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Serum TNF- α in psoriasis after treatment with propylthiouracil, an antithyroid thioureylene

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Abstract

Background: Tumor necrosis factor- α (TNF- α) and its receptors play important roles in the development and persistence of psoriatic plaques. The antithyroid thioureylenes, propylthiouracil and methimazole, are effective in the treatment of patients with psoriasis with a significant number of patients showing clearing or near clearing of their lesions after a several weeks of treatment.

Methods: The present study examined the effect of treatment with propylthiouracil, given in a dose of 100 mg every 8 hours for 3 months, on the serum levels of TNF- α in 9 patients with plaque psoriasis.

Results: Propylthiouracil therapy did not result in a significant decline in serum TNF- α concentrations.

Conclusions: The findings suggest that the therapeutic effect of propylthiouracil in psoriasis appears not to be related to any change in the concentration of TNF- α but occurs via an anti-proliferative mechanism as we have previously speculated.

Background

Psoriasis is a common skin disorder that affects approximately 2.8 percent of the population and is associated with morbidity that is comparable that seen with life threatening disease [1,2]. There is a clearly established genetic predisposition to the disease [3,4] that is often triggered by the processing of bacterial, viral or chemical antigens by skin antigen presenting cells (APC) or Langerhans cells [5-9]. The disease is presently believed to be a T cell disorder that leads to keratinocyte proliferation [6,10,11]. Plaque formation in the disease reflects both the effects of accelerated proliferation as well as reduced apoptosis in proliferated keratinocytes [12,13]. The events responsible for keratinocyte proliferation have been

extensively reviewed [12]. An important cytokine that is associated with keratinocyte proliferation in psoriasis is TNF- α . TNF- α concentrations are higher in psoriatic lesions than in unaffected skin of psoriatic patients and tend to decline with clearing of the lesions after effective therapy [14-16]. This cytokine is produced by keratinocytes and leads to an increased expression of cellular adhesion molecules that promote, propagate, and amplify the immune signals that are responsible for maintaining the events that lead to psoriasis. Recently introduced therapeutic approaches in the management of psoriasis depend on blocking TNF- α binding to its receptor by using TNF- α hybrid antibodies. Patients treated with such agents very often show marked improvement in their disease with

major clearing in several instances [17-19]. Present day therapy of the disease is not particularly satisfactory and the many therapies currently in use are associated with significant cumulative toxicity [17]. The antithyroid thioureylenes have been used in the treatment of patients with hyperthyroidism, particularly Graves' disease, and have well-defined and very limited toxicity. They have been used for management of patients with Graves' hyperthyroidism for many years without any significant problems. We and others have described the effectiveness of these agents in the treatment of patients with plaque psoriasis [20-24]. The mechanism of action of these drugs in psoriasis is unknown but some evidence points to their ability to act as anti-proliferative agents. The drugs reduce expression of proliferative cell nuclear antigen (PCNA) a marker of cellular proliferation [25]. Since plaque formation in psoriasis is dependent on enhanced proliferation of keratinocytes particularly in the basal layers of the epidermis any agent that could reduce this critical event in the pathogenesis of psoriasis would lead to clinical improvement. The present study was performed to examine the effect of treatment with propylthiouracil on circulating TNF- α in patients with stable plaque psoriasis.

Methods

Patients

Nine patients (6 male, 3 female) enrolled in the study. The patients ranged in age from 21 to 65 years (mean \pm SD, 44 ± 16 yrs). None of the patients received phototherapy or systemic treatment for six weeks and none used topical therapy other than emollients for six weeks prior to entry into the study. Patients with allergies to sulfa medication, pregnant patients, and patients with a known diagnosis of thyroid dysfunction were excluded from participating in the study. All patients signed an informed consent document approved by the Institutional Review Board of the University of California, Irvine. The enrolled volunteers had a complete blood count (CBC) and measurement of thyroid stimulating hormone (TSH) before starting treatment with propylthiouracil (PTU). CBC and TSH measurements were obtained again at 2 weeks and later at 4, 8 and 12 weeks. In addition, blood was removed for measurement of TNF- α prior to PTU treatment and again at 2, and 12 weeks later. The blood for TNF- α measurements was collected in tubes containing peptide inhibitors, and the serum removed and stored at -70°C until assayed. Patients were instructed to take 100 mg PTU every 8 hours for twelve weeks.

Clinical assessment

Clinical evaluation was performed by a single dermatologist (VSN). Evaluation was performed before enrollment, and again at 4, 8 and 12 weeks after PTU therapy. Assessment was made using the PASI scoring system.

Measurement of TNF- α

TNF- α levels in serum were measured using a highly sensitive commercially available assay from R&D Systems (Minneapolis, MN). The assay is a sandwich enzyme immunoassay (ELISA) with an analytical sensitivity of < 0.2 pg/ml. Intra- and interassay variations are less than 11.3 and 14.7 % respectively. The reference range for normal volunteers is between 1.2 and 15.3 pg/ml.

Statistical analysis

Statistical analysis was performed using Student's *t* test for paired and grouped data. *P* of < 0.05 was considered significant.

Results

Clinical scores

All patients showed clinical improvement with PASI scores declining from 20.1 ± 6.6 to 15.8 ± 4.9 at 4 weeks ($P < 0.02$), 11.0 ± 4.8 at 8 weeks ($p < 0.0001$) and 6.7 ± 4.3 after 12 weeks ($p < 0.0001$) of PTU therapy.

Serum TNF- α concentrations

Serum TNF- α concentrations were 5.1 ± 2.3 pg/ml before treatment and did not show significant decline at 2 weeks (5.1 ± 2.16 pg/ml) and 12 weeks (4.96 ± 2.8 pg/ml) of treatment.

Side effects

None of the patients experienced any side effects from PTU treatment. As previously described, white blood count remained within the normal range during the entire study, the serum TSH concentration did not rise above the upper normal range, and neither did any patient develop signs or symptoms of hypothyroidism.

Discussion

Activated Th1 cells which produce TNF- α and interferon- γ (IFN- γ) are important in the pathogenesis of psoriasis [12,26]. These cytokines promote expression of adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule (VCAM) on keratinocytes and vascular endothelial cells thereby facilitating migration of additional pro-inflammatory cells to the area of the psoriatic plaque resulting in the cytokine cascade that ultimately results in enhanced keratinocyte proliferation and formation of the lesions characteristic of the disease [27]. Keratinocytes that have undergone proliferation, as well as dendritic cells and skin macrophages, produce TNF- α that leads to an amplification of the Th1 role in formation of the psoriatic plaque. In recent months there have been several studies that have exploited the use of designer antibodies directed against the binding of TNF- α to its receptor (etanercept) [19] or that prevent the association of leucocyte-function associated antigen (LFA) and ICAM-1 (efalizumab) [28]. There

is significant clinical improvement in patients treated with these agents. There is, however, loss of clinical benefit after the drugs are stopped and a small proportion of patients develop antibodies to the agents which is likely to limit their efficacy with repeated use. The antithyroid thioureylenes, in contrast, are easily administered oral medications that cost a mere fraction of the amount necessary to treat a patient with psoriasis with a designer antibody. The mechanism of action of antithyroid thioureylenes in psoriasis is unclear. Based on our previous observations, the drugs do not appear to produce any change in circulating IL-2 receptor or ICAM-1 [29], and lack effects on pro-inflammatory cytokines such as IL-12 or anti-inflammatory cytokines such as IL-10 [30]. The drugs do, however, produce a significant decline in markers of cellular proliferation, particularly in proliferative nuclear cell antigen (PCNA) expression [25] suggesting that the principal therapeutic benefit of these drugs in psoriasis may be exerted via their anti-proliferative effect.

Conclusions

The lack of any effect on circulating TNF- α in this study argues against any effect of propylthiouracil on keratinocyte production of TNF- α . Since PTU and other antithyroid thioureylenes cause a decrease in keratinocyte proliferation one would expect a fall in TNF- α concentration after use of these agents in patients showing significant clinical improvement. The fact that this did not occur requires further investigation.

Competing interests

None declared.

Authors' contributions

ANE was involved in the developing the hypothesis for the study design and writing the manuscript; VSN recruited the patients for the study and performed the necessary clinical assessments; RP assisted with the assay of TNF- α .

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