Journal of Dermatological Science 96 (2019) 110–112

Contents lists available at ScienceDirect

Journal of Dermatological Science

journal homepage: www.jdsjournal.com

Letter to the Editor

Effective treatment with balneophototherapy and narrowband UVB monotherapy reduces skin homing Th17/Tc17 and Th22/Tc22 effector cells in peripheral blood in patients with psoriasis

Psoriasis is a chronic autoimmune disease of the skin that is characterized by epidermal thickening and infiltration of immune cells into the skin. It is a T cell mediated disease with a mixed T helper (Th)1/Th17 phenotype [1]. IL-17 is the key mediator of psoriatic inflammation and drives the production of proinflammatory cytokines and chemokines by keratinocytes, and consequently activates leukocytes and recruits them into the skin [2]. Limited data exists regarding the molecular mechanisms underlying the efficacy of narrow-band (NB)-UVB phototherapy combined with balneotherapy (bathing in geothermal seawater, the Blue Lagoon of Iceland) in psoriasis but it has been previously shown to have beneficial therapeutic effects on psoriasis [3,4]. The aim of this study was to evaluate the impact of phototherapy and balneotherapy in both peripheral blood and lesional skin in psoriasis.

Twenty-one patients with psoriasis were randomly assigned to three groups, where all three received NB-UVB phototherapy for six weeks and two additionally different balneotherapy (closer description of different groups can be found in Eysteinsdóttir et al. 2014 [3]). Blood from healthy individuals was collected as a control. Disease severity (Psoriasis Area and Severity Index; PASI) was recorded, blood and skin samples obtained before, after 2 weeks and at the end of treatment. PASI score was the same for all groups before start of treatment. Expression of cytokines and skin homing molecules by $CD4^+$ and $CD8^+$ T cells was evaluated in blood by flow cytometry. Histological and immunohistological staining of skin samples were used to evaluate the histological score (Trozak) and the expression of $CD4^+$ and $CD8^+$ T cells and IL-17 (evaluated by three independent viewers (visual score)). Only samples of good quality were scored. This research was approved by the Icelandic National Bioethics Committee (08-097-S1) and patients provided written consent to participate in the study.

Patients improved, both in the clinical PASI scores and the histological Trozak score, with all treatment regiments (data not shown). The percentage of circulating Th17 ($CD4^+CD45RO^+IL\text{-}23R^+$ T cells) and Tc17 ($CD8^+CD45RO^+IL\text{-}23R^+$ T cells) cells reduced more than 60% in psoriasis patients after only two weeks and over 80% after six weeks of treatment, which correlated with reduction in both PASI and Trozak scores (Fig. 1A–B). The reduction in Th17 cells in psoriasis patients was confirmed by intracellular IL-17 staining after 6 weeks ($p < 0.05$, data not shown). The percentage of T cells producing IL-22 ($CD4^+IL\text{-}22^+$ or $CD8^+IL\text{-}22^+$ T cells) decreased after both 2 weeks ($p < 0.05$) and 6 weeks ($p < 0.01$) of treatment in psoriasis patients and correlated with the PASI score (data not shown). The percentage of $CD4^+$ and $CD8^+$ T cells secreting IFNγ, TNFα and IL-4 was higher in untreated psoriasis patients compared with healthy controls ($p < 0.05$, except of IL-4 secretion by $CD8^+$ T cells), which was not affected by treatment (data not shown). Immunohistological analysis of psoriatic skin revealed a significant reduction of the number of $CD3^+$, $CD4^+$, $CD8^+$ in the skin after 6 weeks of treatment (Fig. 1C) and the staining score of IL-17 in the dermis decreased in correlation with the PASI score (stained at 0 and 6 weeks, Fig. 1D).

The percentage of circulating Th17 and Tc17 cells expressing the skin homing molecule CLA ($CD4^+CLA^+IL\text{-}17^+$ and $CD8^+CLA^+IL\text{-}17^+$ T cells) was reduced in psoriasis patients after 6 weeks of treatment and the reduction of $CD8^+CLA^+IL\text{-}17^+$ T cells correlated with the PASI score (Fig. 2A–B). The percentage of skin homing Th22 and Tc22 cells T22 ($CD4^+CLA^+IL\text{-}22^+$ and $CD8^+CLA^+IL\text{-}22^+$ T cells) was also reduced in psoriatic patients after 6 weeks of treatment and correlated with reduction in the PASI score (Fig. 2C–D). Additionally, the percentage of skin homing $CD4^+$ and $CD8^+$ T cells that expressed the skin resident marker CD103 ($CD4^+CLA^+CD103^+$ and $CD8^+CLA^+CD103^+$ T cells) was reduced and correlated with reduction in the PASI score (Fig. 2E–F).

This study demonstrates reduction of circulating Th17/Tc17 and Th22/Tc22 effector cells, skin homing Th17/Tc17 and Th22/Tc22 cells, and $CD4^+$ and $CD8^+$ T cells expressing the tissue retention integrin CD103, as well as reduction of $CD4^+$ and $CD8^+$ T cells and IL-17 levels in the skin of psoriasis patients treated with three different UVB regimens. This systemic and local reduction of inflammatory mediators correlated with clinical improvement as measured by the PASI score and the reduction of circulating Th17/Tc17 cells and skin homing Tc22 cells correlated well with

Abbreviations: PBMC, peripheral blood mononuclear cells; Th cells, T helper cells; Tc cells, T cytotoxic cells; PASI, psoriasis area and severity index.

https://doi.org/10.1016/j.jdermsci.2019.10.001

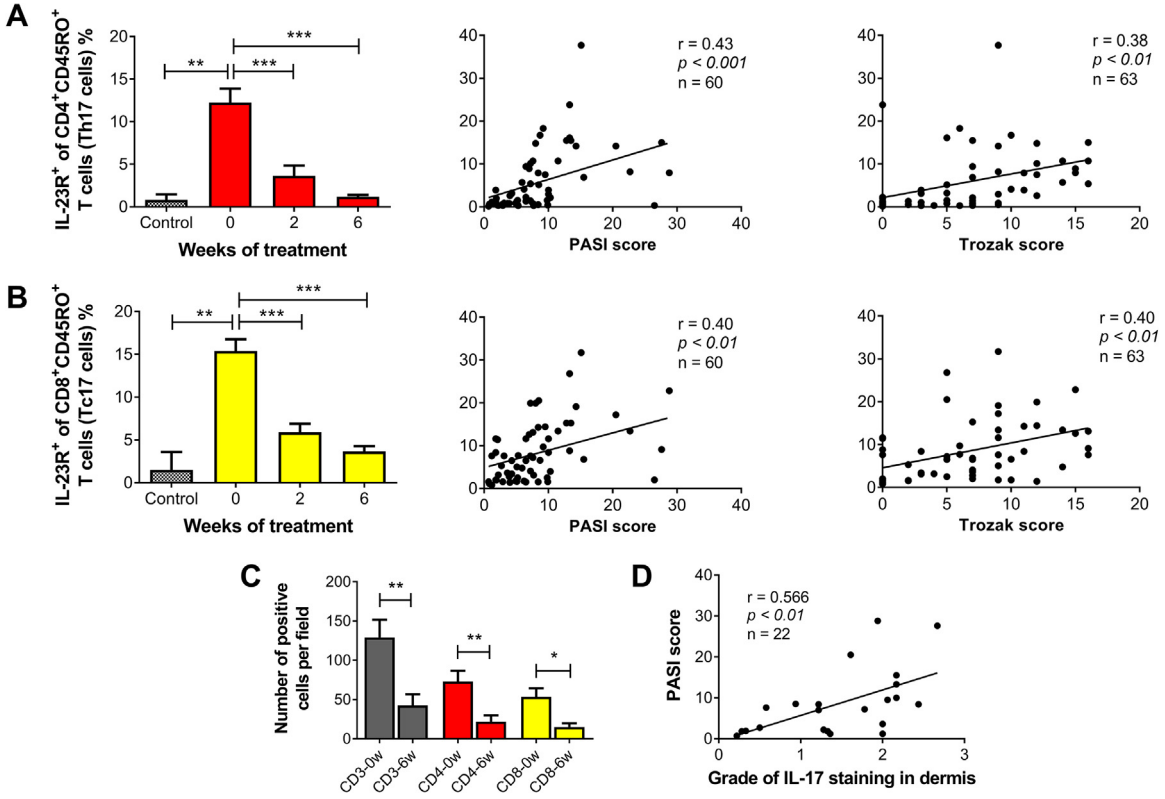

Fig. 1. Bar columns showing the percentage of peripheral blood (A) Th17 (IL23R + of CD4+CD45RO + T cells) and (B) Tc17 (IL23R + of CD8+CD45RO + T cells) of healthy volunteers and of psoriasis patients before and after 2 and 6 weeks of treatment. Dot plots showing correlation between the reduction of peripheral blood (A) Th17 and (B) Tc17 cells and both clinical efficacy (PASI) and improvement in histological changes (Trozak score) with treatment. Healthy controls (n = 3) and psoriasis patients (n = 21). (C) Bar columns showing the number of CD3+, CD4+ and CD8+ cells in high powered field of vision of lesional psoriatic skin before treatment (0 w) and after 6 weeks of treatment (6 w) (n = 10). The results are presented as mean ± SEM. (D) Dot plot showing the grade of IL-17 staining in the dermis and the correlation with the PASI score (n = 22). Pearson's correlation test was used to calculate Pearson correlation coefficients (r) and p values shown on the dot plots, Mann-Whitney test to compare control group to psoriasis patients at 0 weeks and one-way ANOVA test to calculate the difference between multiple time points (* = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$). P values beneath 0.05 were considered significant.
278 × 193 mm (300 × 300 DPI).

histological improvement measured by the Trozak score as well. As no difference was noted after 6 weeks of treatment between the treatment groups, the patients were evaluated as one group.

In agreement with previous reports [4,5], our results highlight the critical role of T17 effector cells in the pathogenesis of psoriasis. IL-17 drives the production of proinflammatory cytokines and chemokines by keratinocytes, and consequently activates leukocytes and recruits them into the skin [2]. In addition, the importance of IL-17 is further supported by the success of anti-IL-17 treatments in psoriasis [6]. Our results also highlight the critical role of IL-22 in psoriasis. IL-22 is a strong inducer for synthesis of antimicrobial peptides in keratinocytes, and participated in epidermal achantosis, a prominent morphological feature in psoriasis [7,8].

Psoriasis is generally regarded as a T cell-mediated immune disease with a mixed Th1/Th17 cytokine environment [1]. Psoriasis lesions have long been known to contain elevated levels of IFNγ [9], and the frequency of circulating Th1 cells in the blood of patients has been shown to be higher than normal [10]. In our results we found no significant reduction of IFNγ-, TNFα- or IL-4-producing $CD4^+/CD8^+$ T cells in the peripheral blood cells and no correlation with the clinical improvement, making the role of T17 cells even more important in the pathogenesis of psoriasis.

In conclusion, this study shows that NB-UVB therapy, with or without balneotherapy, suppresses the Th17/Tc17 and Th22/Tc22 inflammatory axis in peripheral blood of psoriasis patients, concomitant with inflammatory resolution of skin resident T cells, resulting in rapid improvement of the disease, highlighting the critical role of T17 and T22 effector cells in the pathogenesis of psoriasis.

Funding

This work was supported by the Landspitali University Hospital Research Fund, the Icelandic Technology Development Fund and the Blue Lagoon Clinic.

Declaration of Competing Interest

This study was conducted in collaboration with the Blue Lagoon Ltd and Landspitali - The National University Hospital of Iceland. Authors Bárður Sigurgeirsson and Jón Hjaltalín Ólafsson serve in the Advisory Board of the Blue Lagoon. Other authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jdermsci.2019.10.001.

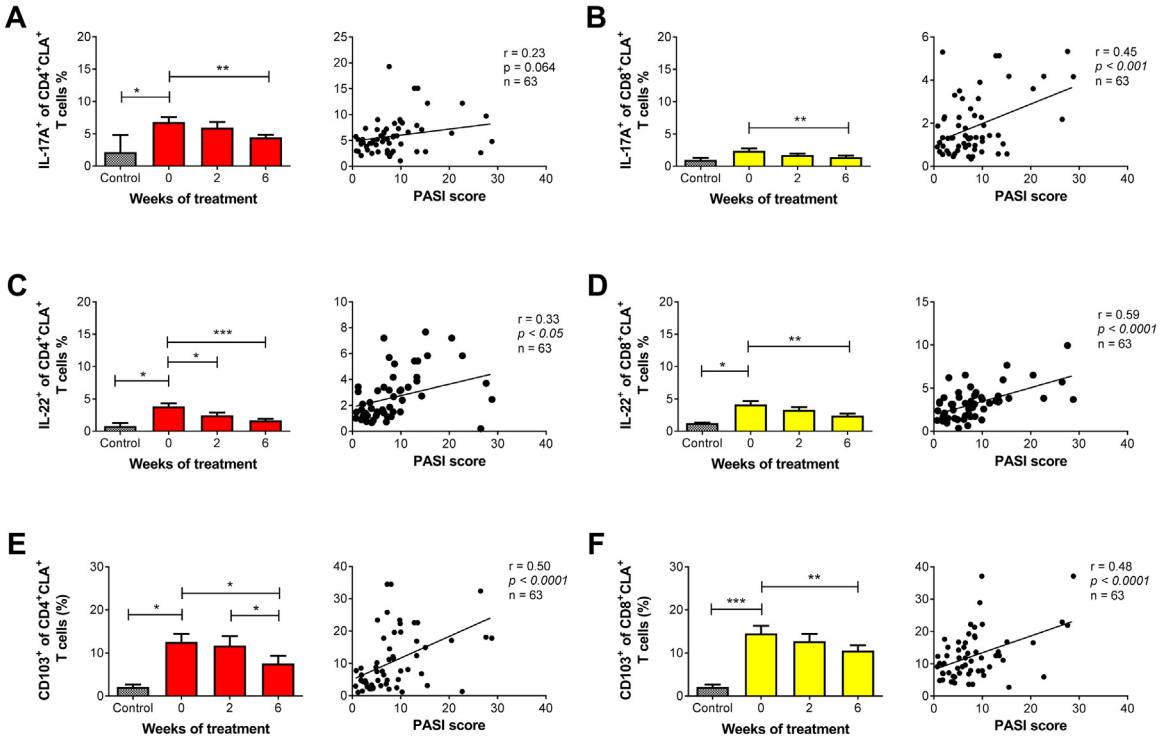

Fig. 2. Bar columns showing percentages of positive cells in peripheral blood from healthy volunteers and psoriasis patients before treatment and 2 and 6 weeks after the induction of treatment and dot plots showing the correlation with the clinical PASI score for: (A) skin homing Th17 cells (IL-17A + of CD4+CLA+ T cells), (B) skin homing Tc17 cells (IL-17A + of CD8+CLA + T cells), (C) skin homing Th22 cells (IL-22+ of CD4+CLA + T cells), (D) skin homing Tc22 cells (IL-22+ of CD8+CLA + T cells), (E) skin resident Th cells (CD103+ of CD4+CLA + T cells) and (F) skin resident Tc cells (CD103+ of CD8+CLA + T cells). The results are presented as mean ± SEM; healthy controls (n = 3) and psoriasis patients (n = 21). Pearson's correlation test was used to calculate Pearson correlation coefficients (r) and p values shown on the dot plots, Mann-Whitney test to compare control group to psoriasis patients at 0 weeks and one-way ANOVA test to calculate the difference between multiple time points (* = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$). P values beneath 0.05 were considered significant.
280 × 182 mm (300 × 300 DPI).

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Received 6 February 2019
Received in revised form 14 August 2019
Accepted 11 October 2019