SHORT PAPER

IL-6/IL-10 Ratio as A Prognostic and Predictive Marker of the Severity of Inherited Epidermolysis Bullosa

Marilina Tampoia[1], Letizia Abbracciavento[1*], Marella Morrone[1], Ruggiero Fumarulo[1]

[1]Clinical Pathology Laboratory, Polyclinic of Bari, Department of Biomedical Sciences and Human Oncology, University of Bari, Piazza Giulio Cesare 11, 70124 Bari, Italy

ABSTRACT

Background: Recent studies have shown that cytokines have an important role in the pathogenesis of inflammatory diseases and can be used as prognostic markers. **Objective:** To evaluate the IL-6/IL-10 ratio in patients with Inherited Epidermolysis Bullosa (EB) as a prognostic marker. **Methods:** Serum levels of IL-6 and IL-10 were measured in 13 patients with recessive dystrophic EB (RDEB) as well as 10 with EB Simplex (EBS), and in 18 healthy subjects. Receiver Operating Characteristics (ROC) analyses were used to assess the diagnostic accuracy of the IL-6/IL-10 ratio for detecting severe form of EB. **Results:** The IL-6/IL-10 ratio was statistically higher in RDEB patients than in EBS patients and healthy subjects. The IL-6/IL-10 ratio significantly correlated with BEBS score. **Conclusion:** Our findings suggest that IL-6/IL-10 ratio >5.6 has a good diagnostic accuracy to identify patients with the highest severity of disease.

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Keywords: Anti-Skin Autoantibodies, Birmingham Epidermolysis Bullosa Severity Score, Cytokines, IL-6/IL-10 Ratio, Inherited Epidermolysis Bullosa

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*Corresponding author: Dr. Letizia Abbracciavento, Clinical Pathology Laboratory, Polyclinic of Bari, Department of Biomedical Sciences and Human Oncology, University of Bari, Piazza Giulio Cesare 11, 70124 Bari, Italy, e-mail: letizia1282@libero.it

INTRODUCTION

Inherited epidermolysis bullosa (EB) is a group of different, rare and genetic diseases, comprising diverse blistering skin disorders with a monogenic basis and either an autosomal dominant or a recessive inheritance (1). At first, the EB types were classified into three major groups on the basis of the level of blisters cleavage. EB simplex (EBS characterized by fragility and blistering confined to the epidermis), junctional EB (JEB associated with blisters developed within the lamina of the skin basement membrane area) and dystrophic EB (DEB with blister occurring within the uppermost regions of the dermis). A fourth type, defined as Kindler syndrome, collectively includes all cases correlated to specific clinical characteristics (mainly photosensitivity), and blister development in multiple levels in the skin basement membrane zone (2). However, various clinical subtypes have been identified and described for each group, recently a new approach to classification (known as "onion skinning") has been established (2). This approach distinguishes EB taking into consideration the account type, the mode of inheritance, phenotype, immunofluorescence antigen-mapping findings, and mutations. EB results from mutations that specifically encode for structural skin proteins; however, genotype–phenotype correlations were not always shown, and subjects with the same genetic mutations were often found to have very different clinical features. These remarks led researchers to consider the possibility that other factor could be involved in the origin of EB besides all the alterations caused by genetic mutations.

First of all, specific anti-skin autoantibodies were found in several patients with EB, and their serum levels correlated to the severity of disease (3,4). Moreover, a cytokine imbalance was shown in EB, suggesting that EB represents a systemic inflammatory disorder classified into distinct types which are largely influence by a number of factors determining their development and severity (4). Furthermore, the concentration of anti-skin autoantibodies and cytokines has been observed to have a role in disease severity and could constitute a useful tool for establishing EB prognosis (4,5).

The amount of the inflammatory response has been found of significant importance in conditioning autoimmune activity and, as a consequence, for the severity of the disease. In previous studies, some authors have demonstrated that the level of most of the pro-inflammatory cytokines (for instance, IL-1β, IL-2, IL-6, TNF-β and IFN-γ) was considerably higher in patients with EB than in healthy subjects, in turn, these levels were higher in RDEB patients than in other EB patients. In addition to this, IL-6 serum levels were noted to be significantly correlated with EB extension, anti-skin specific autoantibody levels and severity (5).

Increased levels of many cytokines, such as IL-1 and IL-6, which are not considerably different from those found in these studies, have been detected in both sera and blister fluid of patients and experimental animals with acquired EB. In most cases, disease activity was proved to be linked to cytokine levels, confirming the pathogenic role of these proteins in the development of skin lesions (6). In contrast with the data that were published years ago by Chopra *et al.* some authors have also shown an increase in IL-2 serum levels in all of the patients with EB (4,5,7,8). Regarding anti-inflammatory cytokines, IL-10 is the most important cytokine with anti-inflammatory and immunosuppressive properties that has multiple immune regulatory functions, located in the central link of immune regulation (9). The anti-inflammatory effects of IL-10 have been shown in models of autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, Crohn's disease, multiple sclerosis

and psoriasis. However, the exact mechanisms of IL-10 in auto-immune diseases is still to be clarified (9). Futhermore, a dysregulation of IL-19 and IL-20 seems to be involved in the pathophysiology of inflammatory diseases, such as SLE, rheumatoid arthritis and psoriasis (10,11). Additionally, serum IL-20 levels are reduced in patients with scleroderma spectrum disorders compared with those in normal subjects (12). In EB patients serum levels of IL-10 were investigated and they showed to be significantly higher in patients with a lower BEBS score than in those with a higher score (5).
The cytokines IL-6 and IL-10 are released by cells of the adaptive and innate arms of the immune system and they appear to play key roles in genetically diverse autoimmune diseases (13). Whereas previous researches focused on the production of autoantibodies and their role in immune-mediated pathogenesis of these diseases, more recent attention has been focused on the contribution of cytokines, including IL-6 and IL-10 (9,14,15). Our study was planned to evaluate the diagnostic accuracy of the IL-6/IL-10 ratio in predicting the severity of disease in patients with EB.

MATERIALS AND METHODS

Patients. This is a retrospective study performed between January 2010 and December 2012 in 23 consecutive outpatients with inherited forms of EB, regularly followed by the Dermatological Department of the University Hospital in Bari. All patients examined had typical clinical characteristics of EB with a variable phenotype as well as immuno-fluorescence mapping and transmission electron microscopy findings consistent with EB. According to skin cleavage, patients were divided into two groups: 13 patients with recessive dystrophic EB (RDEB), mean age 21.5 years, range 2-50, 4 male and 12 female; 10 patients with EB simplex (EBS), mean age 17.6 years, range 4-56, 3 male and 7 female. In all patients, the Birmingham Epidermolysis Bullosa Severity (BEBS) score was used to assess the severity of the disease. It assesses the area of damaged skin, the involvement of nails, mouth, eyes, larynx and esophagus, the scarring of hands, skin cancer, chronic wounds present for at least six months, alopecia and nutritional compromise. Area is allocated 50 points and the 10 other items 5 points each, providing a maximum score of 100 (16). The BEBS score was performed by a dermatology specialist at blood sample collection.
A BEBS score over the second tertile (corresponding to 56 points) was considered severe EB. Sera from 18 healthy subjects (mean age 47.8 years, range 36-65, 8 males and 10 females) were used as control group. All sera were stored at -20°C until assayed. All patients remained anonymous and gave informed consent to be included in the study. The study was conducted according to the ethical standards as formulated in the Helsinki Declaration.
Cytokine Assay. Serum levels of IL-6 and IL-10 were measured in all samples using a commercially available enzyme-linked immunosorbent assay (ELISA) (Bender MedSystems GmbH, Vienna, Austria) with a fully automated system (DSX, Technogenetics, Lodi, Italy).
Statistical Analysis. Data are reported as median and range (min-max). The non-parametric Mann-Whitney Unpaired U-test and Kruskall-Wallis test were performed for comparison of cytokine levels between two and more groups, respectively. Receiver Operating Characteristics (ROC) analyses were carried out to estimate the diagnostic accuracy of the IL-6/IL-10 ratio for detecting BEBS score ≥56 points. The optimal cut-

off for this value of the BEBS score was the corresponding value of the IL-6/IL-10 ratio that gave a percent sensitivity and specificity closest to the point of a perfect marker (sensitivity and specificity of 100%). Clinical utility of IL-6/IL-10 ratio was evaluated by likelihood ratios (LR). Per convention, tests yielding positive LR (pLR) >10 or negative LR (nLR) <0.1 are considered clinically useful. Correlation analyses were run using the Spearman rank test. A P-value below 0.05 was considered statistically significant for all tests. MedCalc software (Mariakerke, Belgium) was used for ROC curve analysis and all statistical analyses were performed using GraphPad Prism Version 5.

RESULTS and DISCUSSION

Table 1 shows demographic, clinical and serological features of patients with EB. In patients with RDEB, the median concentrations of IL-6 and IL-10 were 15.10 pg/ml (range 2.50–36.60) and 1.60 pg/ml (range 0.83–4.40), respectively; in patients with EBS, they were 2.50 pg/ml (range 1.20–5.20) and 3.90 pg/ml (range 1.00–19.80), respectively (Table 2).

The table 2 shows also the comparisons of the cytokine serum levels between the two groups of EB patients and healthy subjects. The median concentration of IL-6 was statistically higher in patients with RDEB compared to patients with EBS and healthy subjects (P=0.0001), while the median concentration of IL-10 was statistically lower in patients with RDEB than in EBS patients and healthy subjects (P=0.002).

Regarding the IL-6/IL-10 ratio, it resulted statistically higher in RDEB patients than EBS patients (P=0.0002) and healthy subjects (P=0.0001), no significant difference was observed between EBS patients and healthy subjects (P=0.712) (Table 2).

In all patients, serum levels of IL-6 were found to be correlated with anti-BP180 (P=0.002, Spearman r=0.60), anti-BP230 (P<0.0001, Spearman r=0.75) and anti-type VII collagen autoantibodies (P<0.0001, Spearman r=0.80).

In addition, serum levels of IL-6 showed a significant correlation with “Birmingham Epidermolysis Bullosa Severity” (BEBS) score (P<0.0001, Spearman r=0.88), while serum levels of IL-10 were inversely correlated with the BEBS score (P=0.05, Spearman r=-0.41).

Finally, in patients with EB, the IL-6/IL-10 ratio resulted statistically higher than in healthy subjects and significantly correlated with both anti-skin autoantibodies levels (Figure 1a, 1b, 1c) and BEBS score (Figure 2).

The area under the curve (AUC) for criterion variable, IL-6/IL-10 ratio, and for condition variable BEBS score ≥56 points, resulted 0.98 (95% CI, 0.82–1.0). The ROC analysis showed that, at a cut-off value >5.6, the IL-6/IL-10 ratio had a sensitivity of 87.5% (95% CI, 47.4–97.9) and an absolute specificity (95% CI, 78–100), a positive pLR of ∞ and a nLR of 0.13. Positive and negative predictive value were 100% and 93.8%, respectively (Figure 3 and Table 3).

Table 1. Demographic, clinical and serological features of patients with recessive dystrophic epidermolysis bullosa (RDEB) and with epidermolysis bullosa simplex (EBS).

				Anti-skin autoantibodies			
n. pt	**Sex**	**Age years**	**Type EB**	**Anti-BP180***	**Anti-BP230***	**Anti-Coll VII***	**BEBS score**
1	M	12	RDEB	36	26.7	20.1	67
2	F	19	RDEB	37.5	37.8	14.9	63
3	F	45	RDEB	6.8	3.3	1.1	39
4	F	29	RDEB	34.5	18.2	5.9	78
5	M	9	RDEB	16.8	13.9	5.8	34
6	F	28	RDEB	1.8	2.9	2.8	31
7	M	5	RDEB	14.9	8.5	2.8	40
8	F	2	RDEB	56	27.1	12.4	64
9	F	4	RDEB	23.5	20.3	8.5	56
10	M	34	RDEB	93	53.4	24.5	79
11	F	15	RDEB	77.8	69.8	44.4	60
12	F	50	RDEB	2.8	3.3	1.2	11
13	F	27	RDEB	1.4	110	53.5	69
14	F	6	EBS	14.7	13.8	2.1	2
15	M	34	EBS	2.9	3.2	1.3	2
16	F	10	EBS	3.5	3.5	1.2	2
17	F	7	EBS	13.4	3.5	1.4	2
18	F	7	EBS	10.1	6.3	1.9	2
19	F	56	EBS	15.1	13.1	10.8	36
20	F	17	EBS	4.5	8.9	2.1	2
21	M	13	EBS	15.1	8.4	2.2	2
22	M	22	EBS	2.7	4.1	1.2	2
23	F	4	EBS	1	1.2	1.4	2

* Cut-off value: anti-BP180 autoantibodies, cut-off 8.5 U/mL; anti-BP230 autoantibodies, cut-off 8.0 U/mL; anti-type VII collagen autoantibodies, cut-off 5.0 U/mL. The bold and italic numbers indicate values above the cut-off.

Table 2. Comparison between cytokine levels and ratio in different types of EB patients and healthy subjects.

Cytokine (pg/mL)	RDEB patients (n.13) Median value (*range min-max*)	EBS patients (n. 10) Median value (*range min-max)*	Healthy subjects (n. 18) Median value (*range min-max*)	P value† RDEB vs. EBS	P value† RDEB vs. HS	P value† EBS vs. HS	P value‡ RDEB vs. EBS vs. HS
IL-6	15.10 (2.5-36.6)	2.50 (1.2-5.2)	2.9 (2-5.4)	0.0003	0.0007	0.325	0.0001
IL-10	1.60 (0.83-4.4)	3.90 (1.0-19.8)	4.5 (2.7-7.4)	0.0300	0.0003	0.904	0.002
IL-6/IL-10 ratio	11.3 (1.1-21.5)	0.45 (0.2-2.9)	0.6 (0.3-1.5)	0.0002	0.0001	0.712	<0.0001

Median and range (min-max) of cytokine levels in patients with recessive dystrophic epidermolysis bullosa (RDEB), with epidermolysis bullosa simplex (EBS) and healthy subjects (HS). † Mann-Whitney Unpaired U-test, ‡ Kruskall Wallis test.

The area under the curve (AUC) for criterion variable, IL-6/IL-10 ratio and for condition variable, EB types, resulted 0.97 (95% CI, 0.80–0.99). The ROC analysis showed that, at a cut-off value >2.9, the IL-6/IL-10 ratio had a sensitivity of 92.3% (95% CI, 63.9–98.7) and an absolute specificity (95% CI, 69–100), a positive pLR of ∞ and a nLR of 0.08. Positive and negative predictive value were 100% and 90.9%, respectively (Figure 3 and Table 3).

Table 3. Diagnostic sensitivity, specificity and likelihood ratios (pLR, nLR) in patients with EB.

Criterion variable	Condition variable	
IL-6/IL-10 ratio	**BEBS score**	**EB type**
Cut off value (U/mL)	> 5.6	> 2.9
AUC	0.98 (95% CI, 0.82 – 1.0)	0.97 (95% CI, 0.80 – 0.99)
Sensitivity (%)	87.5% (95% CI, 47.4 – 97.9)	92.3% (95% CI, 63.9 – 98.7)
Specificity (%)	100% (95% CI, 78 – 100)	100% (95% CI, 69 – 100)
Accuracy§	87.5	92.3
pLR	∞	∞
nLR	0.13	0.08
Positive predictive value	100%	100%
Negative predicitve value	93.8%	90.9%

§Accuracy = (Sensitivity × Specificity)/100

Autoimmunity and inflammatory responses are often activated in EB with a possible implication in conditioning clinical manifestations of the disease.

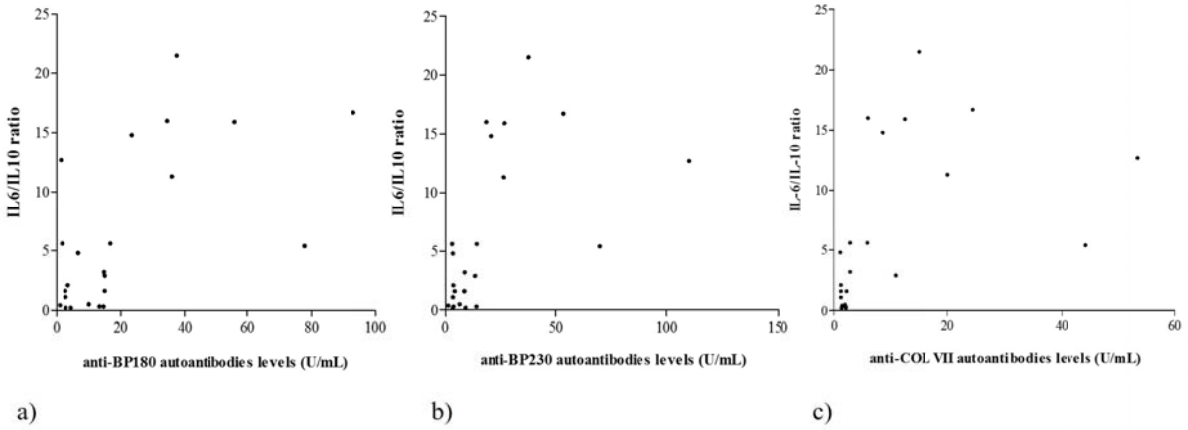

Figure 1. Correlation between anti-skin autoantibodies and IL-6/IL-10 ratio. a) Correlation between anti-BP180 autoantibodies levels and IL-6/IL-10 ratio. Spearman rank test, P=0.003, r=0.59. **b)** Correlation between anti-BP230 autoantibodies levels and IL-6/IL-10 ratio. Spearman rank test, P=0.0005, r=0.67. **c)** Correlation between anti-type VII collagen autoantibodies levels and IL-6/IL-10 ratio. Spearman rank test, P=0.0001, r=0.71.

Serum levels of specific anti-skin autoantibodies were found significantly higher in patients with EB than in healthy subjects, and the increase was strictly associated to the severity of the disease and to the inflammatory process (mainly evidenced by the IL-6 increase) (5). Indeed, cytokines represent soluble mediators aiding in cell-to-cell communication in immune responses, and IL-6 is a prototypical cytokine presenting redundant and pleiotropic activity.

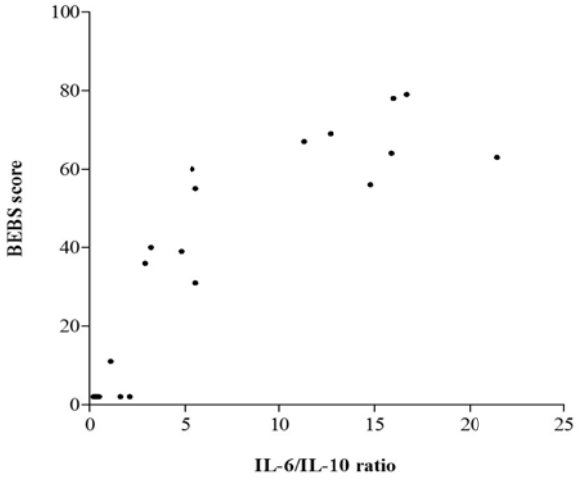

Figure 2. Correlation between IL-6/IL-10 ratio and BEBS score. Correlation of IL-6/IL-10 ratio and BEBS score in patients with inherited epidermolysis bullosa. Spearman rank test, P<0.0001, r=0.90.

Considering that patients with the more severe EB phenotype commonly have a greater number of skin infections, an altered microbial variety may determine a worsening of skin inflammation and autoimmunity. When tissue injure or inflammation caused by infections or damages occurs, in response to pathogens, antigen presenting cells (APC), including B cells, release IL-6 and IL-10 in order to up- or down-regulate immune cell

activation and effector responses (17). Evidence of high levels of the pro-inflammatory cytokine IL-6 has been frequently detected during inflammatory reactions in autoimmune diseases (9,13,14,18,19). IL-6 production is promptly initiated, contributing to the host defense by the stimulation of acute-phase immune reactions and hematopoiesis. The synthesis of IL-6 is terminated when tissue homeostasis is reestablished. However, the dysregulated continual production of IL-6 has been involved in the development of several diseases, such as autoimmune and chronic inflammatory diseases and cancers (17). IL-6 has the capability of promoting autoantibody production and of causing an imbalance between Th17 and Treg (20,21). The autoantibody production in patients with EB would be induced by both IL-6 on self-reactive B cells and inhibition, which is in turn caused by IL-6 itself, on the action of regulatory T cells secreting IL-10, which is lower in these patients. Dysregulation of IL-10 leads to severe immune-pathology, in the form of immune-deficiency or autoimmunity. The contribution of IL-10 in inflammatory processes during infection and autoimmunity has been elucidated in several models of infection and autoimmunity. Reduced expression of IL-10 is associated with a number of autoimmune diseases in mice and humans, such as psoriasis, inflammatory bowel disease and rheumatoid arthritis (11).

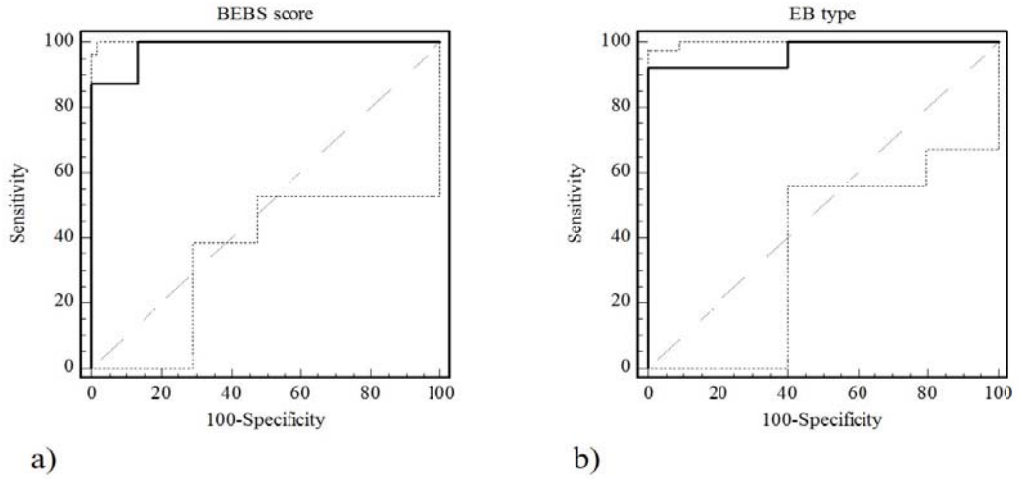

Figure 3. ROC analysis of IL-6/IL-10 ratio. a) Receiver operating characteristic (ROC) plot analysis of IL-6-IL-10 using BEBS score ≥56 point as condition variable. AUC, area under the curve, was 0.91. **b)** Receiver operating characteristic (ROC) plot analysis of IL-6/IL-10 using EB type as condition variable. AUC, area under the curve, was 0.99.

It should be clinically relevant to develop an accurate test for identifying patients with more severe EB to submit to further evaluation and treatment and our study was undertaken with the aim to evaluate the prognostic value of the IL-6/IL-10 ratio on severity disease in patients with EB. We proved that the IL-6/IL-10 ratio >5.6 has a good diagnostic accuracy to identify patients with the highest severity of disease and can induce advantages in management of the autoimmune diseases.

Nowadays, a current frontier of therapy counts on biologic drugs which are able to alter the balance between the generation of proinflammatory cytokines IL-6 and TNF-α, in

contrast to the regulatory cytokine IL-10; this has been recently demonstrated by the inhibited phosphorylation of B cells receptor by epratuzumab CD22 targeting in systemic lupus erythematous immune treatment (22). Moreover, the protective role played by IL-6 monoclonal antibodies has been reported in experimental autoimmune myocarditis, where these antibodies neutralized IL-6 and increased IL-10 expression by suppressing Th17 and Treg cells (23).

Although the pathophysiological meaning of IL-6/IL-10 balance is far from being elucidated in detail, it is possible to suppose that it plays a role in homing of inflammatory cells and therefore in the outcome of inflammation. The presence of increased IL-6/IL-10 balance can somehow modulate the cascade of inflammatory phenomenon occurring in EB. Of course, the relevance of this kind of phenomenon in vivo on damaged skin is object of speculation. It would be of interest, in this respect, a longitudinal evaluation of changes in serum IL-6 and IL-10 levels in single patient in relation with different clinical outcome and disease treatments.

In conclusion, we cannot exclude that both effects, the overproduction of autoantibodies and abnormal cytokine profile, can self-renew reciprocally. Furthermore, our results suggest a role of IL-6/IL-10 balance as a possible marker of damage in EB, in addition to its potential involvement in inflammatory process. However, further studies are needed in order to establish the role of cytokines and autoantibodies as possible clinical markers of disease and therapeutic monitoring.

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REFERENCES

1. Fine JD. Inherited epidermolysis bullosa: Past, present, and future. Ann N Y Acad Sci. 2010; 1194:213–222.
2. Fine JD. Inherited epidermolysis bullosa: Recent basic and clinical advances. Curr Opin Pediatr. 2010; 22:453–458.
3. Tampoia M, Bonamonte D, Filoni A, Garofalo L, Morgese MG, Brunetti L, et al. Prevalence of specific anti-skin autoantibodies in a cohort of patients with inherited epidermolysis bullosa. Orphanet J Rare Dis. 2013; 4:132-142.
4. Annicchiarico G, Morgese MG, Esposito S, Lopalco G, Lattarulo M, Tampoia M, et al. Proinflammatory Cytokines and Antiskin Autoantibodies in Patients with Inherited Epidermolysis Bullosa. Medicine (Baltimore). 2015; 94:e1528.
5. Esposito S, Guez S, Orenti A, Tadini G, Scuvera G, Corti L, et al. Autoimmunity and Cytokine Imbalance in Inherited Epidermolysis Bullosa. Int J Mol Sci. 2016; 24:1625-1638.
6. Ludwig RJ, Zillikens D. Pathogenesis of epidermolysis bullosa acquisita. Dermatol Clin. 2011; 29:493–501.
7. Chopra V, Tyring SK, Johnson L, Fine JD. Patients with severe forms of inherited epidermolysis bullosa exhibit decreased lymphokine and monokine production. J Clin Immunol. 1990; 10:321–329.
8. Chopra V, Tyring SK, Johnson L, Fine JD. Peripheral blood mononuclear cell subsets in patients with severe inherited forms of epidermolysis bullosa. Arch Dermatol. 1992; 128:201–209.

9. Tian G, Li JL, Wang DG, Zhou D. Targeting IL-10 in auto-immune diseases. Cell Biochem Biophys. 2014; 70:37–49.
10. Alanara T, Karstila K, Moilanen T, Silvennoinen O, Isomaki P. Expression of IL-10 family cytokines in rheumatoid arthritis: elevated levels of IL-19 in the joints. Scand J Rheumatol. 2010; 39:118-26.
11. Hofmann SR, Rösen-Wolff A, Tsokos GC, Hedrich CM. Biological properties and regulation of IL-10 related cytokines and their contribution to autoimmune disease and tissue injury. Clin Immunol. 2012; 143:116–127.
12. Kudo H, Jinnin M, Asano Y, Trojanowska M, Nakayama W, Inoue K, Honda N, et al. Decreased interleukin-20 expression in scleroderma skin contributes to cutaneous fibrosis. Arthritis Rheumatol. 2014; 66:1636-47.
13. Ireland SJ, Monson NL, Davis LS. Seeking balance: Potentiation and inhibition of multiple sclerosis autoimmune responses by IL-6 and IL-10. Cytokine. 2015; 73:236-244.
14. Davis LS, Hutcheson J, Mohan C. The role of cytokines in the pathogenesis and treatment of systemic lupus erythematosus. J Interferon Cytokine Res. 2011; 31:781–9.
15. Narazaki M, Tanaka T, Kishimoto T. The role and therapeutic targeting of IL-6 in rheumatoid arthritis. Expert Rev Clin Immunol. 2017; 13:535-551.
16. Moss C, Wong A, Davies P. The Birmingham Epidermolysis Bullosa Severity score: Development and validation. Br J Dermatol. 2009; 160:1057–1065.
17. Tanaka T, Kishimoto T. The Biology and Medical Implications of Interleukin-6. Cancer Immunol Res. 2014; 2:288–94.
18. Cénit MC, Simeón CP, Vonk MC, Callejas-Rubio JL, Espinosa G, Carreira P, et al. Influence of the IL6 gene in susceptibility to systemic sclerosis. J Rheumatol. 2012; 39:2294–2302.
19. Barr TA, Shen P, Brown S, Lampropoulou V, Roch T, Lawrie S, et al. B cell depletion therapy ameliorates autoimmune disease through ablation of IL-6-producing B cells. J Exp Med. 2012; 209:1001–1010.
20. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 cells. Annu Rev Immunol. 2009; 27:485–517.
21. Kimura A, Kishimoto T. IL-6: Regulator of Treg/Th17 balance. Eur J Immunol. 2010; 40:1830–1835.
22. Fleischer V, Sieber J, Fleischer SJ, Shock A, Heine G, Daridon C, et al. Epratuzumab inhibits the production of the proinflammatory cytokines IL-6 and TNF-α, but not the regulatory cytokine IL-10, by B cells from healthy donors and SLE patients. Arthritis Res Ther. 2015; 17:185-192.
23. He S, Han LN, Wang YT, Liu JW, Ding GL. The protective role of interleukin-6 monoclonal antibody on experimental autoimmune myocarditis and its mechanism. Zhongguo Ying Yong Sheng Li Xue Za Zhi. 2014; 30:119-123.