INVESTIGATIVE REPORT

Increased Serum Tumour Necrosis Factor-α in Hidradenitis Suppurativa Patients: Is There a Basis for Treatment with Anti-Tumour Necrosis Factor-α Agents?

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Hidradenitis suppurativa (HS) is a recurrent, debilitating suppurative skin disease. Nowadays the major challenge is the choice of optimal treatment. Many conservative therapies seem to have only a supportive character and do not prevent progression of the disease. Early surgical intervention with complete excision of the involved areas is still considered to be the most efficient therapy, but anti-tumour necrosis factor (TNF-α) agents may offer a possible non-surgical treatment. The aim of this study was to determine the serum concentration of TNF-α and its probable alterations during the disease process in patients with HS. Analysis of TNF-α serum concentration in 54 individuals with HS revealed significantly higher levels than in the sera of healthy controls (p = 0.006). To the best of our knowledge, this is the first report of increased TNF-α serum concentration in patients with HS.

Key words: hidradenitis suppurativa; acne inversa; TNF-α; infliximab; etanercept; adalimumab.

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Sotiriou et al. (1) report the usage of etanercept for the treatment of hidradenitis suppurativa (HS). With reference to this paper and other reports of similar treatment regimens in HS we hypothesized that serum levels of tumour necrosis factor (TNF-α) are increased in patients with HS.

HS is accompanied by physical and psychological symptoms. Fever and fatigue are often present in extreme cases and may prevent individuals from performing common everyday tasks (2, 3). Many conservative therapies (including systemic antibiotics, retinoids, sulphones, and anti-androgens) seem to have only a supportive character and do not prevent progression of the disease. Early surgical intervention with complete excision of the involved area is considered the most efficient therapy (4, 5). There are a few case reports of effective treatment of HS with anti-TNF-α agents, such as infliximab (6–9), etanercept (1, 10–12) or adalimumab (13–15), used as off-label drugs. This study measured serum levels of TNF-α cytokine in subjects with HS.

MATERIALS AND METHODS

The subjects were 54 patients (28 women, 26 men) aged 16–65 years (mean 39.9 ± 11.6 years) with HS who qualified for surgical treatment in our department. The disease duration was in the range 1.5–36 years (mean 10.1 ± 7.6 years). Clinical manifestation of disease severity was based on Hurley’s 3-degree scale (16). Among the 54 subjects 13 (24.1%) were diagnosed as Hurley stage I, 29 (53.7%) as Hurley stage II and 12 (22.2%) as Hurley stage III. All patients with any significant diseases or abnormalities that could interfere with the obtained results were excluded. One woman also refused to provide blood samples and was therefore excluded from the studied cohort. Thirty healthy volunteers (22 women, 8 men) constituted the control group. The mean age of the controls was 42.8 ± 10.2 years (age range 25–60 years) and was not significantly different from the HS patients.

Blood (7.5 ml) was sampled from each subject in the morning. A commercially available enzyme-linked immunosorbent assay (ELISA) kit to quantify TNF-α concentrations (Bender Med-Systems™ GmbH, Vienna, Austria; catalogue no. BMS223/4CE) was used. All procedures were carried out according to the manufacturer. Quantitative analysis of the TNF-α concentration was assessed after absorbance reading of each ELISA kit’s microwell containing evaluated serum on a spectrophotometer (Multilabel Counter 1420 VICTOR™, Wallac, Turku, Finland) with a wavelength of 450 nm. After determination of the serum level of TNF-α, correlation with selected clinical parameters of HS was carried out, including sex, age, smoking, presence of diabetes mellitus, positive family history, body mass index (BMI), severity of disease and its duration.

The study was approved by the local ethics committee and written informed consent was obtained from all studied individuals. Statistical analysis was performed with the Mann-Whitney U test, Kruskal-Wallis test and Spearman’s rank correlation coefficient. Results with p-values less than 0.05 were treated as statistically significant.

RESULTS

The mean TNF-α serum level of the patients with HS was 8.8–13.1 pg/ml (range 6.0–99.6 pg/ml), which was significantly elevated (p = 0.006) compared with that found in healthy volunteers (6.3 ± 0.4 pg/ml (range 5.8–7.5 pg/ml)). We did not observed any significant differences between the Hurley’s groups (p = 0.91) (Table I). Moreover, there was no tendency towards higher serum concentration of TNF-α in patients with
Table I. Tumour necrosis factor-alpha (TNF-α) serum concentrations according to clinical severity of hidradenitis suppurativa (HS) (Hurley’s clinical grading system)

<table>
<thead>
<tr>
<th>Clinical grade of HS</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hurley I</td>
<td>13</td>
<td>6.90</td>
<td>1.46</td>
<td>6.16</td>
<td>11.26</td>
<td></td>
</tr>
<tr>
<td>Hurley II</td>
<td>29</td>
<td>10.71</td>
<td>17.74</td>
<td>6.00</td>
<td>99.56</td>
<td>0.91</td>
</tr>
<tr>
<td>Hurley III</td>
<td>12</td>
<td>6.37</td>
<td>0.18</td>
<td>6.16</td>
<td>6.70</td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation.

more advanced disease (R = –0.06, p = 0.69). The number of skin areas involved by the HS lesions did not correlate with TNF-α serum levels (R = –0.17; p = 0.23). Analysing several other factors, including gender, smoking habits, presence of diabetes mellitus and family history of HS, we found no significant correlations between those factors and TNF-α serum concentration (detailed data are shown in Table II). Moreover, there was no correlation between serum concentration of TNF-α, BMI and duration of HS (R = –0.15, p = 0.28 and R = –0.11, p = 0.43, respectively).

DISCUSSION

To the best of our knowledge, this is the first report of increased TNF-α serum concentration in patients with HS. No significant dependence or correlation was shown between TNF-α serum levels and the other factors evaluated, in particular disease severity (including intensity of inflammation).

TNF-α serum concentrations reported in other studies also suggest that this cytokine may be increased in various inflammatory skin conditions, including psoriasis (17–19), lupus erythematosus (20, 21), pemphigus vulgaris and bullous pemphigoid (22) and lichen planus (23). The TNF-α levels found in the above-mentioned dermatoses were 5.5–35.6 pg/ml and <0.1–17.1 pg/ml among healthy volunteers, i.e. ranges which encompass our results. Moreover, the observed elevations of TNF-α serum levels were rarely significantly correlated with disease severity, even in studies of psoriasis (17, 18), which is very responsive to anti-TNF-α treatment.

It is noteworthy that the results of our study do not concur with those obtained by Giamarellos-Bourboulis et al. (24). To the best of our knowledge their publication is the first to study probable changes in TNF-α due to the alterations in the immune system state occurring in HS. They assumed that monocytes isolated from HS patients’ peripheral blood had poorer ability to respond to lipopolysaccharide (LPS) stimulation, as manifested in the production and secretion of TNF-α (and IL-6), than monocytes isolated from healthy people. On the subject of immunological state in HS, opinions are divided; Giamarellos-Bourboulis et al. (24) revealed some defects, whereas other authors (25, 26) have not identified any alterations in patients’ immune functioning.

It should be pointed out, however, that Giamarellos-Bourboulis et al.’s study (24) was performed in vitro, while ours was carried out in vivo, with whole relationships between cells and secreted cytokines due to immune system influence. This is one factor that may account for discrepancies in the obtained results. Moreover, prior exposure of macrophages to bacterial ligands may decrease their ability to produce TNF in response to subsequent LPS-stimulated activation (27). Therefore, it is possible that the reported monocyte “exhaustion” (24) may be due to their earlier exposure to the bacterial ligands in vivo.

Another factor that may influence outcome and cause a lack of consistent results, is that Giamarellos-Bourboulis et al. (24) focused only on monocytes. Although that monocytes are the main source of TNF-α secretion, it should be remembered that other cells also secrete this cytokine, including T cells and B cells, natural killer cells, neutrophils, mastocytes, fibroblasts, keratinocytes, osteoblasts, astrocytes, adipocytes and smooth muscle cells (28).

In conclusion, we believe that increased serum levels of TNF-α exist in patients with HS and that this may support wider usage of treatment with anti-TNF-α agents in this group of patients. However, based on current data, TNF-α does not appear as a good marker for conducting clinical monitoring of disease activity. Further blinded, controlled studies are mandatory to clarify the effectiveness of TNF-α antagonists, however the recent article clearly suggests its value in HS (29).

Table II. Statistical data and differences between particular groups of patients with hidradenitis suppurativa (HS) with reference to tumour necrosis factor-alpha (TNF-α) serum concentrations

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>26</td>
<td>10.21</td>
<td>18.29</td>
<td>6.00</td>
<td>99.56</td>
<td>0.12</td>
</tr>
<tr>
<td>Females</td>
<td>27</td>
<td>7.57</td>
<td>4.80</td>
<td>6.10</td>
<td>31.08</td>
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<tr>
<td>Non-smokers</td>
<td>15</td>
<td>8.75</td>
<td>6.48</td>
<td>6.10</td>
<td>31.08</td>
<td>0.09</td>
</tr>
<tr>
<td>Smokers</td>
<td>38</td>
<td>8.91</td>
<td>15.13</td>
<td>6.00</td>
<td>99.56</td>
<td></td>
</tr>
<tr>
<td>Diabetes – No</td>
<td>46</td>
<td>7.21</td>
<td>3.85</td>
<td>6.00</td>
<td>31.08</td>
<td>0.6</td>
</tr>
<tr>
<td>– Yes</td>
<td>7</td>
<td>19.72</td>
<td>35.21</td>
<td>6.22</td>
<td>99.56</td>
<td>0.5</td>
</tr>
<tr>
<td>History of HS – No</td>
<td>46</td>
<td>7.21</td>
<td>3.85</td>
<td>6.00</td>
<td>31.08</td>
<td>0.5</td>
</tr>
<tr>
<td>– Yes</td>
<td>4</td>
<td>6.49</td>
<td>0.26</td>
<td>6.16</td>
<td>6.70</td>
<td></td>
</tr>
</tbody>
</table>

*Family history; partial data provided by patients.

REFERENCES

Increased serum TNF-α in hidradenitis suppurativa


Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. Mediators Inflamm 2005; 2005: 273–279.


