Serum Level of Interleukin 17 in Alopecia Areata Patients and Its Relation with the Severity of the Disease: a Case Control Study

Thesis

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List of Abbreviations

Abb.	Full term
AA	Alopecia areata
AAF	Alopecia areata focalis
AAT	Alopecia areata totalis
AAU	Alopecia areata universalis
AD	Atopic dermatitis
ADTA	Acute diffuse and total alopecia
AT	Alopecia totalis
AU	Alopecia universalis
CD	Cluster of differentiation
CXC	Chemokine
DPCP	Diphenylcyclopropenone
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
IBD	Inflammatory bowel disease
IFN	Interferon
IGF-1	Insulin growth factor- 1
IgG1	Immunoglobulin G1
IgG4	Immunoglobulin G4
IL	Interleukin
IL-17	Interleukin-17
IL-17R	Interleukin-17 receptor
ILCS	Intralesional corticosteroids
IP	Immune privilege
IQR	Inter quartile range
JAK	Janus kinase
MHC	Major Histocompatibility Complex

List of Abbreviations Cont...

Abb.	Full term
mRNA	Messenger ribonucleic acid
NB-UVB	Narrow band ultraviolet B
NK	Natural killer
PASI	Psoriasis Area and Severity Index
PGF2a	Prostaglandin F2-a
PRP	Platelet-rich plasma
PsA	Psoriatic arthritis
pSS	Primary Sjogren's syndrome
PUVA	Psoralen + UVA
SADBE	Squaric acid dibutylester
SALT score	Severity of Alopecia Tool
Sc	Subcutaneous
SD	Standard deviation
SPSS	Statistical Package for Social Science
Th cells	T helper cells
TNF-α	Tumor necrosis factor- α
Treg cells	T regulatory cells
UVB	Ultraviolet B

INTRODUCTION

Alopecia areata (AA) is an organ-specific autoimmune disease characterized by T-cell infiltrates and cytokine production around anagen-stage hair follicles. AA affects 1.7% of the population and shows no gender or ethnic predilection ***(Han, 2017).*** The severity of hair loss or disease phenotype is variable and can fluctuate over time. Regrowth occurs in most patients. Patchy AA is characterized by well-defined local patches of hair loss. Alopecia totalis is total scalp hair loss while alopecia universalis is hair loss over the scalp and body. These two types are the most severe phenotypes ***(Barahmani et al., 2009).***

AA has devastating effects on the patient's quality of life ***(Montegomery et al., 2017).*** Although it is one of the most common dermatological diseases, its pathogenesis is not fully understood, and the available therapies are disappointing. The leading hypothesis points to a T-cell-mediated attack on anagen hair follicles in genetically susceptible individuals. Cells, especially Th1, Th2, Th17 cells and T regulatory cells, have been implicated in several autoimmune diseases including AA ***(Elela et al., 2016).***

Interleukin-17 (IL-17) is an inflammatory cytokine secreted mainly by Th17 cells and other cells like neutrophils, natural killer cells, CD8+ T cells and γδ T cells. It has gained much interest in recent years due to its main role in the

pathogenesis of a number of inflammatory and autoimmune disorders. This interest has increased following the recent development of specific inhibitors of this cytokine and its receptors, which show very promising efficacy in several inflammatory conditions, such as psoriasis ***(Ramot et al., 2018)***.

Alopecia areata (AA) is one of the skin conditions being explored as a potential target for IL-17 inhibitors due to the possible role of IL-17 and Th17 in its pathogenesis. Much of these data have been published in the last 5 years. The reported results show a more or less clear picture on its role in the pathological mechanism of the disease ***(Ramot et al., 2018)***.

Aim of the Work

The aim of this work is to compare the serum level of interleukin-17 (IL-17) between alopecia areata patients and healthy controls to demonstrate its proposed role in the pathogenesis of alopecia areata and to correlate it with the severity of the disease.

Chapter 1

ALOPECIA AREATA OVERVIEW

A- Epidemiology

Alopecia Areata (AA) is one of the most common autoimmune diseases ***(Skogberg et al., 2017).*** It's characterized by hair loss on the scalp and/or body ***(Borowska and Wasylyszyn, 2017).*** It equally affects men and women ***(Skogberg et al., 2017).*** Although some reports suggest a slight predominance in women, however, this can depend on the population studied ***(Juárez-Rendón et al., 2017).*** Most studies report a lifetime risk of about 2% ***(Skogberg et al., 2017) (Renert-Yuval and Guttman-Yassky, 2017)*** and a frequency of 0.7% to 3.8% of patients attending dermatology clinics ***(Borowska and Wasylyszyn, 2017).***

AA may appear at any age. About 60% of patients will present with their first patch before 20 years of age ***(Roest et al., 2018).*** The age range of AA presentation is between 4-5 years and 15-40 years of age, with a higher prevalence between 10 and 25 years (60%). AA rarely occurs in adults older than 60 years ***(Juárez-Rendón et al., 2017).***

B- Etiopathogenesis

The pathogenesis of AA is not yet fully understood; however, there is evidence of an autoimmune T cell-mediated

process, in which the breakdown of immune privilege is followed by the destruction of hair follicles ***(El-morsy et al., 2016).***

The basic structure of the hair follicle is considered the most complicated and important adnexa of the skin. It has many functions including protection from ultraviolet radiation, prevention of heat loss, and touch sensation. The follicle passes through three phases during a normal growth cycle: anagen, catagen and telogen ***(Juárez-Rendón et al., 2017).***

The anagen phase is considered the growth phase (approximately 1 cm per month) and thus it is the longest (2-6 years). In the catagen phase (2-4 weeks), hair growth is interrupted, i.e., a process of keratinocyte apoptosis occurs; in addition, there is preparation for the last phase of the cycle. The telogen phase (2-3 months) is characterized by a stage of inactivity in which the hair is gradually lost before beginning a new growth cycle ***(Juárez-Rendón et al., 2017).***

In AA, hair loss could be due to an alteration of one of these follicle growth phases, in other words, a premature transition from the anagen to the catagen or the anagen to telogen phase could happen. Since this event cannot occur alone, several reports have suggested that despite the fact that the etiology of AA is not well known, it is possible that environmental, genetic and immunologic factors are responsible for its development ***(Wang and Christiano, 2017).***

1) Environmental factors

Stress could be one of the factors that could contribute to the development of AA. Studies have reported that at least 23% of patients have had an emotional event or an identity crisis before the onset of AA ***(Wang and Christiano, 2017).***

Other factors such as infections, toxins and even food, could be associated with immune dysregulation processes and thus have been proposed as possible triggers of the disease, although not all have been proved ***(Juárez-Rendón et al., 2017).***

2) Genetic factors

Most cases of AA are sporadic. However, there are reports that mention a strong association between genetic factors and development of the disease. A positive family history of 10 to 42% for AA has been reported. Three percent of patients have at least one brother with the disease and 2% have at least one affected child, with an estimated risk of 6%, in children of patients with AA. On the other hand, it has been found that AA has a polygenic origin, in other words, multiple genes intervene causing a greater susceptibility to developing the disease ***(Wang and Christiano, 2017).***

3) Immunological factors

The concept of autoimmunity in AA is supported by the high rate of association with other immune-mediated diseases

like vitiligo, thyroiditis, diabetes mellitus, rheumatoid arthritis, pernicious anemia, Addison's disease, systemic lupus erythematosus, myasthenia gravis, scleroderma, allergic rhinitis, atopic dermatitis, asthma and psoriasis ***(Juárez-Rendón et al., 2017)*** and the response seen to immune-modifying treatments ***(Rajabi et al., 2018).***

AA is caused due to development of an immune response that affects the structure of hair follicles in the anagen phase, specifically, CD4+ and CD8+ T lymphocytes infiltrate the bulb of the hair follicle. CD8+ lymphocytes are mainly responsible for follicular damage and predominate during activity of the disease, while CD4+ lymphocytes are fewer and only contribute together with CD8+ cells in the development of AA, although it has been proposed that not only CD4+ and CD8+ lymphocytes are involved in these processes but also, natural killer cells, macrophages, Langerhans cells ***(Wang and Christiano, 2017).***

The pathophysiological hypothesis for AA mainly emphasizes the loss of the hair follicle immune privilege (IP) ***(Rajabi et al., 2018).***

- **What's immune privilege (IP)?**

Some of the vital organs in the body have limited regenerative ability, and the slightest inflammation within them may have devastating outcomes. A revolutionary adaptation