

Serum Interleukin (IL)-17 in Psoriasis

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Abstract: Psoriasis is characterized by increased activation of CD4+T lymphocytes, and systemic and local over expression of pro-inflammatory cytokines indicating that immunopathogenesis of the disease is T helper 1 (Th1) mediated. Upon antigenic stimulation CD4+ T-cells differentiate to either Th1 or Th17 according to local cytokine milieu environment. This study was designed to detect the serum level of IL-17 in 30 chronic plaque psoriasis patients within age range 20 -40 years as compared to sex and age- matched 20 control subjects. There was a statistically significant elevated serum IL17 level in patients group versus control subjects. Topical therapy with a combination of betamethasone dipropionate and salicylic acid ointment, two times a day for three weeks induced statistically significant lower serum IL17 levels in patients. Suppression of serum IL17 levels after therapy was not associated with a statistically significant change in PASI score. **Conclusion:** Blocking of the IL-23/Th17 pathway can be achieved at different levels producing striking improvement in psoriasis patients

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1.Introduction

Psoriasis affects nearly 2-3% of the world's population and presents as erythematous, indurated, scaly plaques over the skin sometimes with involvement of the nails and joints (**Christophers, 2001**). It is characterized by exaggerated and disordered epidermal cell proliferation and keratinization. Though tremendous leaps have been made in our understanding of the disease, the chain of events that culminates in this aberrant keratinization has not yet been elucidated. A host of abnormalities seen in psoriasis, like increased levels of cyclic-adenosine monophosphate (cAMP), epidermal growth factor receptor binding, protein kinase C and transforming growth factor- α (TGF- α), collectively point to a disturbance in T cell function. Currently, the most accepted hypothesis is that psoriasis is an immune-mediated inflammatory skin disease that manifests in a genetically predisposed person exposed to certain environmental agents or triggers (**Mahajan and Handa, 2013**). The successful use of cyclosporine in the treatment of psoriasis nearly three decades ago first brought into focus the role of the immune system in the pathogenesis of psoriasis (**Mahajan and Handa, 2013**). Activated T cells are believed to be the primary modulators in the pathogenesis of psoriasis (**Ellis et al., 1998, Ellis, 2005 and Nograles et al., 2010, Krueger**). Disordered cellular immunity involving inflammatory cytokines (IL-1, IL-6, Tumour necrosis factor- α [TNF- α]) and proinflammatory transcription factor (NF- κ B, signal transduction and transcription and AP-1) has also been implicated (**Ruissen et al., 1995; Tomic-Canic et al., 1998 and Van Barker, 2012**).

Activated T cells are believed to be the primary modulators in the pathogenesis of psoriasis and the role of the IL-23/Th17 pathway has been intensely researched in recent years (**Chiu et al., 2012**). The aim of this study was to measure the serum level of interleukin (IL)-17 in patients with chronic plaque psoriasis versus otherwise healthy sex and age-matched control subjects and to find whether or not there was a statistically significant correlation between serum IL17 and clinical severity of psoriasis as assessed using Psoriasis Area Severity Index (PASI) Score (**Robinson et al., 2012**). The effect of topical corticosteroid therapy on serum IL17 was also investigated among patients.

2. Subjects and Methods

Thirty patients with chronic plaque psoriasis and their age (ranged from 20-40 years old) and sex matched otherwise healthy control subjects (20) group were included in this study. All were recruited from Dermatology Department, Zagazig University Hospitals

Patients selection

None of psoriasis patients had received topical (e.g. corticosteroids, vitamin D analogue.. etc.) or systemic (e.g. corticosteroids, methotrexate ...etc.) therapy for one month before being included in this study. Pregnant or lactating ladies or patients with other autoimmune diseases were excluded All patients were subjected to the following:

- (1) Psoriasis Area Severity Score Index PASI assessment on day 0 of the study before topical therapy application.
- (2) Patients were instructed to apply (0.64mg of Betamethasone Dipropionate, equivalent to 0.5mg

(0.05%) of Betamethasone and 30mg (3%) of Salicylic acid) ointment twice/day for three weeks. For scalp psoriasis patients were advised to use (0.64 mg of Betamethasone Dipropionate, equivalent to 0.5mg (0.05%) of Beta-methasone and 20mg (2%) of Salicylic acid) lotion two times for three weeks.

(3) Evaluation of PASI at end of therapy (on Day21).

(4) Detection of possible side effects of topical therapy (e.g skin atrophy, telangiectasia, hypo pigmentation, etc).

Blood sample collection & serum IL17 measurement

Blood samples (3ml) were collected from control subjects on day 0 and from patients with psoriasis on day 0 at start of therapy and on day 21 after completion of 3 week therapy period. All samples were collected and complete aseptic precautions using sterile needles. All subjects were asked to attend fasting at 8:30morning.All serum samples were kept frozen at -20°C till used. Interleukin (IL)-17 was detected in serum by Enzyme Linked Immune Sorbent Technique (ELISA) using Human IL-17 ELISA Kitfor serum, plasma, cell culture supernatant, and urine. Catalog Number **RAB0262**. Storage Temperature -20°C, Sigma-Aldrich Co. LLC (sigma-aldrich.com)

Statistical Evaluation

All results were evaluated using analysis of variance (ANOVA) and T-paired test (12).

3.Results

Serum interleukin (IL- 17) assessment.

A Control group (n=20) Serum IL- 17 levels were in the range of 8.1 - 116.5 pg/ml (mean 43.2 ± 32.4)

B Psoriasis patient group (n=30)

I. Before therapy (Day 0): Serum IL-17 levels were in the range of 67.96-503.32 pg/ml (mean 225.2 ± 122.8).

II. After therapy (Day 21): Serum IL-17 levels were in the range of 0.1 - 497.96 pg/ml (mean 145.9 ± 104.9).

There was a statistically significant ($p < 0.05$) higher serum IL-17 levels in patients versus control group. Moreover There was a statistically significant ($p < 0.05$) lower serum IL-17 levels in patients following topical corticosteroid therapy (on day 21) as compared to IL-17 levels in patients before therapy. Clinically, there was a statistically insignificant difference ($p > 0.05$) in PASI in patients before (Day 0) versus after (Day 21) therapy. See tables (1-3). None of the patients was manifested with side effects of topical steroid therapy.

Table (1): Serum Interleukin (IL)-17 (pg /ml) in Psoarisis Patients (chronic plaque type) (no.30) versus control group (no.20)

	n	IL-17 X ± SD (RANGE)
Psoarisis group	30	225.2 ± 122.8 (67.96 - 503.30)
Control group	20	43.2 ± 32.4 (8.1 -116.5)

n: number; x: Mean; SD: standard deviation; Range: Minimum – Maximum; Test: Anova and Paired t - test

Table (2): Serum Interleukin (IL)-17 (pg /ml) in psoriasis group (chronic plaque type) (no.30) before versus after therapy

	Before (Day 0) n=30	After (Day 21) n=30	Paired	
			t	P
IL-17 x ± SD Range	225.2 ± 122.8 6 7.96-503.32	145.9 ± 104.9 0.1-497.96	2.979	0.005* S.

S: Significant; x: mean; SD: standard deviation; n: Number of patient; Range = Minimum - Maximum

Table (3): Changes in Psoarisis Area Severity Index (PASI) Score before and after therapy in psoriasis patients group (chronic plaque type) (no.30)

	Before therapy (Day 0)	After therapy (Day 21)	Paired	
			t	P
PASI score X ± SD RANGE	15.71 ± 11.56 2.7 - 51	14.3 ± 11.3 2.3 - 49	19	0.06 Insignificant

X ± SD: Mean ± Standard deviation

4. Discussion

Psoriasis is a chronic inflammatory papulosquamous disease characterized by multiple remissions and relapses. For long, it was believed to be primarily a disorder of keratinization. However, the successful use of traditional immunosuppressants and newer immunomodulatory agents in the treatment of psoriasis led to the belief that psoriasis is primarily a disease of Th1 cell immune dysregulation. Recent developments have brought up several new findings such as the role of Th17 cells and evidence of skin barrier dysfunction in psoriasis (Christophers, 2001; Chiu *et al.*, 2012 and Mahajan and Handa, 2013). Naïve T-cells can differentiate into any of the four types of inflammatory cells (viz. Th1, Th2, Th17 or T regulatory cells) depending on the presence of TNF- α , TGF- β and IL-6 (Stockinger and Veldhoen, 2007). In the presence of TGF- β and IL-6, naive T-cells transform into Th17 cells (Bettelli *et al.*, 2006; Mangan *et al.*, 2006). These Th17 cells are CD4+ effector cells distinct from the classic Th1 and Th2 lineages and are responsible for providing both innate and adaptive immunity against pathogens. The activated cells enter the circulation and extravasate through the endothelium to the sites of inflammation in skin where they produce the Th1-Th2-Th17 imbalance. The role of the IL-23/Th17 pathway has been intensely researched in recent years. Interleukin (IL)-23 produced by dendritic cells and macrophages (Lee *et al.*, 2004; Ouyang *et al.*, 2008). causes activation of Th17 cells to produce IL-17 and IL-22. IL-17 (also known as IL-17A) is part of a group of cytokines, called the IL-17 family, consisting of six ligands (A to F), and with five receptor family members. IL-17 cytokines are probably critical for the pathogenesis of psoriasis. IL-17A and IL-17F are the predominant cytokines released by Th17 cells, but are also produced by $\gamma\delta$ T cells, whereas IL-17C is produced by keratinocytes. The effect of IL-17 cytokines is mediated via the adaptor protein connection to I κ B kinase and stress-activated protein kinases (SAPK)/JNK (Martin *et al.*, 2013).

In the present study there were statistically significant elevated serum levels of IL-17 in patients with chronic plaque psoriasis patients as compared to relevant serum levels in control subjects. Such IL 17 could result in an increase in levels of pro-inflammatory cytokines like S-100, A7, β -defensins and lipocalin. In addition, increased levels of β -defensins are associated with relative resistance to infections (Henseler and Christophers, 1995; Liang *et al.*, 2006). Increased levels of IL-17 also promote keratinocytes to produce CXCL-chemokines and CCL-20, both of which attract neutrophils to the site of inflammation (Nogales *et al.*, 2008; Ragab *et al.*,

2010). More over in the present study, there were statistically significant lower serum IL 17 levels in patients with psoriasis after a period (three weeks) of topical corticosteroid therapy as compared to the patients relevant serum IL17 levels before starting such a therapeutic modality (on day 0). However such a suppression in serum IL17 levels in patients did not associate with a marked clinical improvement in psoriasis status among patients as assessed using PASI score. This could have been attributed to several factors. The short duration (21 days) of topical therapy might have been as a factor. Longer period of corticosteroid topical therapy, using another topical therapy (e.g. Pimecrolimus or vitamin D analogue) and/or systemic therapy such as Apremilast (Wada *et al.*, 2012), which is an orally administered compound that selectively suppresses synthesis of IL-12 and IL-23 might have given a better improvement in the disease severity. A more prolonged suppression of IL-17 together with suppression other cytokines (e.g. IL-22) could have induced overt suppression in PASI. Suppression of other interleukins, e.g. IL-22 & IL-23 (Lee *et al.*, 2004; Ouyang *et al.*, 2008) could have induced substantial improvement in psoriasis. A new subtype of cells, Th-22 cells, is also considered important in the pathogenesis of psoriasis. These cells, on activation by TNF- α , IL-6 and CCL20, exclusively produce IL-22 and are involved in epidermal immunity and remodeling. They express CCR10, CCR6 and CCR4 receptors on their surface [24]. Different dendritic cell subsets might also regulate the Th17 versus Th22 activation with CD11c+ dermal dendritic cells promoting Th17 cells while epidermal Langerhans cells stimulate the Th22 cells (Fujita *et al.*, 2009).

In conclusion psoriasis is a complex disease. Based on the increased insight into the pathogenesis of psoriasis, several new therapeutic approaches targeting the effector functions of Th17 cells have been developed. Blocking of the IL-23/Th17 pathway can be achieved at different levels. Since IL-23 enhances Th17 cell proliferation and IL-17 production, monoclonal antibodies directed against p40, a shared subunit of IL-23 and IL-12, and other biologic agents have produced striking improvement in psoriasis patients (Papp *et al.*, 2008 and Khandpur & Bhari, 2013).

No conflict of interest to disclose

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References

- 1- Christophers E. Psoriasis-Epidemiology and clinical spectrum. *Clin Exp Dermatol* 2001; 26:314-20.
- 2- Mahajan R, Handa S. Pathophysiology of psoriasis. *Indian J Dermatol Venereol Leprol* 2013;79:1-9
- 3- Fitch E, Harper E, Skorcheva I, Kurtz SE, Blauvelt A. Pathophysiology of psoriasis: Recent advances on IL-23 and Th17 cytokines. *Curr Rheumatol Rep* 2007; 9: 461-7
- 4- Nograles KE, Davidovici B, Krueger JG: New insights in the immunologic basis of psoriasis. *Semin Cutan Med Surg* 2010; 29:3-9.
- 5- Krueger G, Ellis CN: Psoriasis-Recent advances in understanding its pathogenesis and treatment. *J Am Acad Dermatol* 2005; 53:S94-100.
- 6- Ellis CN, Gorsulowsky DC, Hamilton TA, Billings JK, Brown MD, Headington JT, *et al.*: Cyclosporine improves psoriasis in a double-blind study. *JAMA* 1986; 256: 3110-6.
- 7- Tomic-Canic M, Komine M, Freedberg IM, Blumenberg M: Epidermal signal transduction and transcription factor activation in activated keratinocytes. *J Dermatol Sci* 1998; 17:167-81.
- 8- Van Ruissen F, Van de Kerkhof PC, Schalkwijk J: Signal transduction pathways in epidermal proliferation and cutaneous inflammation. *Clin Dermatol* 1995; 13: 161-90.
- 9- Barker JN: The pathophysiology of psoriasis. *Lancet* 1991; 338:227-30.
- 10- Chiu H, Pin Cheng L, Fang Tsai T: T- helper type 17 in psoriasis: From basic immunology to clinical practice *Dermatologica Sinica* (2012), 30:136e-141
- 11- Robinson A, Kardos M, Kimball AB, *et al.*: Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI): Why do both? A systematic analysis of randomized controlled trials of biologic agents for moderate to severe plaque psoriasis, *J Am Acad Dermatol* (2012): 66:369-75.
- 12- Rupert G. Miller Jr: ANOVA in *Beyond ANOVA: Basics of Applied Statistics*. Publisher: Chapman and Hall/CRC (January 1, 1997) pp 35-59
- 13- Stockinger B, Veldhoen M: Differentiation and function of Th17 T cells. *Curr Opin Immunol* 2007;19:281-6.
- 14- Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, *et al.*: Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature* 2006; 441: 235-8.
- 15- Mangan PR, Harrington LE, O'Quinn DB, Helms WS, Bullard DC, Elson CO, *et al.*: Transforming growth factor-beta induces development of the Th17 lineage. *Nature* 2006;441:231-4.
- 16- Lee E, Trepicchio WL, Oestreicher JL, Pittman D, Wang F, Chamian F, *et al.*: Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. *J Exp Med* 2004; 199: 125-30.
- 17- Ouyang W, Kolls JK, Zheng Y. The biological functions of T helper 17 cell effector cytokines in inflammation. *Immunity* 2008; 28:454-67.
- 18- Martin DA, Towne JE, Kricorian G, Klekotka P, Gudjonsson JE, Krueger JG, *et al.* The Emerging Role of IL-17 in the Pathogenesis of Psoriasis: Preclinical and Clinical Findings. *J Invest Dermatol* 2013;133:17-26
- 19- Henseler T, Christophers E. Disease concomitance in psoriasis. *J Am Acad Dermatol* 1995; 32:982-6.
- 20- Liang SC, Tan XY, Luxenberg DP, Karim R, Dunussi-Joannopoulos K, Collins M, *et al.* Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. *J Exp Med* 2006; 203:2271-9.
- 21- Nograles KE, Zaba LC, Guttman-Yassky E, Fuentes-Duculan J, Suárez-Fariñas M, Cardinale I, *et al.*: Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. *Br J Dermatol* 2008; 159:1092-102.
- 22- Ragab H M, Abdel Maksoud N, Farid Roaiah MM.: Biochemical Significance of Proinflammatory Cytokines in Psoriasis vulgaris among Egyptian Patients. (2010): *J. American Science*. 6(10):423-429.
- 23- Wada Y, Cardinale I, Khatcherian A, Chu J, Kantor AB, Gottlieb AB, *et al.*: Apremilumab inhibits the production of IL-12 and IL-23 and reduces dendritic cell infiltration in psoriasis. *PLoS One* 2012; 7:e35069
- 24- Nograles KE, Davidovici B, Krueger JG.: New insights in the immunologic basis of psoriasis. *Semin Cutan Med Surg* 2010; 29: 3-9.
- 25- Fujita H, Nograles KE, Kikuchi T, Gonzalez J, Carucci JA, Krueger JG: Human Langerhans cells induce distinct IL-22-producing CD4+ T cells lacking IL-17 production. *Proc Natl Acad Sci USA* 2009; 106:21795-800.
- 26- Papp KA, Langley RG, Lebwohl M, *et al.*: Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* (2008);371:1675e-84.
- 27- Khandpur S&Bhari N: New targeted therapy in psoriasis. *Indian J. Dermatol Venereol Leprol* (2013), 79:47-52.