Assessment of Serum and Tissue Level of Interleukin 33 in Patients with Atopic Dermatitis

Thesis

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Engy Aly

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List of Abbreviations

Abb.	Full term
AD	*Atopic Dermatitis*
AMPS	*Antimicrobial Peptides*
AZA	*Azathioprine*
BB	*Broadband*
c-AMP	*Cyclic Adenosine Monophosphate*
CIU	*Chronic Idiopathic Urticaria*
CYA	*Cyclosporine*
DDC	*Dermal Dentritic Cell*
EASI	*Eczema Area and Severity Index*
EDC	*Epidermal Differentiation Complex*
ESL	*E-selectin Ligand*
FLG	*Fillaggrin Gene*
HDM	*House Dust Mite*
HSPG	*Heparan Sulfate Proteoglycan*
HSV	*Herpes Simplex Virus*
IDEC	*Inflammatory Dendritic Epidermal Cell*
IEDC	*Inflammatory Epidermal Dendritic Cell*
IL	*Interleukin*
INF-α	*Interferon Gamma*
INF-β	*Interferon Beta*
INF-γ	*Interferon Gamma*
JAK	*Janus Kinase*
JAM	*Junctional Adhesion Molecules*
KC	*Keratinocyte*
LC	*Langerhans Cell*
LFA	*Leukocyte Function-Associated Antigen*
MCC1	*Mast Cell Chymase 1*

List of Abbreviations (Cont...)

Abb.	Full term
MCV	*Molluscum Contagiosum Virus*
MED	*Minimal Erythema Dose*
MHC	*Major Histocompatibility Complex*
MMF	*Mycophenolate Mofetil*
MTX	*Methotrexate*
NB	*Narrowband*
NF	*Nuclear Factor*
NMF	*Natural Moisturizing Factor*
NPs	*Neuropeptides*
PAR-2	*Protease Activated Receptor-2*
pDCs	*Plasmacytoid DCs*
PDE	*Phosphodiesterase Enzyme*
PDE4	*Phosphodiesterase Type 4*
PECAM-1	*Platelet/Endothelial Cell Adhesion Molecule 1*
PML	*Progressive Multifocal Leukoencephalopathy*
PSGL	*P-Selectin Glycoprotein Ligand*
PUVA	*Psoralen plus UVA*
RAST	*Radioallergosorbent Test*
S.aureus	*Staphylococcus Aureus*
SCCE	*Stratum Corneum Chymotryptic Enzyme*
ST2	*Supression of Tumorigenicity 2*
TCI	*Topical Calcineurin Inhibitors*
TCR	*T- Cell Receptor*
TCS	*Topical Corticosteroids*
TGF α	*Tissue Growth Factor Beta*
Th	*T helper*
TIM-1	*T-cell Immunoglobulin Domain and Mucin Domain 1*

List of Abbreviations (Cont...)

Abb.	Full term
TNF	*Tumor Necrosis Factor*
TNF-α	*Tumour Necrosis Factor Alpha*
TSLP	*Thymic Stromal Lymphopoietin*
VCAM-1	*Vascular Cell Adhesion Molecule-1*
VIP	*Vaso Active Intestinal Peptide*
VLA	*Very Late Antigen*
WWT	*Wet-Wrap Therapy*

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease characterized by an early T helper type 2 (Th2) immune response in which patients suffer from relapsing eczematous and occasionally generalized lesions associated with severe pruritus ***(Bonness and Bieber, 2007 & Boguniewicz and Leung, 2011).*** Scratching reactions to pruritus typically exacerbate the inflammatory skin reactions ***(Hong et al., 2011).***

The key events in AD may be subdivided as an interplay among infiltrating immune cells (Th2 cells and later Th1 cells, macrophages, dendritic cells, mast cells, and eosinophils), skin-resident keratinocytes & endothelial cells and activated peripheral sensory nerves. The multicellular action is believed to orchestrate disease onset and progression ***(Steinhoff et al., 2006 & Cevikbas et al., 2007).***

Interleukin (IL)-33 is a recently described member of the IL-1 family ***(Schmitz et al., 2005)***, which has been shown to induce the production of Th2 cytokines (IL-4, IL-5 and IL-13), and exerts its effects by activating the supression of tumorigenicity 2 (ST2) receptor on different type of cells, including mast cells and Th2 cells ***(Chackerian et al., 2007).***

IL-33 is a nuclear cytokine released by the epithelial cells in various tissues and organs, including keratinocytes, endothelial cells, and immune cells, and by necrotic structural cells, as fibroblast or keratinocytes ***(Chackerian et al., 2007 & Liew et al., 2010).***

IL-33 has been described as an epithelial ‘‘alarmin’’ defense system, released upon cellular damage through the activation of various immune cells through its ST2 receptor, which leads to the production of various molecules ***(Allakhverdi et al., 2007; Ohno et al., 2012; Gangemi et al., 2013 & Vocca et al., 2015).***

The IL-33 induced production of proinflammatory cytokines is a critical event that aggravates atopic diseases, playing an important role as a bridge between innate and adaptive immune responses in allergic diseases ***(Lloyd, 2010 & Vocca et al., 2015).***

Savinko et al. (2012) investigated the expression profiles of IL-33 and ST2 in different mouse models of atopic-like dermatitis, emphasizing a regulatory role for this novel cytokine pathway. Different allergens, when applied topically (ovalbumin, house dust mites, or staphylococcal enterotoxin B) to mice, led to the upregulation of IL-33 and ST2 messenger RNA expression. These results indicate that IL-33 as well as its

receptor may be induced in AD when exposed to AD trigger factors. Whether these results reflect the human situation remains unknown and needs further evaluation.

Tamagawa-Mineoka et al. (2014) measured serum level of IL-33 in patients with AD for quantitative detection of IL-33 and found that serum level of IL-33 is significantly elevated in patients with AD compared with healthy control subjects. Serum IL-33 level was significantly associated with the disease severity of AD. These findings suggest that IL-33 released from mechanically injured or barrier-disrupted skin may increase inflammation in AD.

AIM OF THE STUDY

To quantify serum and tissue IL-33 level in patients with AD and to correlate its level with the disease severity.

Chapter 1

ATOPIC DERMATITIS

Atopy is defined as a genetically determined state of hypersensitivity to environmental allergens. AD is a common, complex and chronic inflammatory skin disorder characterized by eczema, pruritus and cutaneous hyper-reactivity to allergic, irritant or microbial triggers, and affected individuals suffer significant morbidity ***(Vickery, 2007).***

The word atopic comes from atopy, which is derived from a Greek word (atopos) that means "out of place" ***(Gale, 2006).***

AD has been given many other names like "Besnier prurigo", "neurodermitis", "endogenous eczema", "flexural eczema", "infantile eczema" and "prurigo diathsique" ***(Abels and Proksch, 2006).***

Incidence and Prevalence:

The lifetime prevalence of AD is 10-20% in children and 1-3% in adults ***(Leung et al., 2004)***.

The prevalence of AD is higher in children of cold countries, 19.7% in Norweigen children ***(Selnes et al., 2002)***, 22.9% in Danish children, 13.1% in German children, 15.5% in Sweden children ***(Larsen et al., 1996)***, 11.5-14% in English children ***(William, 1995)*** and 9.5-24% in Japanese children ***(Sugiura et al., 1997).*** In contrast, in children of hot countries like Tanzania the prevelance of AD is only 0.7% ***(Henderson, 1995).***