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The role of inflammatory markers in assessing disease severity and response to treatment in patients with psoriasis treated with etanercept

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Summary

Background. Psoriasis is a chronic, systemic, inflammatory disease. Inflammatory markers are used in clinical practice to detect acute inflammation, and as markers of treatment response. Etanercept blocks tumour necrosis factor (TNF)-α, which plays a central role in the psoriatic inflammation process.

Aim. To reveal any possible association between disease severity [measured by Psoriasis Area and Severity Index (PASI)] and the inflammatory burden (measured by a group of inflammatory markers), before and after etanercept treatment.

Methods. In total, 41 patients with psoriasis vulgaris, eligible for biological treatment with etanercept, were enrolled in the study. A set of inflammatory markers was measured, including levels of white blood cells and neutrophils, fibrinogen, ferritin, high-sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), haptoglobin, ceruloplasmin and α1-antitrypsin, before and after 12 weeks of etanercept 50 mg twice weekly.

Results. All markers were reduced after treatment ($P < 0.001$). PASI correlated with fibrinogen and hs-CRP. Of the 41 patients, 19 (46.3%) achieved reduction of 75% in PASI (PASI75). An increase in hs-CRP and ESR difference (values before minus values after treatment) was related to higher likelihood of achieving PASI75.

Conclusions. Inflammatory markers, particularly hs-CRP and to a lesser extent, fibrinogen and ESR, can be used to assist in assessing disease severity and response to treatment in patients with psoriasis. A combination of selected inflammatory factors (which we term the Index of Psoriasis Inflammation) in combination with PASI might reflect inflammatory status in psoriasis more accurately than each one separately.

Introduction

Psoriasis is a chronic, systemic, inflammatory disease, affecting mainly the skin and the joints, which is estimated to affect approximately 2% of the general population. It is considered to be an immune cell-mediated disease in which T-lymphocyte activation is of major importance. Although the precise aetiology of

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psoriasis is unknown, it is widely accepted that the inflammatory response plays a central role in the pathogenesis of psoriasis.[1,2] The latter is indicated by cutaneous and systemic overexpression of proinflammatory cytokines, such as tumour necrosis factor (TNF)-α, interleukin (IL)-2, IL-6, IL-8, IL-12, IL-17, IL-19, IL-20, IL-22, IL-23 and IL-24, interferon-γ, and other similar substances.[3,4] This cascade of events eventually leads to the formation of the psoriatic lesion. Systemic inflammation can also be reflected by an array of markers including white blood cell count (WBCC), fibrinogen, ferritin, high-sensitivity C-reactive protein (hs-CRP) and erythrocyte sedimentation rate (ESR). These are generally nonspecific markers that are used in clinical practice to detect acute inflammation, and as markers of treatment response. Researchers have previously investigated possible links between some of these markers and psoriasis severity and response to treatment. Of these markers, hs-CRP has attracted most attention.[5–7]

Several agents used for psoriasis treatment, such as methotrexate, ciclosporin and some of the newer biological agents (e.g. TNF-α antagonists and IL-12/23 blockers), target different components of the underlying inflammation mechanisms. Etanercept is a soluble TNF-α blocker that binds and neutralizes TNF-α. It is a fully human, dimeric fusion protein consisting of the extracellular ligand-binding domain of the TNF-α receptor linked to the Fc portion of human immunoglobulin G1. Its main uses are in psoriasis, psoriatic arthritis and Crohn disease.[8]

In this study, we investigated the possible association between disease severity [as measured by the Psoriasis Area and Severity Index (PASI)] and the inflammatory burden (measured by a group of inflammatory markers), before and after etanercept treatment in patients with psoriasis. The PASI is a widely used method to assess disease severity based on the extent of psoriasis lesions, and the associated erythema, induration and scaling.

Methods

The study was approved by the ethics committee of Attikon General University Hospital, and informed consent was obtained from all participants.

Patients

The study population comprised 41 adult patients with psoriasis vulgaris (24 men, 17 women; mean ± SD 46 ± 16.7 years, range 21–71) from the Dermatology Outpatient clinic of this hospital. All patients had white ethnicity. All patients were eligible for treatment with biological agents, and fulfilled the required recommendations according to European guidelines.[8] All patients had a baseline PASI of 10 or more, and were intolerant or unresponsive to or had a contraindication for standard systemic treatment.

Exclusion criteria were: any apparent sign of acute or chronic inflammation (e.g. hepatitis, arthritis or autoimmune disease); previous exposure to biological agents; excessive alcohol consumption (maximum 2 units/day for women, 3 units/day for men); presence of psoriatic arthritis, acute or chronic infections, or liver or renal impairment; pregnancy or breast-feeding; history of cancer within the previous 5 years; and major trauma. Patients had to be off treatment (topical or systemic) for at least a month before treatment start.

Treatment and assessment

Laboratory blood and urine tests, chest X-ray and Mantoux tuberculosis test were performed before start of treatment. All patients were started on etanercept 50 mg subcutaneous injections twice a week for a period of 12 weeks. Inflammatory markers (WBCC and neutrophils, fibrinogen, ferritin, hs-CRP, ESR, haptoglobin, ceruloplasmin, α1-antitrypsin) and PASI were measured at baseline and after 12 weeks of treatment.

Statistical analysis

SPSS software (version 17.0; SPSS Inc. Chicago, IL, USA) was used for all analyses, and $P < 0.05$ was considered significant. All continuous variables are described as mean, median and interquartile range (IQR) (75th to 25th percentile). The normality of continuous variables was assessed with graphical and mathematical methods (Shapiro–Wilk test). Most variables deviated from normal distribution, thus nonparametric statistical tests were used. Spearman rank correlation coefficients were calculated for PASI and each of the inflammatory markers at baseline and after treatment, and median percentage decrease for each inflammatory marker and PASI were calculated. As the achievement of 75% reduction in PASI is usually considered a satisfactory response rate, a new binary variable (PASI75) was created, indicating whether 75% reduction in PASI was achieved (0 = no, 1 = yes). The nonparametric Wilcoxon test (Wilcoxon signed-rank test) for paired observations was used to compare PASI and inflammatory markers before and after treatment with etanercept, and to compare PASI and inflammatory markers at baseline and after treatment in the two

subgroups (non-PASI75 and PASI75). The Mann–Whitney *U*-test was used to compare PASI and inflammatory markers between the PASI75 and non-PASI75 groups at baseline and at the end of treatment. Multiple binary logistic regression was used to evaluate the effect of the differences in inflammatory markers between baseline and the end of treatment (difference equal to inflammatory marker at baseline minus end of treatment) in patients achieving PASI75.

Results

There was a significant positive correlation between PASI and fibrinogen at baseline (Spearman $\rho = 0.36$, $P < 0.05$), and between PASI and hs-CRP at the end of treatment (Spearman $\rho = 0.42$, $P < 0.01$).

There was a significant reduction from baseline to the end of treatment for all variables (PASI and inflammatory markers) (Table 1). There was a median decrease in PASI of 73.3% (Table 2). Of the inflammatory markers, ESR and hs-CRP had the highest percentage decrease (50.0% and 46.4%, respectively) (Table 2).

Of the 41 patients, 19 (46.3%) achieved PASI75 and 22 (53.7%) did not (Table 3). For all variables (PASI and inflammatory markers), there was a significant reduction between baseline and end of treatment for both groups (within-group analysis).

Analysis of the difference in inflammatory markers between the two groups at baseline and end of treatment (between-groups analysis) revealed a significant difference only for hs-CRP after treatment (median 0.76 and 1.21 for PASI75 and non-PASI75, respectively; $P < 0.01$, Mann–Whitney), with no differences seen for the other markers.

Table 2 Median percentage decrease of PASI and inflammatory markers ($N = 41$)

Parameter	Median decrease, %
Psoriasis Area and Severity Index	73.3
White blood cells	14.9
Neutrophils	16.9
Fibrinogen	10.6
Ferritin	12.6
High-sensitivity C-reactive protein	46.4
Erythrocyte sedimentation rate	50.0
Haptoglobin	15.0
Ceruloplasmin	4.6
α1-Antitrypsin	13.2

A multivariate logistic regression model was used with PASI75 as the dependent variable, and the difference in hs-CRP and ESR as independent variables, adjusted for gender and age to measure the correlation between PASI and these inflammatory markers between baseline and the end of treatment. The hs-CRP difference was strongly related (OR = 10.13, 95% CI 1.39–73.65, $P < 0.05$) with the outcome of achieving PASI75, i.e. a one-unit increase in hs-CRP difference increased the odds of achieving PASI75 by approximately 10 times. Similarly, a one-unit increase in ESR difference increased the odds of achieving PASI75 by a factor of 1.21 (OR = 1.21, 95% CI 1.05–1.39 $P = 0.01$), and a five-unit increase in ESR difference, increased the odds of PASI75 achievement by a factor of 2.59 [$OR^5 = (1.21)^5 = 2.59$].

Discussion

The inflammatory response is fundamental in the host defence against various stimuli. It is composed of a series

Table 1 PASI and inflammatory markers before and after etanercept treatment.

		Before treatment ($n = 41$)				After treatment ($n = 41$)				
Variable	Normal range	Mean	Median	25th–75th quartile	IQR	Mean	Median	25th–75th quartile	IQR	*P**
PASI	–	16.52	17.00	15.00–18.95	3.95	6.11	4.70	4.00–7.95	3.95	< 0.001
WBC, $\times 10^9$/L	4.0–11.0	8.16	7.90	6.99–9.39	2.41	6.68	6.40	5.88–7.37	1.49	< 0.001
Neutrophils, $\times 10^9$/L	2.0–8.0	5.73	5.67	4.67–6.08	1.41	4.66	4.23	3.78–5.35	1.58	< 0.001
Fibrinogen, mg/dL	200–400	360.84	370.00	296.00–402.50	106.50	331.19	330.00	282.50–376.00	93.50	< 0.001
Ferritin, ng/mL	30–400	157.61	143.00	94.50–188.50	94.00	142.59	125.00	88.50–162.00	73.50	< 0.001
hs-CRP, mg/L	0.0–6.0	2.14	1.99	1.67–2.24	0.57	1.23	1.02	0.66–1.47	0.82	< 0.001
ESR, mm/h	0–20	14.93	16.00	9.50–20.00	10.50	7.78	8.00	4.50–10.00	5.50	< 0.001
Haptoglobin, g/dL	0.3–2.0	2.15	2.23	1.95–2.55	0.60	1.86	2.04	1.65–2.22	0.57	< 0.001
Ceruloplasmin, mg/L	200–600	393.78	405.00	300.00–486.00	186.00	376.66	390.00	280.00–465.00	185.00	< 0.001
α1-Antitrypsin, g/L	0.9–2.0	1.68	1.70	1.44–1.87	0.43	1.44	1.49	1.25–1.63	0.38	< 0.001

hs-CRP, high-sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; PASI, Psoriasis and Severity Index; WBC, white blood cells. *Wilcoxon signed-rank test.

Table 3 PASI and inflammatory markers before and after etanercept treatment, separately for those who have achieved PASI75 and those who have not.

	Baseline (n = 41)			After treatment (n = 41)			
Variable	Median	25th–75th quartile	IQR	Median	25th–75th quartile	IQR	P*
Group that did not achieve PASI75 (n = 22)							
PASI	16.60	14.75–19.00	4.25	7.70	4.78–9.88	5.10	< 0.001
WBC, $\times 10^9$/L	7.66	6.73–9.39	2.67	6.72	5.84–7.33	1.49	< 0.001
Neutrophils, $\times 10^9$/L	5.67	4.40–7.04	2.64	4.17	3.63–5.83	2.21	< 0.001
Fibrinogen, mg/dL	353.50	292.00–436.25	144.25	325.00	274.00–384.00	110.00	0.001
Ferritin, ng/mL	152.00	94.75–191.00	96.25	131.00	84.50–166.25	81.75	0.001
hs-CRP, mg/L	1.89	1.73–2.26	0.53	1.21†	0.96–1.71	0.76	< 0.001
ESR, mm/h	12.00	9.00–19.25	10.25	8.50	5.00–12.00	7.00	0.004
Haptoglobin, g/dL	2.29	1.98–2.50	0.53	2.06	1.75–2.25	0.51	0.001
Ceruloplasmin, mg/L	380.50	290.75–487.00	196.25	370.50	278.75–469.25	190.50	0.003
α1-Antitrypsin, g/L	1.70	1.45–1.88	0.43	1.54	1.39–1.61	0.22	0.004
Group that did achieve PASI75 (n = 19)							
PASI	17.00	15.00–18.90	3.90	4.00	3.50–4.50	1.00	< 0.001
WBC, $\times 10^9$/L	8.60	7.00–9.39	2.39	6.30	5.90–7.45	1.55	< 0.001
Neutrophils, $\times 10^9$/L	5.67	5.00–6.06	1.06	4.29	3.80–5.29	1.49	0.001
Fibrinogen, mg/dL	372.00	298.00–400.00	102.00	335.00	300.00–370.00	70.00	0.002
Ferritin, ng/mL	135.00	90.00–190.00	100.00	125.00	87.00–160.00	73.00	0.001
hs-CRP, mg/L	2.00	1.60–2.23	0.63	0.76†	0.57–1.10	0.53	< 0.001
ESR, mm/h	18.00	11.00–21.00	10.00	8.00	3.00–10.00	7.00	< 0.001
Haptoglobin, g/dL	2.20	1.75–2.70	0.95	1.90	1.59–2.10	0.51	< 0.001
Ceruloplasmin, mg/L	456.00	300.00–485.00	185.00	400.00	280.00–465.00	185.00	0.003
α1-Antitrypsin, g/L	1.80	1.44–1.85	0.41	1.29	1.15–1.65	0.50	< 0.001

hs-CRP, high-sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; PASI, Psoriasis and Severity Index; WBC, white blood cells. *Wilcoxon signed-rank test; †Mann–Whitney U-test, $P < 0.01$.

of cellular and tissue events leading to local haemodynamic changes and alterations in microvascular permeability, resulting in the accumulation of activated leucocytes. This activation triggers a parallel set of metabolic actions, including generation of reactive oxygen species, which can be harmful to both the host and the attacking stimulus. Endogenous antioxidant systems exist to counterbalance these effects.[9]

We chose to measure a group of inflammatory markers that are common in clinical practice, and easily measured in an ordinary laboratory. Total WBCC and neutrophils were measured as markers of neutrophil activation, ceruloplasmin and α1-antitrypsin as markers of the endogenous antioxidant and antiprotease system, and ferritin, fibrinogen, ESR, hs-CRP and haptoglobin as markers of acute inflammation. Although these markers are not specific for a particular disease, they depict an inflammatory burden that can be attributed to psoriasis, as long as other possible causes of inflammation are excluded.

We found a significant correlation between PASI and fibrinogen at baseline, and PASI and hs-CRP after treatment. Fibrinogen is an acute-phase reactant, therefore it is plausible for this to be increased when an active inflammation, such as psoriasis, is present. We found median fibrinogen levels at baseline (370 mg/dL) to be towards the upper end of the normal range (200–400 mg/dL). Higher fibrinogen levels can also be attributed to a hypercoaguable state associated with psoriasis. A previous study[10] found a nonsignificant tendency for patients with psoriasis to have higher levels of fibrinogen and homocysteine. Increased homocysteine is a well-established risk factor for cardiovascular disease (CVD), mainly through its role in the atherothrombotic process, and psoriasis is itself a risk factor for CVD. It is now believed that psoriasis and atherosclerosis share common pathogenic mechanisms, and that the formation process of the psoriatic and atherosclerotic plaque have many similarities.[11]

These correlations indicate a relationship between inflammatory burden and PASI. Increased levels of certain inflammatory markers correspond to increased PASI, supporting the concept that psoriasis may in part be a generalized autoinflammatory process.

PASI is widely used in clinical trials and in routine clinical practice, but it has limitations. It is subjective by nature, and perhaps the most difficult element to assess accurately is the extent of the affected body surface area (BSA). For example, a difference in BSA estimation of only 1% for a specific body area results in a twofold

increase in PASI for that area. Alternative or complementary scales include the Physician Global Assessment, a six-point scale that summarizes the overall quality (erythema, scaling and thickness) and extent (BSA) of plaques relative to baseline.

We found that all inflammatory markers were reduced after 12 weeks of treatment. This finding accompanied clinical improvement, reflected in reduction in PASI. Clinical improvement after etanercept treatment correlated with reduction in inflammatory markers, with the highest percentage decrease in ESR and hs-CRP (Table 2). These two inflammatory markers were also associated in the multivariate logistic regression analysis with the likelihood of achieving PASI75 reduction. Although they are both acute-phase reactants, hs-CRP and ESR are not interchangeable. ESR rises slowly after onset of an acute stimulus, and remains raised for several weeks afterwards, largely dependent on fibrinogen levels. By contrast, hs-CRP rises within hours, has a short half-life of 6–8 h, and falls rapidly after successful treatment. Thus hs-CRP is more appropriate for daily monitoring, whereas ESR reflects changes that have taken place in the previous couple of weeks. In our study, both hs-CRP and ESR were reduced after successful treatment (achievement of PASI75), confirming that limiting the extent of short-term and long-term inflammatory processes by etanercept results in clinical improvement.

By splitting our initial group into two subgroups, those who achieved PASI75 and those who did not, we tried to identify any differences between them. The percentage of patients achieving PASI75 (46.3%) is in accordance with the percentage expected after 12 weeks of etanercept therapy (48%), as large clinical trials have found.[12] Within-group analysis verified that a significant reduction was seen for all variables (Table 3). We then compared inflammatory markers values before and after treatment between the two groups, e.g. fibrinogen in PASI75 and in non-PASI75 patients, both in baseline and after treatment. The only significant finding was a higher hs-CRP in non-PASI75 patients after treatment compared with PASI75 patients after treatment (Table 3). In other words, a higher inflammatory burden after treatment – as this is depicted by hs-CRP – might be associated with failure to achieve PASI75 levels. Conversely, lower hs-CRP levels correlate well with PASI75 achievement. The above findings support the findings from the multivariate logistic regression analysis.

Multivariate logistic regression analysis found that the more the inflammatory difference increases, the more the inflammatory burden is reduced, and subsequently the more likely it is to achieve a significant treatment response.

We acknowledge the fact that ESR is affected by a wide variety of factors, such as obesity, age, race, anaemia and medications.[13] Therefore, there is great variability in ESR measurement. A one-unit increase in ESR difference cannot be clinically evaluated, although it was found to be significant. A five-unit increase in ESR difference raises the odds of achieving PASI75 by a factor of 2.59, which could be explained by the reduced inflammatory burden after and during treatment, as ESR reflects a rather longer period than does hs-CRP.

It would certainly be very interesting and useful to have a pretreatment tool, such as an inflammation marker, that would predict response to treatment. Unfortunately, we do not have such a tool in our disposal yet. However, what we do have is a suggestion that the higher the hs-CRP difference, the more likely it is to achieve PASI75.

Although it sounds logical to expect that clinical assessment of psoriasis and laboratory findings assessing inflammation go hand in hand, it is difficult to draw solid conclusions from these observations. Our study is limited by the relatively small number of patients and perhaps the relatively wide standard deviation in age. Further studies with larger number of participants and more than one therapeutic agent are needed in order for these suggestions to be verified.

It seems likely that inflammatory markers (fibrinogen and hs-CRP in our case) reflect disease severity in a similar way to the PASI. In our study, the data scatter clearly shows that a single inflammatory marker cannot correlate sufficiently with the PASI to be useful in assessing severity or response to treatment. However, a combination of these parameters might be useful. A combination of the most significant predictors of the inflammation response will require a multiple logistic regression model, where response to treatment as the dependent variable, and inflammatory markers as independent variables. We propose such a model, which we term the Index of Psoriasis Inflammation (IPI), given by the formula

$$\mathrm{IPI} = \alpha_1 x_1 + \alpha_2 x_2 + \cdots,$$

where x_1, x_2, etc., are the significant inflammatory markers, and α_1, α_2 etc. are the corresponding regression coefficients. This new index would be expressed as a single numerical value, and perhaps could be assessed in parallel with PASI or one of the alternative sign scores, resulting in a novel tool, which would depict psoriasis activity both by clinical and laboratory measures. Unfortunately, we do not yet have enough data to

support such an approach, which would need to be validated in a larger subsequent study.

Conclusion

Inflammatory markers, mainly hs-CRP and to a lesser extent, fibrinogen and ESR, can be used to assess disease severity and response to treatment in patients with psoriasis. In our study, we found all three to be reduced after treatment, both in patients achieving and those not achieving PASI75. The greater the reduction in inflammatory burden after etanercept treatment (as measured by hs-CRP and ESR), the more likely patients were to achieve PASI75.

Our findings need to be confirmed by larger randomized controlled trials, perhaps with more than one therapeutic agent. We suggest a new index (the IPI), using a combination of all the significant inflammatory markers we identified. A combination of inflammatory markers and clinical assessment could be used in the formation of a new diagnostic tool to evaluate psoriasis severity and response to treatment.

What's already known about this topic?

- Psoriasis is a chronic, systemic, inflammatory disease.
- Inflammatory markers are used in clinical practice to detect acute inflammation and as markers of treatment response.
- CRP has attracted the greatest attention because of its relationship with psoriasis.
- Etanercept blocks TNF-α, which plays a central role in the psoriatic inflammation process.

What this study adds

- Inflammatory markers, mainly hs-CRP and to a lesser extent, fibrinogen and ESR, can be used to assist in assessing disease severity and response to treatment in patients with psoriasis
- We suggest a new index (the Index of Psoriasis Inflammation Index, IPI) using a combination of significant selected inflammatory factors, which could reflect psoriasis inflammatory status more accurately than each one separately.

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