

RESEARCH LETTER

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Serum IL-22 binding protein as a marker for atopic dermatitis activity and response to dupilumab treatment

To the Editor,

We investigated here the interleukin-22 (IL-22)/IL-22 Binding Protein (IL-22BP) axis in Atopic Dermatitis (AD) and its modulation upon treatment with Dupilumab, and our findings support its relevance in the clinical management of severe AD.

IL-22 has been emerging as an important player in AD, and its serum levels were shown to be increased in moderate-to-severe AD.¹ IL-22 assumes major cross-talk functions between immune and epithelial cells, promoting epithelia homeostasis and skin barrier integrity.^{2,3} However, it should be tightly regulated, as IL-22 constitutes one of the cytokines which leads to local inflammation, induction of keratinocyte proliferation and inhibition of its terminal differentiation.^{3,4} Part of these effects are likely associated with the role of IL-22 in the regulation of molecules critically involved in skin barrier.⁵ Interestingly, recent data showed that targeting IL-22 may positively impact on severe AD in the subgroup of patients expressing high level of IL-22 at baseline.⁴ This preliminary study evaluating the clinical outcomes of a small cohort of moderate-to-severe AD with the anti-IL-22 antibody, Fezakinumab,⁴ further supports the relevance of the IL-22 pathway in AD, given the significant improvement of SCORAD at week 20 ($p = .049$). Another player in this axis is the IL-22BP that inhibits the IL-22 binding to its membrane bound receptor, IL-22R.^{3,6,7} IL-22BP was shown to bind IL-22 with a considerable higher affinity, up to 2000fold, than the binding of IL-22 to its receptor.⁶ We investigated here, for the first time, the possible contribution of serum IL-22BP to AD pathogenesis.

We enrolled 28 adult AD patients (Table 1). Detailed clinical characteristics, eosinophil counts and total serum IgE levels were compared with age and gender-matched groups of atopic patients, defined by positive skin prick tests to aeroallergens without cutaneous disease, and of healthy/non-atopic individuals. IL-22 and IL-22BP serum levels were quantified by ELISA (RayBiotech®, Norcross, GA). We found that the IL-22BP serum levels were inversely correlated with AD severity, as assessed by SCORAD (Figure 1A, Spearman rank correlation test). Conversely, we found a positive correlation between SCORAD and IL-22 serum levels in AD (Figure 1B, Spearman rank correlation test), in agreement with previous reports.^{1,2} Moreover, patients with severe AD, based on SCORAD >50 or EASI >21, tended to feature lower IL-22BP and significantly higher IL-22 serum levels in comparison with mild AD, as well as

with aged-matched atopic patients without cutaneous disease, and healthy individuals (Figure 1C,D, respectively; Mann-Whitney test). We then calculated serum IL-22/IL-22BP ratio, hypothesizing that it could be a better surrogate marker for free IL-22 effects.⁷ We observed that this ratio was higher in severe AD as compared with the other three groups (Figure 1E, Mann-Whitney test), namely mild AD ($p = .0001$), atopic ($p < .0001$) and healthy ($p = .0002$). The observed increase in serum IL-22 is likely related to the degree of epithelial lesion, which is more marked in severe AD. This is in agreement with previous reports showing distinct IL-22 expression in non-lesioned, perilesional and lesioned skin from psoriasis patients.⁷ In this clinical setting, a protective role for IL-22BP was also reported, and further supported by a mice model of psoriasis in which treatment with anti-IL-22BP was associated with disease worsening.⁷ In line with this observation, IL-22BP expression in the skin was found to be decreased in psoriatic patients as compared with healthy donors.⁶ Our severe AD cohort featured high eosinophil counts and total serum IgE (Table 1), in agreement with a strong T_H2 -skewing and allergic pathogenesis, which supported the starting of treatment in twelve patients with the anti-IL-4R α monoclonal antibody Dupilumab (Table 1). The therapy was effective in controlling disease activity, as attested by the marked decrease in the clinical scores DLQI, SCORAD and EASI, from baseline (T0) to 12 months (T12), after a loading dose of 600 mg, followed by 300 mg of Dupilumab every other week (Figure 1F, Wilcoxon matched-pairs signed rank test, and Table 1). Consistently, there was a positive post-treatment correlation between IL-22 and SCORAD and EASI scores (SCORAD: $r = .62$, $p = .028$; EASI: $r = .76$, $p = .0045$) and between EASI and IL-22/IL-22BP ratio ($r = .62$, $p = .03$). Importantly, we found a significant increase in IL-22BP at T12 (Figure 1G, Wilcoxon matched-pairs signed rank test, $p = .001$), in contrast to the milder decline documented in IL-22 serum levels (Figure 1H, $p = .266$), and in the ratio (Figure 1I, Wilcoxon matched-pairs signed rank test, $p = .176$). Reduction in both serum and transcription levels of IL-22 has been recently reported upon AD treatment with Dupilumab.^{8,9} Interestingly, the two patients who presented a significant unexpected increase in IL-22 from T0 to T12 featured a poor clinical response to Dupilumab. We report here for the first time an increase in serum levels of IL-22BP upon Dupilumab in severe AD. Our data support the further exploration of IL-22BP serum levels as a useful biomarker for AD pathogenesis and response to treatment, in larger

cohorts and in comparison with other relevant AD biomarkers. The mechanisms underlying this interplay between an anti-IL-4R therapy, typically targeting Th2 pathways, and the changes observed in the IL-22/IL-22BP axis remain unclear, and their investigation may provide new clues to better understand AD pathogenesis.⁶ Our data also suggest that recombinant IL-22BP or IL-22BP encoding mRNA may offer novel therapeutic options for AD, the most common chronic inflammatory skin disease.

In conclusion, our data strength the key role of IL-22/IL-22BP in AD, and provide a rationale for the use of IL-22BP to antagonize the IL-22-induced barrier dysfunction and epidermal hyperplasia. Moreover, we suggest that the ratio of serum IL-22/IL-22BP may be relevant to evaluate AD activity in clinical practice, and

Key Messages

- IL-22/IL-22BP is an important axis of immune regulation of the Atopic Dermatitis pathways
- IL-22BP modulatory role deserves being explored to optimize Atopic Dermatitis treatment
- The ratio of serum IL-22/IL-22BP may be relevant to evaluate AD activity in clinical practice

IL-22BP should be further explored as a surrogate marker of skin recovery.

TABLE 1 Epidemiological and clinical characterization of the cohorts of Atopic Dermatitis, Atopic without cutaneous disease, and healthy individuals

	Severe AD			Mild AD	Atopic ^a	Healthy ^b
	Total	Dupilumab therapy T0 T12				
Number (female)	14 (8)	12 (8)		14 (8)	14 (8)	14 (9)
Age (years)	28 [25–39.5]	32.5 [22.3–46.8]		26 [20.5–29.8]	30 [27.5–38]	28.5 [28–47.3]
Atopic/allergic diseases						
Allergic rhinitis, <i>n</i> (%)	11 (79)	9 (75)		11 (79)	13 (93)	0
Asthma, <i>n</i> (%)	10 (71)	10 (83)		5 (36)	7 (50)	0
Food allergy, <i>n</i> (%)	4 (29)	4 (33)		4 (29)	2 (14)	0
Eosinophilic esophagitis, <i>n</i> (%)	0	0		1 (7)	2 (14)	0
Eosinophils ($\times 10^9/L$)	555 [435–903]	555 [450–960]	510 [217.5–1310]	300 [88–633]	175 [80–325]	60 [40–127.5]
Total IgE (mg/dl)	9062 [1973–18,177]	11,792 [3337–19,931]	2123 [720–3542]	181 [40–881]	91 [59–200]	23 [10–44]
EASI score	24.3 [18.9–36.6]	23.1 [17.8–30.5]	3 [1.1–5.7]	0.81 [0–3]	NA	NA
EASI score (range)	9.6–55.8	9.6–51	0.5–29.2	0–3.2	NA	NA
SCORAD score	77.3 [58.4–86.2]	75.7 [58.1–89.9]	21.8 [14.6–32.9]	16.5 [0–23.1]	NA	NA
SCORAD score (range)	32.6–103	32.6–103	6.6–67.8	0–24.5	NA	NA
DLQI score	20 [16.5–23.3]	20 [15.5–22.8]	1.5 [1–4.8]	1 [0–4.3]	NA	NA
DLQI score (range)	5–29	5–27	0–12	0–21	NA	NA
Previous use of systemic therapies for AD						
Cyclosporin A, <i>n</i> (%)	13 (93)	11 (92)		0	NA	NA
Methotrexate, <i>n</i> (%)	1 (7)	1 (8)		0	NA	NA
Azathioprine, <i>n</i> (%)	2 (14)	2 (17)		0	NA	NA
Immunoglobulin G, <i>n</i> (%)	2 (14)	2 (17)		0	NA	NA
Phototherapy, <i>n</i> (%)	3 (21)	3 (25)		0	NA	NA

Abbreviations: AD, Atopic Dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; MAD, Mild Atopic Dermatitis; SAD, Severe Atopic Dermatitis; SCORAD, Scoring Atopic Dermatitis; T0, Baseline; T12, After 12 months of treatment with Dupilumab.

^aAtopy was based on the clinical history and positive prick tests to aeroallergens in patients without cutaneous disease.

^bNon-atopic controls. Median [Inter-quartile range] are shown. All participants provided written informed consent.

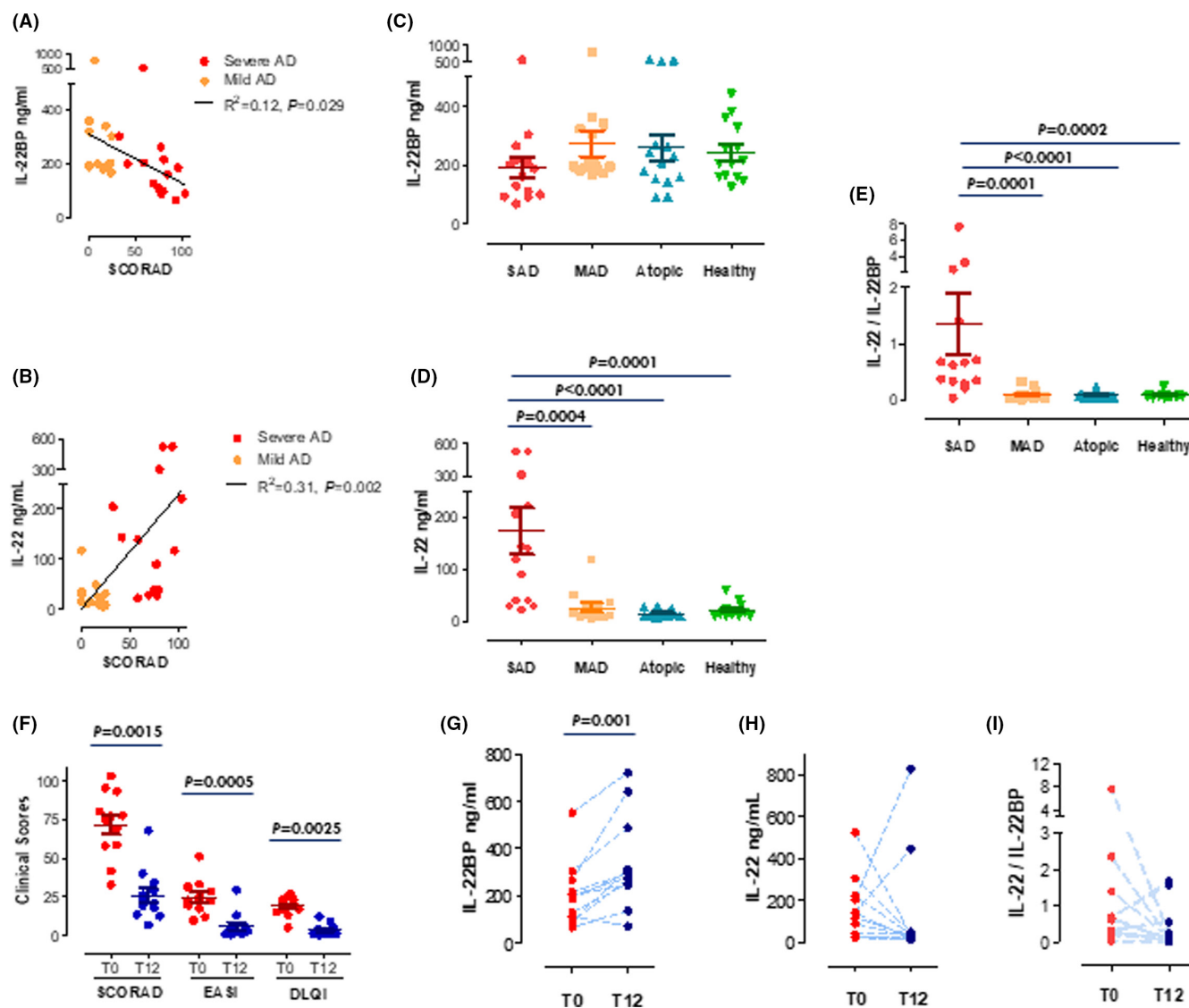


FIGURE 1 Serum IL-22BP, IL-22 and IL-22/IL-22BP ratio in Atopic Dermatitis (AD). Correlation of baseline (BL) IL-22BP (A) and IL-22 (B) with SCORAD. Comparison of BL IL-22BP (C), IL-22 (D), and IL-22/IL-22BP (E) between Severe AD (SAD), Mild AD (MAD), atopic without cutaneous disease and healthy subjects. BL (T0) and after 12 months Dupilumab (T12) clinical scores (F), IL-22BP (G), IL-22 (H) and IL-22/IL-22BP (I)

KEYWORDS

anti-IL-4R therapy, atopic dermatitis, IL-22, IL-22 binding protein

CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

CV, MCPS, AES and SLS designed research; CV and MCPS performed research and analysed data; CV, MN and AL collected clinical data; AL and SLS supervised the study; CV, MCPS, AES and SLS wrote the paper.

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