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Experience of dupilumab treatment in inherited epidermolysis bullosa: A short series

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3 **Title: Experience of dupilumab treatment in inherited epidermolysis bullosa: a short**
4 **series**

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43 **Key words:** Genodermatoses, inherited epidermolysis bullosa, pruritus, dupilumab, biologics,
44 cytokines, inflammation, pediatric dermatology

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46 **Attachments:** research protocol and methods; Epidermolysis bullosa physician's global
47 assessment score

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Body of the manuscript:

53 Inherited epidermolysis bullosa (EB) are orphan diseases with untractable pruritus as a main
54 and frequent complaint (1). Dupilumab (IL-4-IL-13 blocking agent), a treatment of moderate-
55 to-severe atopic dermatitis (AD), has been used off-label in few cases of genodermatoses
56 including EB pruriginosa. We report the use of dupilumab in a series of dystrophic (DEB),
57 junctional (JEB) and simplex (EBS) EB patients with major pruritus and failure of classical
58 antipruritic treatments.

59 From March 2021 to April 2023, 11 EB patients (median age: 9[3-50] years, SR 7/4
60 F/M) received dupilumab for pruritus. Molecular diagnosis confirmed recessive DEB (RDEB,
61 n =7: 6 severe, 1 intermediate), dominant DEB (DDEB, n = 2), *KRT14* mottled pigmentation
62 EBS (n = 1) and integrin $\alpha6\beta4$ JEB (n= 1) (table 1, 2s). Previous ineffective antipruritic
63 treatments were topical corticosteroids and oral anti-histaminics for all patients, and doxepin,
64 aprepitant, gabapentin, clonazepam, apremilast, dapsone, cyclosporin and cannabidiol for
65 some patients (table 1). Dupilumab was administrated according to AD treatment doses.

66 After 6 months of dupilumab administration, median NRS (numerical rating scale of
67 pruritus) scores (8 [7.00-10.00] then 3 [0.00-8.00] after treatment, $p<0.05$) and median
68 erythema scores (3 [1-3] then 1 [0-2] after treatment, $p<0.05$) were significantly lower (fig.1,
69 table 1). Median BSA (body surface area) and PGA (physician's global assessment) scores
70 remained not significantly lower (25% [2-28] then 10% [7-80], $p=0,457$ after treatment and
71 18 [3-23] then 12 [1-22], $p=0,184$ after treatment respectively). Other antipruritic treatments
72 were stopped for all patients. Median of follow-up under dupilumab was 16 [6-25] months.
73 Plasma levels of 40 cytokines and chemokines implicated on Type 1, Type 2, and Type 17
74 inflammation were measured in 6 patients before and after dupilumab treatment, showing a
75 tendency to decreased IL-2, IL-4, IL-6, IL-17A, IL-17F and IL-22 levels in RDEB patients,
76 and TSLP and IL-33 levels in 4 out of 6 EB patients (Fig.2 supplementary data). Treatment
77 was well-tolerated in all patients.

78 In previous reports, dupilumab has been tried with efficacy on pruritus and wound
79 healing in DEB pruriginosa, characterized by a skin mast cell infiltration, elevated IgE and
80 increased Th2 subset, supporting the role of Th2-mediated immunity in this EB subtype (2).
81 Although different pathomechanisms are involved in EB subtypes, the efficiency of Th2
82 pathway blockade and the frequency of increased serum total IgE levels in these
83 genodermatoses may indicate a shared Th2 signature, with a chronic barrier disruption leading

84 to sensitizations and inflammation. A few studies have highlighted cytokine imbalances in EB
85 with increased levels of interleukin (IL)-1 β , IL-2, IL-6, IL-10, IL-12, tumor necrosis factor- β ,
86 and interferon- γ , correlated with disease severity (3,4). Despite heterogeneous results, which
87 can possibly be related to the clinical and molecular diversity of the patients in this series, it is
88 noteworthy that several IL, TSLP and IL-33 levels decreased, as observed in AD (5).

89 To conclude, in this short series, dupilumab was an effective treatment for pruritus and
90 erythema in different orphan itchy EB including severe RDEB, and not only in DEB
91 pruriginosa, reducing scratching and the secondary skin involvement, with a rapid and durable
92 response.

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95 References:

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Table 1:

Follow-up (months)	<u>13</u>	<u>21</u>	<u>16</u>	<u>22</u>	<u>6</u>	<u>6</u>	<u>16</u>	<u>25</u>	<u>15</u>	<u>20</u>
Eo after (IgE/I)	<u>0.07</u>	<u>0.18</u>	<u>0.11</u>	<u>0.17</u>	<u>0.14</u>	<u>0.15</u>	<u>0.20</u>	<u>0.0</u>		<u>0.05</u>
Eo before (IgE/I)	<u>0.27</u>	<u>0.3</u>	<u>0.4</u>	<u>0.23</u>	<u>0.19</u>	<u>0.06</u>	<u>0.07</u>	<u>0.1</u>	<u>1.36</u>	<u>0.17</u>
Total IgE after (kU/L)	<u>2.8</u>			<u>842</u>	<u>10.4</u>		<u>392</u>	<u>44.4</u>		<u>223</u>
Total IgE before (kU/L)					<u>15.4</u>	<u>22.7</u>	<u>669</u>	<u>65.2</u>		<u>965</u>
Erythema after	<u>1</u>	<u>1</u>	<u>2</u>	<u>2</u>	<u>1</u>	<u>2</u>	<u>1</u>	<u>1</u>	<u>0</u>	<u>1</u>
Erythema before	<u>3</u>	<u>2</u>	<u>3</u>	<u>3</u>	<u>3</u>	<u>2</u>	<u>2</u>	<u>2</u>	<u>1</u>	<u>3</u>
BSA after	<u>10</u>	<u>12</u>	<u>7</u>	<u>18</u>	<u>20</u>	<u>28</u>	<u>6</u>	<u>3</u>	<u>6</u>	<u>2</u>
Previous BSA	<u>15</u>	<u>12</u>	<u>25</u>	<u>40</u>	<u>38</u>	<u>30</u>	<u>9</u>	<u>7</u>	<u>14</u>	<u>30</u>
PGA after	<u>12</u>	<u>18</u>	<u>12</u>	<u>13</u>	<u>15</u>	<u>22</u>	<u>4</u>	<u>2</u>	<u>2</u>	<u>1</u>
Previous PGA	<u>18</u>	<u>18</u>	<u>19</u>	<u>19</u>	<u>20</u>	<u>23</u>	<u>10</u>	<u>3</u>	<u>4</u>	<u>11</u>
NRS after	<u>2</u>	<u>8</u>	<u>2</u>	<u>4</u>	<u>3</u>	<u>4</u>	<u>3</u>	<u>3</u>	<u>2</u>	<u>0</u>
Previous NRS	<u>8</u>	<u>8</u>	<u>10</u>	<u>7</u>	<u>7</u>	<u>7</u>	<u>10</u>	<u>8</u>	<u>8</u>	<u>9</u>
Previous treatments	Doxepin, anti- histaminic	clonazepam, doxepin, acaricidant, Clonazep	clonazepam, doxepin, aprepitant,	Doxepin, aprepitant, betamethaso	clonazepam, amitriptyline, Anti-	Doxepin, Anti- Cannabidiol,	histaminic, gabapentin, diazepam	betamethaso anti- pruriginos	betamethaso anti- pruriginos	betamethaso anti- pruriginos
EB subtype	RDEB severe	RDEB severe	RDEB severe	RDEB severe	RDEB severe	RDEB severe	RDEB intermedi ate	DDER pruriginos	DDER pruriginos	JEB integrin alpha4
Age (years)	<u>7</u>	<u>7</u>	<u>3</u>	<u>4</u>	<u>12</u>	<u>18</u>	<u>9</u>	<u>21</u>	<u>9</u>	<u>50</u>
Patients, Sex	<u>1, F</u>	<u>2, F</u>	<u>3, F</u>	<u>4, F</u>	<u>5, F</u>	<u>6, F</u>	<u>7, M</u>	<u>8, M</u>	<u>9, M</u>	<u>10, M</u>

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172 **Figure legend**

173 **Figure 1:** Photographs before and under dupilumab treatment

174 Photographs: Examples of marked decrease of erythema and wounds in different subtypes of
175 EB under dupilumab treatment: A, B: Patient 1 (RDEB) before (A) and after (B) 9 months of
176 dupilumab; C, D: patient 4 (RDEB) before (C) and after (D) 15 months of dupilumab: marked
177 decrease of erythema, wounds and milia; E, F, G: patient 7 (RDEB) before (E) and after 7
178 months (F) and 13 months (G) of dupilumab; H, I, J, K: patient 10 (JEB) before (H, J) and
179 after (I, K) 14 months of dupilumab.

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182 **Figure 1S (supplementary data):** Heat map analysis of plasmatic cytokines

183 Heat map analysis of plasmatic cytokines ratios calculated as: levels measured after
184 dupilumab treatment/levels measured before dupilumab treatment. Decreased cytokine ratios
185 are represented in blue, and increased cytokine ratios in red. The rows and columns are
186 ordered based on the results of the agglomerative hierarchical clustering, with dendrograms
187 for the patients (7, 3, 10, 4, 1 and 6) and cytokines shown on the vertical and horizontal axes
188 respectively. Heat map was created using Qlucore Omics Explorer software 3.7.

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190 **Tables legend:**

191 **Table 1:** Baseline patients' characteristics and scores, evolution of disease severity scores
192 under dupilumab treatment and baseline and follow-up IgE and blood eosinophil counts (Eo)
193 levels before and after dupilumab treatment. F: female; M: male; RDEB: recessive dystrophic
194 epidermolysis bullosa; DDEB: dominant dystrophic epidermolysis bullosa; JEB: junctional
195 epidermolysis bullosa; EBS: epidermolysis bullosa simplex; NRS: numerical rating scale of
196 pruritus; PGA: EB physician's global assessment; BSA: body surface area. NRS ranges from
197 0 to 10. PGA scores <4.5, between 4.5 and 13 and >13 respectively correspond to mild,
198 moderate and severe disease. Erythema score ranges from 0 (no erythema) to 3 (marked
199 erythema). Eosinophil count ranges from 0 to 0.3×10^9 /L. IgE normal values: <114 kU/L.

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201 **Table 2S (supplementary data):** Molecular diagnosis

