Montrouge, le 04/11/2011

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paru dans
European Journal of Dermatology, 2011, Volume 21, Numéro 1

John Libbey Eurotext

Eur J Dermatol 2011; 21(1): 53-7

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Article accepted on 10/26/2010

Systemic photochemotherapy decreases the expression of IFN-γ, IL-12p40 and IL-23p19 in psoriatic plaques

Psoriasis vulgaris (PV) is a chronic skin disease with unclear pathogenesis. In the present study we investigated the effect of systemic photochemotherapy (PUVA therapy- psoralen and UVA therapy) on the expression of IFN-γ, IL-12p40 and IL-23p19 in lesional psoriatic skin. Fifteen patients with chronic plaque type psoriasis selected to be treated with PUVA therapy were recruited for this study. Expression of IFN-γ, IL-12p40 and IL-23p19 in psoriatic lesions before and after twenty PUVA treatments was established by using immunohistochemistry (IHC). A significant decrease in expression ($p < 0.05$) of IFN-γ, IL-12p40 and IL-23p19 in epidermis and dermis of psoriatic lesions was observed. The immunosuppressive effect of PUVA therapy presented with decreased expression of biologically active IL-23 (IL-12/IL-23p40 + IL-23p19) as a part of the Th17 pathway, and IFN-γ (Th1 pathway) led, in our patients, to a marked clinical improvement as shown by PASI (before therapy 20.55 and after therapy 3.33).

Key words: interferon-γ, interleukins, psoriasis, PASI, PUVA therapy

Psoriasis vulgaris (PV) is a chronic skin disease with an unclear pathogenesis. It affects 2-3% of the population worldwide [1]. It is generally accepted that in persons with a genetic predisposition to psoriasis, immunological disturbance leads to the metabolic and inflammatory changes. These changes result in an increased epidermal turnover and hyper proliferation, vascular hyperplasia and infiltration of inflammatory cells in affected skin [1-3].

First, it was considered that psoriasis is mediated by Th1 cells that secrete interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) [1]. Interleukin-12 (IL-12), (consisting of the p40 subunit which is covalently bound to unique p35 subunit) induces differentiation of naïve T cells to Th1 cells which produce IFN-γ [4, 5]. IFN-γ is highly expressed in psoriatic lesions compared to non-psoriatic skin [6]. Antigenic stimulation leads to production of IL-12 mainly by dendritic cells, macrophages and neutrophils [4]. The discovery of IL-23 [7], led researchers to believe that IL-23 promotes similar functions to IL-12 since they are structurally related (IL-23 consists of the common p40 subunit bound to unique p19) [4, 5]. However, recent findings suggest that IL-23 has a role in the development/maintenance of a distinct T cell subset, known as Th17 cells. Th17 cells are involved in the production of interleukin-17 (IL-17A), interleukin-17F (IL-17F), interleukin-6 (IL-6), TNF-α and interleukin-22 (IL-22) [1, 8]. IL-23 (overproduced by dendritic cells and keratinocytes in psoriatic patients) is elevated in psoriatic lesions, as indicated by an increased expression of p40 and p19. However, expression of p35 is not increased in psoriatic skin [1]. These findings imply that Th17 cytokines (IL-23 and IL-17) play a more dominant role than Th1 cytokines (IFN-γ and IL-12) in psoriasis [1].

Previously, it was generally accepted that IFN-γ has a suppressive effect on Th17 cells and IL-17 production [9]. But the fact that these two cytokines (IFN-γ and IL-17) often colonize same pathogenic environment gave rise to the idea that their action is not so divergent [10]. It has been demonstrated that a small subset of Th17 cells (IFN-γ+IL-17+ Th cells) produce IFN-γ in humans [11]. Moreover, IFN-γ promotes trafficking, induction and functioning of IL-17 + T cells in people with psoriasis [10]. In psoriasis, it is proposed that IL-17 and IFN-γ have a synergized effect on the increased production of proinflammatory cytokines (TNF-α, interleukin-1β, interleukin-6 and interleukin-8), antimicrobial peptides and various chemokines by keratinocytes [12]. This disturbance in the cytokine network leads to the development of inflammation in the psoriatic skin [12]. With these mediators, keratinocytes have active support for further influx of immune cells (T cells, natural killer T cells, dendritic cells and neutrophills) in the skin. The biology of keratinocytes changes, resulting in increased proliferation and altered differentiation [12, 13]. Since their importance in its pathogenesis has been established, therapies targeting especially Th17 (IL-23/IL-17) and also Th1 (IFN-γ/IL-12) pathways have become highly recommended for psoriasis [14].

Abbreviations: PV, psoriasis vulgaris; IFN-γ, interferon gamma; IL-12p40, interleukin-12p40 subunit; IL-23p19, interleukin-23p19 subunit; PUVA, psoralen and UVA therapy; IL-17, interleukin-17; IL-17F-, interleukin-17F; IL-6-, interleukin-6; TNF-α, tumor necrosis factor α; IL-22, interleukin-22; ICAM-1, intracellular adhesion molecule 1; IHC, immunochistochemistry; PASI, psoriasis area and severity index

doi:10.1684/ejd.2010.1199

To cite this article: Ravić-Nikolić A, Radosavljević G, Jovanović I, Zdravković N, Mitrović S, Pavlović S, Arsenijević N. Systemic photochemotherapy decreases the expression of IFN-γ, IL-12p40 and IL-23p19 in psoriatic plaques. *Eur J Dermatol* 2011; 21(1): 53-7 doi:10.1684/ejd.2010.1199