

Monitoring of serologic immune parameters in inflammatory skin diseases

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This paper deals with the correlation of clinical scoring and serologic markers of inflammation in atopic dermatitis and psoriasis. Serum eosinophil cationic protein (ECP), soluble interleukin-2 receptor (sIL-2R), total serum IgE, IgG and IgM anti-IgE antibodies, and IgE immune complexes were evaluated in monitoring inflammatory skin diseases such as atopic dermatitis and psoriasis. Well-established clinical activity scores were used as standards in recording skin improvement under treatment in a clinical setting. Serum ECP was found to be increased in both atopic dermatitis and psoriasis patients compared to normal controls; sIL-2R and IgE immune complexes were increased only in atopics with increased serum IgE. Anti-IgE antibodies did not show any deviation in both groups of patients. There was a significant elevation of sIL-2R and IgE immune complexes and a nonsignificant elevation of ECP in high-IgE atopics in comparison to those with normal serum IgE. In both groups of patients, there was a significant reduction of ECP and sIL-2R accompanying the improving skin condition. Serum IgE and the other immune parameters failed to respond. In contrast to other studies, serum ECP failed to correspond significantly with disease activity in our study. Our results showed measurable changes of ECP and sIL-2R for atopic dermatitis and/or psoriasis under treatment, but comparison to clinical scores remains difficult due to the different basis of the two systems. The only significant correlation was established for relative changes in sIL-2R and psoriasis area and intensity (PASI), a correlation which might be a useful approach in psoriasis.

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Several clinical scoring systems have been introduced during the last decades for atopic dermatitis, psoriasis, and other inflammatory skin diseases. These systems are useful in evaluating the efficacy of therapeutic measures, monitoring the long-term clinical course of a disorder, or estimating its prognosis, as in traumatic skin burns, but the handicap of all such scoring systems is the subjectivity of the investigator. Therefore, much interest has focused on the establishment of serologic parameters for monitoring the clinical course of particular skin diseases.

Psoriasis is a common inflammatory skin disease, basically caused by an increased proliferative response of the keratinocyte. Activated T cells of the helper subset, as well as keratinocytes, neutrophils, and monocytes, are pathogenetically involved, resulting in an interleukin (IL)-1-, IL-6-, and IL-8-dominated lymphokine pattern. Activated

adhesion molecules on endothelial cells of dermal vessels contribute to the inflammatory response. They have been found to be elevated in correlation to the extent of the disease (1–4).

Elevated serum IgE is considered to be a marker of atopic dermatitis, although some patients express normal IgE (5). Eosinophils infiltrate the skin during atopic inflammation and they are a feature of atopic white blood count (6, 7). Eosinophil cationic protein (ECP) is a 21-kDa basic protein, released on activation from granules of eosinophils together with several toxic proteins. Recently, elevated levels of ECP have been shown in serum and other media of patients with atopic diseases, especially atopic dermatitis (8–14). Eosinophils have been detected in postcapillary venules as early as 2 h after epicutaneous application of house-dust-mite allergen, eventually peaking at 24–48 h in the dermal infiltrate. Almost all eosi-

nophils were positive for antibodies to major basic protein and half of them for ECP (15). ECP seems to be a marker of total eosinophil activity rather than of eosinophil count (16, 17). Recent results show a correlation of ECP with disease activity (8, 17–21).

In both atopic dermatitis and psoriasis, activated T cells are pathogenetically involved. Therefore, a role for the soluble IL-2-receptor (sIL-2R), a marker of T-cell activation, has been suggested. Elevated IL-2R serum levels have been observed in malignant tumors as well as in inflammatory and allergic conditions (22–25). Several authors have reviewed the importance of sIL-2R as a marker of activity in atopic eczema and psoriasis, with contradictory results (8, 19, 20, 22). sIL-2R was reported to be elevated in both atopic dermatitis and psoriasis in correlation to more extensive involvement without establishing its role in monitoring in the same patients (4, 22).

Anti-IgE autoantibodies have been viewed both as epiphenomenon of atopic dermatitis and as specific response to allergen-specific IgE (26–28). IgE and anti-IgE antibodies are bound in serum immune complexes in large amounts (29, 30). Anti-IgE of the IgG1 and IgG4 classes are increased in atopic as compared to nonatopic subjects (26). Immune complexes involving anti-IgE antibodies might cause the low levels of free serum IgE in some atopic patients (31).

Material and methods

Study population

All patients with atopic dermatitis fulfilled well-defined diagnostic criteria (32). Patients suffering from psoriasis have been included in our study due to the diagnostic criteria of Roenigk & Maibach (33). Some 69 patients with atopic dermatitis (34 female, aged 5–79 years) and 46 psoriatic patients (13 female, aged 12–81 years) contributed to the study. Some 99 healthy volunteers with no history of atopy or psoriasis served as control.

Scoring the disease activity

The clinical activity of psoriasis has been scored before and after therapy in a clinical setting by the same investigator (H.C.W.) using the psoriasis area and intensity (PASI) criteria described elsewhere (34). In atopic eczema, three different clinical scores, the Clinical Severity Score (ASCO) (8), the Simple Scoring System of Atopic Dermatitis (SSS) (35), and the SCORAD Index (36), have been used to assess the severity in addition to distribution and involvement of skin surface areas.

All patients with atopic dermatitis received emollients and, if appropriate, UV treatment, topical steroids, topical tar, or antibiotics and antihistamines. Psoriasis was treated with petrolatum containing salicylic acid, cignoline, saline baths, UV, and topical steroids or vitamin D₃ creams, if needed. The use of systemic corticoids, immune modulators or suppressants, or PUVA and high-dose UV-A₁ treatment were exclusion criteria from the study in both groups.

Monitoring of serologic parameters

sIL-2R, serum ECP, total serum IgE, IgG anti-IgE antibodies, IgM anti-IgE antibodies, and IgE immune complexes were chosen to monitor atopic dermatitis and psoriasis.

ELISA for sIL-2R

sIL-2R was assessed with the Cellfree™ kit (T Cell Diagnostics, Inc., Cambridge, MA, USA). Briefly, the Cellfree sIL-2R kit is a sandwich enzyme-immunoassay, consisting of a solid-phase, bound, monoclonal anti-IL-2R antibody as capture antibody and a horseradish peroxidase-conjugated secondary antibody to a different molecule of sIL-2R. It can detect sIL-2R in serum, plasma, or cell-culture supernatants.

Detection of ECP

The CAP System ECP FEIA (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden) was used. Monoclonal anti-ECP, bound to immuno-CAP, was the target of serum sample ECP. β -Galactosidase-linked ECP antibodies were used as secondary antibodies. The results for serum are reliable at 2–200 μ g/l. The handling of the samples is important for the test results. The blood sample is required to rest at room temperature for at least 60 min before serum separation (10 min, 1000 g, twice). False-positive results may be obtained by using blood without serum separation. Calculation of the test results was done automatically by the MasterCAP™ System using Phamas software.

Assay for anti-IgE autoantibodies

We used the procedure reported by Nawata et al. (37). Briefly, myelome IgE (The Binding Site, Birmingham, UK) was purified by FPLC and served as primary antibody. Biotinylated Fc-specific F(ab'2)-fragments of rabbit anti-human IgG (Dianova, Germany), for assessment of IgG anti-IgE, respective to anti-IgM for IgM anti-IgE, were the secondary antibodies. In calculation of

results, due to the number of standard deviations from median of control serum, values >2 were considered positive.

IgE immune complexes

A two-sided monoclonal sandwich ELISA was used to detect IgE immune complexes. Complex-bound serum IgE was separated from monomer IgE by precipitation of the samples with 2.5% polyethylene glycols 6000. Resolubilized complexes were used as the sample in the assay. Dilution series of human IgE standards served for quantification (N Latex IgE-kit®, Behring-Werke). Values were rated positive when higher than 3 IU IgE/ml.

Statistical evaluation

Differences for each score were evaluated with the Wilcoxon matched-pairs, signed-ranks test for dependent parameters and the Mann-Whitney U-test for independent parameters. Correlations between disease activity and serologic parameters, as well as between different parameters, were calculated with Spearman's rank correlation coefficient for monotonous correlations. That coefficient was calculated not only for absolute values but also for relative changes (percentage of initial value).

Results

t_1 represents data of untreated patients, and t_2 of recovered patients. The following units were used in assaying the parameters: total serum IgE: IU/ml; ECP: $\mu\text{g/l}$; sIL-2R: U/ml; IgG-anti-IgE and IgM-anti-IgE antibodies: number of standard deviations from mean of normal serum; IgE immune complexes: IU/ml.

Scoring clinical activity

A total of 46 psoriatic and 69 atopic dermatitis patients were enrolled in the study. The activity of the dermatologic disorder was scored at the beginning and the end of treatment in a clinical setting. Each score confirmed significantly the visual impression of a reduction in disease activity and extent (Table 1). Both "intensity" and "body surface" involvement were obtained from the SCORAD calculation (36).

Relation of various serologic markers to clinical conditions

We looked for differences between patients and normal controls for all immune parameters. The

Table 1. Monitoring of disease activity by different scoring systems

Scoring system	t_1		t_2		Wilcoxon matched-pairs, signed-ranks test (U1 to U2) Two-tailed P
	Mean	SD	Mean	SD	
ASCO	110.15	62.11	49.16	45.50	<0.001
SSS	43.56	11.84	21.63	10.89	<0.001
SCORAD	65.00	11.70	36.46	15.73	<0.001
Intensity	13.33	2.40	8.06	3.14	<0.001
Body surface (%)	42.79	22.8	20.64	17.09	<0.001
PASI	15.53	7.11	8.52	6.35	<0.001

results are shown for ECP and sIL-2R in Tables 2–5. In both atopic dermatitis and psoriasis, ECP differed significantly from healthy controls at t_1 and t_2 due to elevated ECP in patients. There was a tendency to higher sIL-2R than in healthy controls in all conditions before treatment; however, significantly increased sIL-2R was found only in atopic eczema with elevated IgE. Unexpectedly, psoriatic patients showed significantly reduced sIL-2R compared to healthy controls after treatment.

Comparing the two conditions, atopic dermatitis and psoriasis, before and after treatment, we found significant differences for only two parameters. Patients with atopic dermatitis and elevated total IgE differed from psoriatic patients by increased sIL-2R levels ($P<0.001$ t_1 , NS t_2) and IgE immune complexes ($P<0.001$ t_1 , $P=0.008$ t_2). That difference was not significant between normal IgE atopics and psoriatics. After treatment, patients with atopic dermatitis and normal IgE had significantly higher IgM anti-IgE levels than psoriatics. IgE immune

Table 2. ECP ($\mu\text{g/l}$) at t_1 in patients and controls

Patients	n	Mean	SD	Mann-Whitney-U test Two-tailed P
Total atopics	69	30.76	35.52	<0.001
Elevated IgE	45	35.88	40.7	<0.001
Normal IgE	24	21.14	20.32	<0.001
Psoriatics	45	20.69	19.92	<0.001
Controls	99	4.40	—	n.a.

Table 3. ECP ($\mu\text{g/l}$) at t_2 in patients and controls

Patients	n	Mean	SD	Mann-Whitney-U test Two-tailed P
Total atopics	68	17.50	19.04	<0.001
Elevated IgE	45	18.46	20.41	<0.001
Normal IgE	24	15.74	16.48	<0.001
Psoriatics	45	16.14	18.45	<0.001
Controls	99	4.40	—	n.a.

Table 4. sIL-2R (U/ml) at t_1 in patients and controls

Patients	<i>n</i>	Mean	SD	Mann-Whitney-U test
				Two-tailed <i>P</i>
Total atopics	61	655.69	487.43	0.004
Elevated IgE	39	778.54	524.85	<0.001
Normal IgE	22	437.91	320.38	0.955
Psoriatics	41	468.99	527.86	0.788
Controls	30	388.80	152.90	n.a.

Table 5. sIL-2R (U/ml) at t_2 in patients and controls

Patients	<i>n</i>	Mean	SD	Mann-Whitney-U test
				Two-tailed <i>P</i>
Total atopics	52	431.41	387.18	0.908
Elevated IgE	32	480.01	449.48	0.662
Normal IgE	20	353.66	249.81	0.706
Psoriatics	40	299.14	288.20	0.007
Controls	30	388.80	152.90	n.a.

complexes were higher for atopics with increased serum IgE than for psoriatics at this time. Because of the different results for atopic dermatitis with and without elevated serum IgE, we looked for further significant relationships between the serologic parameters due to their serum IgE (Table 6). Untreated patients with increased serum IgE demonstrated higher sIL-2R and IgE immune complex levels than patients with normal IgE. The same differences were not confirmed for t_2 .

Interparameter correlations per disease

IgG anti-IgE and IgM anti-IgE have been correlated in both psoriatic ($P=0.048$) and atopic ($P<0.001$) patients. IgE immune complexes corresponded well to serum IgE ($P=0.002$) and sIL-2R ($P=0.022$) in atopic dermatitis patients. No other correlation of significance or importance could be obtained.

Changes in serologic parameters during treatment

Looking for changes in the data under treatment, we compared the two times for each item. The

Table 6. Differences of serum parameters due to IgE in atopic dermatitis at t_1

	Increased serum IgE			Normal serum IgE			Mann-Whitney-U test Two-tailed <i>P</i>
	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	
ECP ($\mu\text{g/l}$)	45	35.88	40.70	24	21.14	20.32	0.407
sIL-2R (U/ml)	39	778.54	524.85	22	437.91	320.38	0.013
IgG-anti-IgE	42	0.40	1.41	23	0.62	1.87	0.836
IgM-anti-IgE	43	0.97	2.12	23	1.18	2.06	0.332
IgE immune complexes	43	5.42	9.40	24	1.96	0.90	0.011

results are shown in Tables 7 and 8. In both groups of patients, there was a significant reduction of ECP as well as sIL-2R levels caused by the improvement of the skin condition under treatment. ECP changes were more obvious in eczema patients, and sIL-2R changes in psoriasis patients. No significant changes were recorded for either IgE, IgE immune complexes, or anti-IgE antibodies.

Correlations of serologic parameters with disease activity

The main purpose of the present paper was to compare well-established clinical scores with immune parameters for compatibility. In both inflammatory disorders, there was a good correlation of activity scores to sIL-2R (positive correlation) and, to a lesser extent, to IgM anti-IgE levels (negative correlation). For sIL-2R, the percentage of involved body surface had the closest correlation. Serum IgE, ECP, IgE immune complexes, and IgG anti-IgE failed to correspond to the activity scores investigated in the present paper (Table 9). However, after treatment, there was no longer such a correlation. Except for a similar profile in psoriasis scoring by the PASI to IgM-anti-IgE ($P=0.012$), the serologic data did not support the clinical observations of clearing skin lesions (data not shown). Moreover, we questioned whether there were any relations of relative values for serologic parameters and severity scores (percentage of values at t_1) (Table 10). No changes were recorded for IgE and IgE immune complexes respective to anti-IgE antibodies. We found corresponding data only in psoriasis patients between the changes (percentage) for ΔPASI and $\Delta\text{sIL-2R}$.

Discussion

Clinical scoring and monitoring are important not only for the evaluation of therapeutic responses to new treatment options but also in long-term recording of skin conditions. Much effort has been put into establishing new serologic or immune

Table 7. Changes of serum parameters in patients with atopic dermatitis

Parameter	t_1			t_2			Wilcoxon matched-pairs, signed-ranks test Two-tailed P
	n	Mean	SD	n	Mean	SD	
Serum IgE	45	2373	4220	42	2338	3388	0.807
ECP ($\mu\text{g/l}$)	69	30.76	35.52	69	17.50	19.04	<0.001
sIL-2R (U/ml)	61	655.69	487.43	52	431.41	387.2	0.001
IgG-anti-IgE	65	0.48	1.58	43	0.28	0.88	0.627
IgM-anti-IgE	66	1.04	2.09	43	1.03	2.29	0.935
IgE immune complexes	67	4.18	7.70	51	3.59	6.00	0.415

Table 8. Changes of serum parameters in patients with psoriasis

Parameters	t_1			t_2			Wilcoxon matched-pairs, signed-ranks test Two-tailed P
	n	Mean	SD	n	Mean	SD	
ECP ($\mu\text{g/l}$)	45	20.69	19.92	43	16.14	18.45	0.030
sIL-2R (U/ml)	41	468.99	527.86	40	299.14	288.2	0.0047
IgG-anti-IgE	41	0.14	0.8	30	0.13	1.36	0.869
IgM-anti-IgE	41	0.21	1.04	30	0.17	1.38	0.680
IgE immune complexes	41	1.51	0.89	36	1.66	0.67	0.445

parameters, such as ECP, sIL-2R, etc., in order to improve the reliability of recording, to create a quantitative system, to minimize subjective influences, and, not least, to introduce new pathogenetic approaches into diagnostic routine. The present paper compares these two different systems, clinical

scoring and immune parameters. An obvious improvement of the clinical scores has been obtained by comparing patients with either atopic dermatitis or psoriasis at the beginning of therapy in our hospital with the condition at the end of inpatient treatment.

Activated T and B cells, and, to a lesser extent, monocytes can produce sIL-2R. Therefore, sIL-2R might be useful as a marker of diseases with enhanced lymphocytic activity (25). As observed by others (18–20), patients with atopic eczema and elevated serum IgE had significantly increased sIL-2R ($P<0.001$) in the present study, whereas such patients with normal IgE and psoriatic patients did not (Table 4). High-level IgE is associated with more severe disease, as is sIL-2R. This might explain the link of the two inflammatory markers in atopy. For psoriasis, this does not correspond to previous results (22). We have even found lower levels of sIL-2R in psoriasis after therapy, a finding never reported before, to our knowledge. However, that may be due to UV treatment, usually selective UV phototherapy, which has been used extensively in our psoriasis group. UV, like systemic glucocorticoids, can lower IL-2R expression, although the latter were not used in our study (38, 39). Patients with atopic dermatitis showed a decrease of their sIL-2R levels (18–20, 40, 41).

Several authors failed to show a correlation between clinical activity and serologic parameters such as ECP and sIL-2R (11, 25, 42). For psoriasis, we found a significant correlation between PASI and sIL-2R ($r=0.44$; $P=0.004$). We and others

Table 9. Correlations of immune parameters to severity scores at t_1

	Serum IgE	ECP	sIL-2R	IgG anti-IgE	IgM anti-IgE	IgE immune complexes
ASCO						
r	−0.042	0.016	0.537	−0.18	−0.37	0.11
n	46	68	60	64	65	66
P	0.778	0.893	<0.001	0.146	0.002	0.346
SSS						
r	0.178	0.046	0.374	−0.09	−0.376	−0.11
n	46	69	61	65	66	67
P	0.235	0.705	0.003	0.429	0.002	0.347
SCORAD						
r	0.238	−0.023	0.447	−0.11	−0.294	0.138
n	44	66	58	62	63	64
P	0.119	0.853	<0.001	0.361	0.019	0.274
Int						
r	0.18	−0.01	0.171	0.033	−0.147	0.075
n	44	66	58	62	63	64
P	0.236	0.924	0.199	0.79	0.249	0.551
Body surface						
r	−0.059	0.0069	0.585	−0.21	−0.308	0.142
n	44	66	58	62	63	64
P	0.70	0.95	<0.001	0.094	0.014	0.262
PASI						
r	n.t.	0.197	0.44	0.082	−0.322	−0.14
n		44	40	41	41	41
P		0.199	0.004	0.607	0.039	0.382

Table 10. Relative changes of parameters (Δx) during treatment

	Δ ASCO	Δ SSS	Δ SCORAD	Δ Intensity	Δ Body surface	Δ PASI
Δ ECP						
<i>r</i>	0.08	0.187	0.09	0.03	0.03	0.29
<i>n</i>	67	68	65	65	65	42
<i>P</i>	0.474	0.126	0.461	0.81	0.794	0.056
Δ sIL-2R						
<i>r</i>	-0.23	-0.14	-0.02	-0.037	-0.15	0.51
<i>n</i>	49	49	47	47	47	36
<i>P</i>	0.106	0.334	0.89	0.80	0.284	0.002
Δ IgE						
<i>r</i>	-0.07	-0.05	0.00	0.20	-0.00	n.d.
<i>n</i>	44	44	42	42	42	
<i>P</i>	0.65	0.74	0.97	0.19	0.99	

could easily correlate disease activity and sIL-2R before treatment (8, 19, 41). The closest relation has been established to the clinical severity score (ASCO) ($r=0.537$; $P<0.001$) and the percentage of involved body surface ($r=0.585$; $P<0.001$). For atopic dermatitis, complicated scores were not superior to simple clinical scoring due to the percentage of affected body surface.

A significant correlation between disease activity and sIL-2R level has been recorded in our study in untreated patients only. This is in contrast to other studies which found a good correlation of sIL-2R to severity in general (40, 41). However, in comparing quantitative values, as in ECP, sIL-2R, etc., with semiquantitative items, such as clinical scores, one cannot expect a straight correlation. In view of this very important reservation, only psoriasis patients correlated well for relative changes of activity scores and sIL-2R ($r=0.51$; $P=0.002$). Only the relative changes of sIL-2R may be helpful in monitoring psoriasis if the correlation to clinical scores is the focus of interest. As with ECP, using the absolute values was of limited benefit.

Eosinophil granulocytes and their cytotoxic products, such as ECP, have been implicated in the pathogenesis of atopic dermatitis for years (11, 18, 19, 43). However, only a few papers have reported effects of eosinophil mechanisms in psoriasis (44). In the present paper, we recorded increased serum ECP compared to normal controls for psoriasis ($n=45$) as well as for atopic dermatitis ($n=69$), before and after treatment. Our results yield more evidence of the involvement of eosinophil mechanisms in the inflammation process of psoriasis despite their absence in skin lesions.

There was a significant reduction of serum ECP in the course of skin improvement for patients with atopic dermatitis ($P<0.001$) and psoriasis ($P=0.030$), with more obvious results for the former (18, 19). However, neither the absolute values nor the relative changes of ECP corre-

sponded well to various clinical scoring systems. Again, although evidence is lacking of a statistical correlation between the systems, both systems should be used separately in monitoring.

As recently predicted, we did not find any link between serum IgE and disease activity in atopic dermatitis nor any significant change in IgE after treatment (31). IgE immune complexes have been reported to be increased in atopic dermatitis (45). We have confirmed and extended this observation, showing a significant difference between high IgE atopics and normal IgE atopics or psoriatics ($P=0.011$) for the occurrence of those complexes. Severe atopic disease in low serum IgE patients has been explained as the binding of large amounts of IgE into immune complexes (31). We could not record either a significant change of IgE immune complexes or any correlation of immune complexes to severity scores. According to De Clerc et al. (46), IgE immune complexes may activate lymphocytes in inflammatory diseases. Indeed, there was a correlation ($r=0.3$; $P=0.022$) between IgE immune complexes and sIL-2R in our study.

Of 35 patients with atopic dermatitis, 17 expressed activity of anti-IgE autoantibodies (45). There was a significant negative correlation between IgM-anti-IgE autoantibodies and ASCO respective to the PASI score for both atopic dermatitis ($r=-0.37$; $P=0.002$) and psoriasis ($r=-0.322$; $P=0.039$). As far as we know, this is the first report of such a correlation. It was shown recently that epitope-specific anti-IgE autoantibodies can inhibit allergic and inflammatory processes. Therefore, low levels may, in turn, be correlated with extensive or severe diseases, as suggested by our results.

It is hard to define a standard for the evaluation of monitoring approaches. Scores are widely used in dermatology because of their reliability. Serologic data may certainly provide additional information on pathogenetic aspects and systemic inflammatory mechanisms. Taken together, the use of immune

parameters such as ECP and sIL-2R is justified, in addition to well-defined clinical scores, in monitoring the course of inflammatory skin diseases. IgE, immune complexes, and anti-IgE antibodies have no benefit.

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