Biomarkers, 2009; 14(6): 432–437

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RESEARCH ARTICLE

Soluble interleukin-2 receptor serum level is a useful marker of hidradenitis suppurativa clinical staging

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Abstract

Hidradenitis suppurativa (HS) is a recurrent, debilitating suppurative skin disease. The major challenge is the choice of optimal treatment. Assessment of treatment effectiveness is currently associated with clinical observations of disease activity based on Hurley's or Sartorius' grading system. Detailed examination of patients with HS and evaluation of disease severity is frequently time-consuming and undoubtedly subjective. With regard to these factors, there is a need for laboratory findings that will help resolve the problem. The aim of this study was to determine the usefulness of soluble interleukin-2 receptor (sIL-2R) serum concentration as a marker of HS clinical staging and comparative analysis with the commonly conducted laboratory measurements, including white blood cell count, C-reactive protein and erythrocyte sedimentation rate. The statistical analysis of all these laboratory parameters conducted within a group of 54 individuals with HS revealed that sIL-2R serum level seems to be the most sensitive measurement for evaluation of disease stage. Moreover, the existence of strong dependences between sIL-2R serum concentration and Hurley's HS grading system were demonstrated. In conclusion, we believe that sIL-2R serum level could be used as a valuable marker for disease staging in patients with HS.

Keywords: *Hidradenitis suppurativa; acne inversa; sIL-2R; WBC; leukocytosis; CRP; ESR*

Introduction

Hidradenitis suppurativa (HS) is a recurrent, debilitating suppurative skin disease characterized by abscesses, fistulas and scarring with involvement of intertriginous regions – most commonly axillary, inguinal and anogenital areas. The symptoms of HS are much more than just physical. In fact, many sufferers also struggle with depression and embarrassment. Feelings of fever and fatigue often arise in extreme cases and may prevent individuals from performing everyday, common tasks (von der Werth & Jemec 2001). The major challenge is to find the exact pathogenetic explanation in order to get to the molecular heart of the disease (Kurzen et al. 2008) and, of course, the choice of optimal treatment (conservative or operative). Assessment of an effective/ineffective treatment approach is currently associated with clinical observations of disease severity based on the grading systems of Hurley (Hurley 1989) or Sartorius (Sartorius et al. 2003), and its modifications (Revuz 2007). Detailed examination of the patients and evaluation of disease activity is frequently time-consuming (especially with Sartorius' grading system) and undoubtedly subjective–deviations commonly occur when assessment is conducted by different physicians. There is a need for laboratory findings that will help resolve these problems. Therefore, there is a question demanding an answer: are the commonly conducted laboratory tests (i.e. white blood cell count (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) or others) sufficient to perform accurate HS staging analysis or do we need an alternative test?

Soluble interleukin-2 receptor (sIL-2R) is commonly regarded as one of the most important laboratory parameters that allows monitoring of the immune activation process *in vivo* (Rubin et al. 1985). Serum

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(Received 13 April 2009; revised 28 May 2009; accepted 28 May 2009)

ISSN 1354-750X print/ISSN 1366-5804 online © 2009 Informa UK Ltd
DOI: 10.1080/13547500903075218

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levels of this peptide have been estimated in many disease entities including malignancies, diseases of autoaggression and inflammation/infectious-based processes, where sIL-2R serum concentration frequently correlated with disease severity (De Rie et al. 1996, Itoh et al. 1998, Kami et al. 2000, Kapp et al. 1988, Matsumoto et al. 1998, Nakata et al. 1998, Niitsu et al. 2001, Spadaro et al. 2001, Suenaga et al. 1998, Tartour et al. 2001, Vonderheid et al. 1998). Monitoring of sIL-2R serum levels is a useful method for the assessment of disease intensity, efficacy of provided treatment, and for prediction of further illness course. A similar situation may occur in HS as it is undoubtedly an inflammatory/infectious type of disease.

Apart from a few published studies (Giamarellos-Bourboulis et al. 2007, Lapins et al. 2001, O'Loughlin et al. 1988, Wortsman et al. 2009), there are still missing data regarding the immune processes that occur in HS. We do not know, unlike in other dermatoses (e.g. psoriasis, atopic dermatitis, etc.) (De Rie et al. 1996, Kapp et al. 1988, Betti et al. 1991, Elias et al. 1993, Kägi et al. 1992, Kemmett et al. 1990), of any immunological exponent that could serve as a marker for evaluation of disease severity, as well as for monitoring effectiveness of the applied therapy. Therefore, this study was undertaken to determine if there are biomarkers for the HS staging.

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Methods

The study was conducted within a group of 54 patients (28 women, 26 men), aged 16–65 years (mean 39.94 ± 11.63) with an active, but stable, course of HS. The diagnosis of HS was established according to the following diagnostic criteria: presence of typical lesions, i.e. deep-seated inflammatory nodules (blind boils), abscesses, and/or fibrosis; involvement of intertriginous areas, i.e. groin and armpit (and secondarily, buttocks, perineum and breast); chronic course with relapses and exacerbations of disease (Poli et al. 2006). The disease duration period was from 1.5 to 36 years (mean 10.16 ± 7.64 years). Clinical manifestation of disease staging was based on the three-degree scale by Hurley (Hurley 1989) (Table 1). Among our subjects 13 patients (24.1%) were diagnosed with first degree of disease staging, 29 subjects (53.7%) fulfilled the criteria for the second degree and 12 (22.2%) suffered from the third degree stage of HS. All patients with any significant diseases or abnormalities, which could interfere with the results and their reliable presentation in the study, were excluded. One woman refused to be a blood donor, so she was also excluded from the studied cohort.

Thirty healthy volunteers (22 women, 8 men) constituted the control group. The control subjects matched for age were randomly selected among the individuals of the survey population who did not declare that they had HS or any other significant abnormalities or diseases which could interfere potentially with the studied parameters (a routine physical examination was also carried out). The mean *age of* the controls was 42.86 ± 10.24 years (range 25–60 years) and was not significantly different from the HS patients.

Table 1. Hurley's clinical grading system of hidradenitis suppurativa (HS) (Hurley 1989).

Degree of HS clinical involvement	Clinical manifestation
1st degree	One or more abscesses with no sinus tract or cicatrization
2nd degree	One or more widely separated recurrent abscesses, with a tract and scarring
3rd degree	Multiple interconnected tracts and abscesses throughout the entire affected area

Blood (7.5 ml) was sampled from each patient in the morning hours after venipuncture of a peripheral vein (vena basilica) under sterile conditions with an apirogenic syringe (S-Monovette® system with addition of coagulation activator; Sarstedt®, Nümbrecht, Germany). Collected blood samples were gently vortexed for 5 s, incubated in ambient temperature for 30 min, then centrifuged for 10 min at 2000*g*. After centrifugation, a 0.5 ml aliquot of serum was pipetted into appropriately prepared and labelled polypropylene *Eppendorf test tubes*, then stored at -70°C in a deep freezer Tiefkühltruhe TT80 (FRYKA®; Kältetechnik GmbH, Esslingen, Germany) until the enzyme-linked immunosorbent assay (ELISA). A commercially available ELISA kit to quantify sIL-2R concentration (Bender MedSystems® GmbH, Wien, Austria; cat. no. BMS212/2CE) was used. All procedures regarding the appropriate use of the ELISA kits were done according to the manuals provided by Bender MedSystems®. Quantitative analysis of sIL-2R concentration was assessed after absorbance reading of each ELISA kit's microwell containing evaluated serum on a spectrophotometer (Wallac Multilabel Counter 1420 Victor2®, Perkin Elmer Life Sciences, Boston, MA, USA) with the wavelength of 450 nm.

The rest of the routinely performed laboratory analyses, i.e. WBC (CELL-DYN® 3700; Abbott Laboratories, Abbott Park, IL, USA), CRP (Dimension® RxL Max®; Dade Behring, Atterbury, Milton Keynes, UK) and ESR (calibrator with the scale) were done after collecting blood from the same venipuncture, under the same conditions with appropriate syringes manufactured by Sarstedt® (S-Monovette® and S-Sedivette®) according to the standard of the Polish Centre for Accreditation.

After determination of the results of the investigated laboratory parameters (i.e. sIL-2R serum level, WBC, CRP, ESR) the relationships and correlations with

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selected clinical parameters of HS and related factors were conducted, including gender, age, smoking, presence of diabetes mellitus, positive family history, body mass index (BMI), Hurley's stage of disease process and disease duration.

The study was approved by the local ethical committee and written informed consents were obtained from all the studied individuals. Statistical analysis was performed with the Mann–Whitney *U* test, Kruskal–Wallis test, analysis of variance followed by the *Scheffé* post hoc test and Spearman's rank correlation coefficient. Results, in which the probability factor of making the first order error (*p*-value) was lower than 0.05, were treated as statistically significant.

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Results

Soluble IL-2 receptor

The mean sIL-2R serum level of the HS patients was 8.88 ± 4.21 ng ml^{-1} (range 2.64–23.62; median 7.9), whereas mean concentration in healthy volunteers' sera was significantly lower at 5.1 ± 1.61 ng ml^{-1} (range 2.01–7.48; median 5.2) ($p < 0.0001$).

Statistically significant differences ($p < 0.0001$) in sIL-2R serum concentrations between groups (according to Hurley's classification) were found. The detailed statistical data and differences between each particular Hurley's stages with reference to individuals' sIL-2R serum levels are shown in Table 2 and Figure 1. The patients with more severe disease had a markedly elevated serum level of sIL-2R.

The results revealed a presence of statistical significant difference regarding sIL-2R sera levels among men and women in the group of HS patients ($p < 0.001$). Among the male patients, the mean concentration of the marker was 10.62 ± 4.19 ng ml^{-1}, and among females 7.2 ± 3.56 ng ml^{-1}. No such significant differences were observed between sexes among the controls, where mean sIL-2R levels were 5.37 ± 1.26 ng ml^{-1} and 5.0 ± 1.74 ng ml^{-}1, respectively ($p = 0.57$). However, in the multivariate analysis of variance we showed that gender in itself *de facto* was not a determining factor for sIL-2R serum concentration. The differences between both groups of patients (female/male) were caused by statistically more frequent occurrence of a more severe course of HS among the male patients (Table 3).

Analysing several other factors including smoking habits, presence of diabetes mellitus and family history of HS we were unable to find any significant relationships between these factors and sIL-2R serum concentration (detailed data are shown in Table 4). Moreover there was no correlation between serum concentration of sIL-2R and BMI and duration of the HS ($R = 0.04$, $p = 0.78$ and $R = -0.03$, $p = 0.84$, respectively).

Leukocytes

Mean WBC in the HS group was $9.58 \pm 3.18 \times 10^3$ mm^{-3} (range 4.7–17.6; median 9.0). WBC was within the normal range ($4.0–10.0 \times 10^3$ mm^{-3}) among 31 patients (58.49%), while the remaining patients had leukocytosis (41.51%) (detailed data shown in Table 5). Concerning the probable alterations of WBC with reference to the disease stage (Hurley I–III) we observed statistically significant differences only between Hurley stages I and II ($p = 0.03$).

Erythrocyte sedimentation rate

Among men suffering from HS, ESR mean values were 36.58 ± 32.64 mm h^{-1} (range 6–116; median 24), whereas among women they were 26.3 ± 25.77 mm h^{-1} (range 5–105; median 16). Therefore all the obtained mean results were above the normal ranges (Table 5.). The significant differences between disease stages (assessed according to Hurley's grading system) with regard to ESR was found only for male patients – Hurley I and III ($p = 0.03$) and Hurley II and III ($p = 0.02$), while the parallel analysis performed among female patients did not reveal any relevant dependences ($p = 0.32$). Moreover, among the men a positive correlation was found between ESR and the number of skin areas involved by the HS lesions ($R = 0.41$; $p = 0.037$).

C-reactive protein

CRP mean values were 29.55 ± 46.39 mg l^{-1} (range 0.6–195; median 8.9). Among 24 patients (45.28%) CRP serum concentration was within the normal range, while in the other patients (54.72%) it was above the normal value, i.e. >7.0 mg l^{-1} (detailed data shown in Table 5). Regarding the fluctuations of CRP serum levels due to alterations of the HS stage (Hurley I–III), we found significant differences only between Hurley stages I and III ($p = 0.02$).

Table 2. Soluble interleukin-2 receptor (sIL-2R) serum concentrations (ng ml^{-1}) according to clinical staging of hidradenitis suppurativa.

						p-Value		
	No. of patients	Mean	SD	Min.	Max.	Hurley I	Hurley II	Hurley III
Hurley I	12	5.22	1.15	2.92	6.86		0.005	<0.0001
Hurley II	29	8.17	2.58	2.64	14.98	0.005		<0.001
Hurley III	12	14.26	4.25	9.54	23.62	<0.0001	<0.001	

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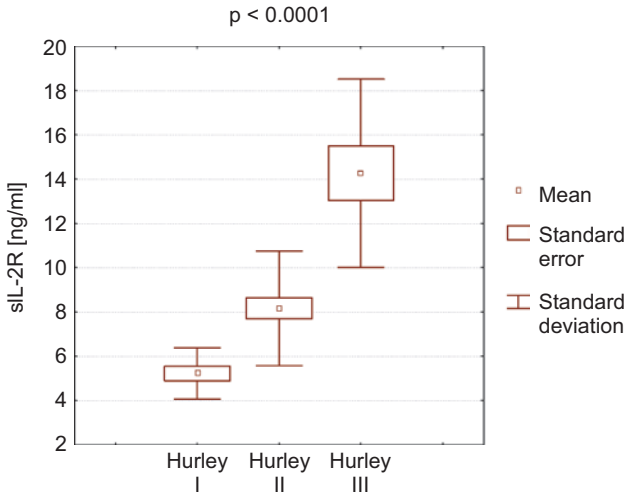

Figure 1. Mean soluble interleukin-2 receptor (sIL-2R) serum concentration (ng ml^{-1}) in hidradenitis suppurativa patients according to Hurley's staging groups.

Table 3. Distribution of hidradenitis suppurativa clinical staging with reference to the sex of the patients.

	No. of patients	Hurley I	Hurley II	Hurley III
Male	26 (100%)	2 (7.69%)	15 (57.69%)	9 (34.62%)
Female	28 (100%)	11 (39.29%)	14 (50.00%)	3 (10.71%)
Total	54	13	29	12

Discussion

According to the literature on HS, leukocytosis and elevated ESR and CRP serum levels are usually reported among the routinely obtained laboratory parameters. Similar results were observed in our study, in which among these laboratory values, CRP seems to be the most sensitive parameter – the patients with more severe clinical manifestation of disease usually had markedly elevated serum concentrations of this protein (Table 5). There was however no statistically significant differences in CRP serum levels between each of the particular Hurley groups (a significant difference was observed only between first and third degree Hurley groups).

After quantifying the sIL-2R serum concentration as the marker for HS clinical staging, it was ascertained that it is considerably more useful for monitoring the grade of immune system activation *in vivo* than the other laboratory values routinely obtained and estimated.

Noteworthy is the fact that in all cases between each of the particular Hurley groups there were statistically significant differences. Moreover, it is clear that elevation of sIL-2R serum levels corresponds with a higher stage of HS. It should be also highlighted that sIL-2R serum levels were independent of the patients' gender and age, cigarette smoking, presence of diabetes mellitus, positive family history, BMI or the disease duration.

It seems that monitoring of the sIL-2R serum concentration could be a highly effective method for performing

Table 4. Statistical data and differences between particular groups of individuals with reference to soluble interleukin-2 receptor (sIL-2R) serum concentrations (ng ml^{-1}).

	No. of patients	Mean	SD	Min.	Max.	Median	*p*-Value
Non-smokers	15	8.24	4.11	2.64	18.50	7.58	0.54
Smokers	38	9.13	4.28	2.92	23.62	8.13	
Absence of diabetes mellitus	46	9.06	4.45	2.64	23.62	8.13	0.6
Presence of diabetes mellitus	7	7.69	1.79	5.52	10.84	7.80	
Negative family history[a]	46	8.43	3.77	2.64	18.50	7.65	0.35
Positive family history[a]	4	9.82	3.98	6.86	15.67	8.38	

[a]Not all data provided by the patients.

Table 5. Statistical data and differences between particular Hurley's groups with reference to white blood cell (WBC) count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

	Hurley's stage	No. of patients	Mean	SD	Min.	Max.	Median
WBC (x 10^3 mm^{-3})	I	12	7.45	2.20	4.9	11.9	7.04
	II	29	10.10	3.11	4.7	17.6	9.70
	III	12	10.43	3.45	6.1	17.0	9.55
ESR (mm h^{-1}), M/F	I	2/10	10.00/19.30	2.83/17.90	8/7	12/66	10/12.5
	II	15/14	25.33/30.64	21.72/31.95	6/5	84/105	15/16.5
	III	9/3	61.22/29.33	37.49/12.86	23/20	116/44	48/24
CRP (mg l^{-1})	I	12	9.16	12.59	0.6	35.1	3.3
	II	29	27.96	49.44	0.9	195.0	8.60
	III	12	53.80	51.86	1.1	167.1	30.35

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a clinical estimation of HS staging, but probably also for an assessment of treatment efficacy or predicting the outcomes.

Our findings show that an increase of immune system activation could be additionally supported by anti-inflammatory therapies that have been suggested as potent treatments for HS (both traditional immunosuppressants and biologicals) (Jemec 2004). The stimulation of the immune system in HS could also be indirectly confirmed by recent reports regarding the highly effective treatment of this disease with anti-tumour necrosis factor (TNF)-α agents such as infliximab, etanercept or adalimumab (Alikhan et al. 2009). Moreover, our recent findings (unpublished data) suggest the presence of increased serum concentrations of TNF-α in HS patients, indicating activation of some other proinflammatory cytokines, including for example IL-2R (Korobowicz 2006), which may additionally support the idea of significant immune alterations in this group of patients.

Similar observations were reported in other studies of distinct dermatoses, in which the sIL-2R serum concentrations correlated positively with the severity of disease processes, being an exponent of the immune system activation level. Proportionate elevation of sIL-2R serum concentration to illness intensity was observed in diseases such as psoriasis (De Rie et al. 1996, Elkayam et al. 2000), atopic dermatitis (Colver et al. 1989, Gebhardt et al. 1997, Halmerbauer et al. 1997, Leonardi et al. 2004), chronic urticaria (Serhat Inaloz et al. 2008), erythema multiformae (Chodorowska et al. 2003), pemphigus (Zillikens et al 1993), alopecia areata (Shohat et al. 2005, Valsecchi et al. 1992) and in nodular erythema (Chodorowska et al. 2003). To the best of our knowledge our results are the first on sIL-2R serum concentration in HS patients.

There is one report (Karvonen et al. 1995) regarding sIL-2R in the patients with severe forms of acne vulgaris, a disease, which according to some authors (Plewig & Steger 1989, Sellheyer & Krahl 2005) belongs with HS in the common 'acne group' (encompassing the diseases with the same mechanism of origin – infundibular hyperkeratosis with occlusion and rupture of the hair follicle). It is noteworthy that our findings seem to be contradictory to those obtained in the study by Karvonen et al. (1995). The results reported by Karvonen et al. (1995) did not indicate any significant alterations in sIL-2R serum levels between the active and remission phases of severe acne (nodular or fulminans). However, it seems highly probable that due to a limited cohort of patients in that study (only 15 patients), their results are statistically unreliable and likely do not reflect reality. Furthermore, with regard to sIL-2R serum concentrations, HS as a disease of distinct localization, clinical course, duration and patient age, could give a completely different image of immunological state (as was demonstrated in our study).

In conclusion, we believe that the sIL-2R serum level in patients with HS could be used as a valuable marker for disease staging, and perhaps also for assessment of its severity (in the recent study by Canoui-Poitrine et al. (2009) a strongly positive association was found between the classic Hurley classification and the Sartorius score as well with intensity and duration of pain and suppuration). Therefore, further studies, especially with Sartorius' grading system may be useful to confirm our current findings.

Acknowledgements

Declaration of interests: The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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