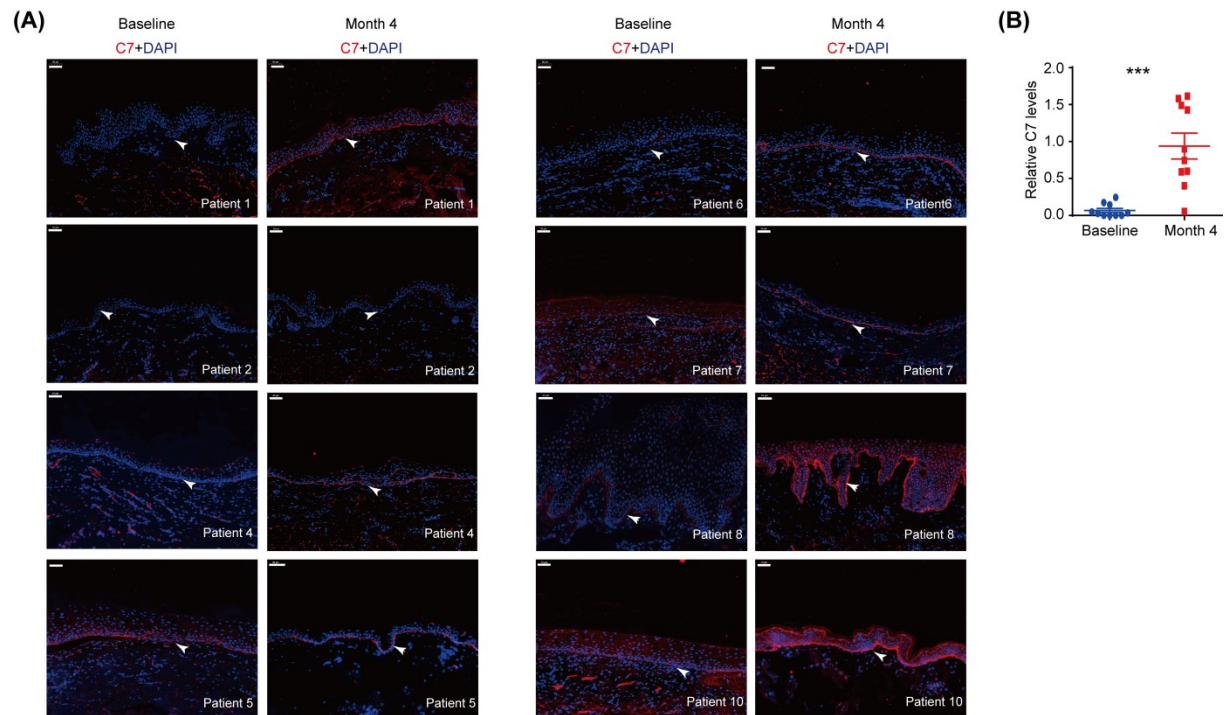


Supplementary Figure 2. H&E staining of skin biopsies derived from patients with RDEB. Histology shows that patients with RDEB with intense pruritus have prominent epidermal thickening, subepidermal blistering, vascular proliferation, subtle fibrosis, numerous eosinophils and lymphocytic infiltrates in the upper dermis at baseline. H&E staining also showed apparently reduced inflammatory cells and epidermal thickness after anti-IgE therapy. Bars, 50 μ m.



Supplementary Figure 3. Anti-IgE therapy efficiently decreased skin IgE levels.

(A) Apparently reduced IgE (green, white arrowhead) expression after anti-IgE therapy compared baseline. Biopsies obtained at month 4 showed only weak IgE expression at the derma. As negative control, we included normal control human skin (ctrl). The cell nuclei were stained with DAPI (blue). Bars, 50 μ m. **(B)** A generally parallel increase of the skin IgE levels with clinical response (BSA reduction) in the RDEB group ($r=0.3717$, $p>0.05$).



Supplementary Figure 4. Anti-IgE therapy efficiently increases type VII collagen (C7) expression at basement membrane zone. (A) Increased C7 (Red) at basement membrane zone (BMZ) (white arrowhead) were observed in biopsies at month 4. **(B)** Quantification of C7 at month 4 and baseline. Bars, 50 μ m.