Original Research Paper

Serum TGF-β and TNF-α During Psoriasis Therapy with Narrowband Ultraviolet B

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Abstract: Although it is now an accepted concept that narrow-band UVB therapy is an efficacious therapy for psoriasis, the relationship between the response rate and the potential effects on serum cytokines is less well-established. The purpose of this study was to investigate the correlation between the response rate and the changes of serum TGF-β and TNF-α necessary for understanding the underlying mechanisms of narrow-band UVB phototherapy. NB-UVB is effective against psoriasis without any obvious side effects and can significantly decrease serum TNF-α and promote TGF-β level of psoriasis patients. Additionally, measurement of TGF-β and TNF-α in serum could be considered as biomarkers of psoriasis activity during NB-UVB therapy.

Keywords: Psoriasis, Narrow-Band Ultraviolet B (NB-UVB), Serum Transforming Growth Factor-β (TGF-β), Tumour Necrosis Factor-α(TNF-α)

Introduction

Psoriasis, a chronic T-cell mediated autoimmune disease characterised by keratinocyte hyperplasia and increased dermal vascularity, affects approximately 2.5% of the population worldwide. It is thought that proliferation of keratinocyctes is due to cytokines produced by activated T cells. These T-cells that are activated generate a number of cytokines such as Tumour Necrosis Factor-alpha (TNF-α), interferon-γ, interleukin-2, interleukin-12 and interleukin-8. Tumour Necrosis Factor-alpha (TNF-α) has an essential role in the pathogenesis of psoriasis, noteably through inducing keratinocytes to express intercellular adhesion molecule-1 and other cell adhesion molecules on dermal microvascular endothelium (Mazza *et al*., 2010; Abbadi *et al*., 2010). Furthermore, keratinocyte hyperproliferation is believed to be a consequence of imbalance of growth factors responsible for epidermal proliferation together with modified metabolism of their receptors in affected skin. Lack of down-regulation of TGF, a potent growth inhibitor for human keratinocytes, is therfore thought to be an important factor in the pathogenesis of psoriasis. Indeed, significant positive correlations between TGF-β and the PASI score have been reported recently (Kitoh *et al*., 2013; Flisiak *et al*., 2008).

Ultraviolet-B (UVB) is currently one of the widely used treatments due to its therapeutic efficacy for patients with moderate to severe psoriasis. UVB treatment is more convenient for the patient to perform, requires fewer precautions to prevent acute adverse reactions and seems to have considerably lower hazardous effects of irradiation than conventional phototherapy (Yuehua *at al*., 2008). Its therapeutic action, which involves several mechanisms, is known to affect cytokine expression. Recognized mechanisms include the induction of anti-inflammatory effect and also immunosuppressive cytokines that deplete dermal and epidermal T cells from psoriatic lesions, probably by increasing apoptosis (Chen *at al*., 2013).

Materials and Methods

Forty-three outpatients with psoriasis vulgaris attending our hospital startnig from January 2003 to January 2006 were selected to participate in the experiment. All patients have typical skin lesions with clear clinical diagnosis. Of the selected subjects 23 were males and 20 females with ages ranging from 16 to 61 years old and a mean age of 37.1+8.3. The course of disease ranged from two weeks to 21 years, with a mean of 7.5+4.3 years. All the selected patients were early-onset psoriasis patients and had not received any kind of phototherapy therapy for three months before the treatment and had no any oral or external drug were taken for one month before the

treatment. None of the subjects had serious heart, liver or kidney disease. The study was cleared by the local institutional ethics committee and formal consent from subjects was obtained before treatment started. Thirty healthy volunteers were selected as a healthy control group. The composition of age and sex for the treatment group and the control group had no statistical significance: Age (t = 0.74, p>0.05), gender (t = 0.55, p>0.05).

The patients in the treatment group were treated with NB-UVB radiation using a UV100L system with a radiant Intensity of 9.13 mW/cm^2 and wavelength of 309-313 nm, produced by Waldmann Co., Ltd of Germany. The Minimal Erythema Doses (MED) were set as 0.6 J/cm^2 and the initial radiant dose was set as 50% MED (0.3 J/cm^2). The dose was increased by 10% at each subsequent exposure and maintained until light erythema appeared at the radiated site. In cases involving the appearance of painful erythema, the treatment was withheld until the erythema had disappeared. After its disappearance, the initial radiant dose was reset at 50% of the previous one and progressively increased by 10% until light erythema appeared, so that the MED could be detected in all subjects. Treatment was delivered three times a week for six weeks or until lesions cleared. The healthy control group did not undergo any treatment.

Venous blood was collected from all subjects before and after radiation; serum was isolated under sterile conditions, sealed and then placed at -20°C for examination. The TGF-β kit and TNF-α Elisa kit were both produced by Jingmei Biotech Co. Ltd and the technique was carried out strictly according to the kit instructions. The minimum detectable dose for each cytokine measured was TGF-β = 9.0 pg/mL and TNF-α = 43pg/mL. On the last day of the study (24 h after the last UV exposure) blood samples were collected. PBS liquid was selected as a negative control, samples were assayed in pairs and results were obtained from their mean.

Results

After the 18 exposures, the mean cumulative dose received was 16.10±4.13 J/cm^2 while the mean PASI score of pre-treatment and post-treatment were (11.6±4.1) and (2.2±0.9), respectively. This showed a statistically significant improvement in PASI (p<0.01).

The comparison of detected results of pre- and post-treatment serum TNF-α and TGF-β for subjects of both groups is shown in Table 1 and 2.

As shown in the tables, differences in TNF- α and TGF-β contents between the healthy control group and psoriasis patients were of statistical significance (p<0.01).

Table 1. Comparison of detected results of before- and after-treatment serum TGF-β in patients of two groups

Groups	Cases	Before Treatment TGF-β(pg/mL)	After treatment TGF-β(pg/mL)	p1	p1
Treatment	43	683.6±118.9	813.4 ±98.5	<0.001	<0.001
Control	30	892.7±120.8			

P^1 values of the treatment group before and after treatment: p2 Values between the two groups

Table 2. Comparison of detected results of before and after-treatment serum TNF-α in patients of two groups

Groups	Cases	Before treatment TNF-α(ng/mL)	After treatment TNF-α(ng/mL)	p1	p2
Treatment	43	53.65±26.78	21.81±8.31	<0.001	<0.001
Control	30	1.28 ±0.57			

P^1 values of the treatment group before and after treatment: p2 Values between the two groups

Discussion

Whereas the primary mechanism triggering psoriasis is still a matter of controversy, the keratinocytes of psoriatic patients are unique in their capacity for hyperproliferation and altered differentiation, controlled by the interactions between keratinocytes and infiltrating immunocompetent cells via nemurous cytokines. Therefore, these cytokines are believed to play specific roles in the immunopathogenesis of psoriasis. Abnormal hyperproliferation of keratinocytes is possibly the result of an insufficient inhibitory effect of TGF-β. TGF-β has regulatory effects on both cell growth and differentiation. TGF-β is a strong inhibitor of epithelial proliferation and its special influence on growth and differentiation have been recognised in cultured keratinocytes and describedas responsible for growth inhibition of the epidermis and maintenance of homeostasis (Mazza et al., 2010).

Three isoforms of TGF-β, namely TGF-β1, TGF-β2 and TGF-β3, have been identified in human tissues. TGF-β can only apply its biological effects, such as inhibiting Malpighian cell growth after being bound with a special receptor. It plays an important role in cell growth, differentiationand immunological regulation (mainly negative regulation). The process of producing is also controlled by other cytokines such as TNF-α (Mazza et al., 2010; Ahmed et al., 2013). Moreover, there is a certain relation between the anti-inflammatory and anti-chemotactic effects of TGF-β and the pathological process of psoriasis. Therefore it is obvious that these cytokines can act as multifunctional regulators of both cell growth and differentiation and seem to be very important in the pathogenesis of psoriasis. The mean values of serum TGF-β levels in patients with psoriasis in this study were obviously lower than those of the healthy control

group. After patients were radiated with NB-UVB, their serum TGF-β contents were markedly increased, which may be related to the decreased multiplication activity of patients' keratinocytes under the effect of NB-UVB radiation. The exact mechanism, however, requires further study.

TNF-α is an important pro-inflammatory cytokine with multi-effects and can promote the generation of many cell factors, quicken inflammatory formation of skin lesions and promote the multiplication of Malpighian cells. One of the possible mechanisms of TNF-α during psoriasis onset is mediated by protease inhibitor, a factor that induces abnormal cell multiplication and differentiation during psoriasis. TNF-α can induce the expression of aprotease inhibitor at both mRNA and protein levels. In addition, TNF-α can stimulate epithelial cells to secrete elafin, which isan elastase inhibitor which can cause neutrophilic granulocyte infiltration in psoriatic lesions. TNF-α can also promote endothelial cells and Malpighian cells to express intercellular adhesion molecule-1, a crucial effect for lymphocytic infiltration in psoriasis lesions. (Mazza *et al.*, 2010;Tanaka *et al.*, 2000).

Mean TNF-α serum levels demonstrated in the psoriatic patients included in our study were much higher than those of the healthy control group, which is in accordance with the results of recent studies (Gan *et al.*, 2005; Zheng *et al.*, 2004; Zalewska *et al.*, 2006). Serum TNF-α level was decreased after the patients were treated with NB-UVB, which indicates NB-UVB radiationapplies its curative effect on psoriasis by inhibiting inflammatory mediators (such as TNF-α).

Finally, our study sheds light on some aspects of the mechanisms of cytokine responses after NB-UVB therapy in psoriatic patients. Although the serum cytokine data appear interesting, it remains unclear if the observed changes represent direct effects of UVB irradiation or if they reflect the overall disease activities before and after the treatments. Future studies are needed to investigate whether these changes in the levels of the cytokines are attributed to consequential effects of UVB radiation on different cells production capacity or due to decreased number of inflammatory cells producing these cytokines. Thus, measurements of TGF-β and TNF-α in serum could be considered as biomarkers of psoriasis activity during NB-UVB therapy.

Conclusion

NB-UVB can significantly decrease serum TNF-α and promote TGF-β level of psoriasis patients. Additionally, measurement of TGF-β and TNF-α in serum could be considered as biomarkers of psoriasis activity during NB-UVB therapy.

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