Serum Th1 Cytokines in Alopecia Areata

Subjects: Allergy

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It was suggested that T helper 1 (Th1) cells have an essential role in the development of alopecia areata. They produce IL-2, IFN-γ, IL-12, IL-18, and IL-23, which positively feed back to promote further Th1 cell differentiation.

Keywords: Alopecia areata ; Interleukin 2 ; Interferon Gamma ; Tumor Necrosis Factor ; Serum Cytokines

1. Introduction

A summary of current literature considering the serum T helper 1 (Th1) cytokine levels in patients with alopecia areata is presented in **Table 1**.

Table 1. Summary of current literature considering the serum Th1 cytokine levels in patients with alopecia areata.

Cytokine	An Increased Serum Level (Number of Patients with Alopecia Areata)	A Decreased Serum Level (Number of Patients with Alopecia Areata)	Comparable to Healthy Controls (Number of Patients with Alopecia Areata)
IL-2	Teraki et al., 1996 (14), Barahmani et al., 2010 (269), Tembhre et al., 2013 (51) Alzolibani et al., 2016 (25), Kasumagić-Halilovic et al., 2018 (60), Gautam et al., 2020 (40), Aşkın et al., 2021 (61)	Tabara et al., 2019 (42)	Gong et al., 2020 (33)
IFN-γ	Omar et al., 2021 (72), Teraki et al., 1996 (14), Arca et al., 2004 (40), Barahmani et al., 2010 (269), Kasumagic-Halilovic et al., 2010 (60), Tembhre et al., 2013 (51), Ma et al., 2017 (100), Song et al., 2018 (30), Tabara et al., 2019 (42), Gong et al., 2020 (33), Manimaran et al., 2020 (33), Tomaszewska et al., 2020 (30), Gong et al., 2021 (33)	-	Loh et al., 2018 (55), Bain et al., 2020 (39)
TNF	Omar et al., 2021 (72), Alzolibani et al., 2016 (25), Atwa et al., 2016 (47), Bilgic et al., 2016 (40), Kasumagic-Halilovic et al., 2011 (60), Loh et al., 2018 (55), Bain et al., 2020 (39)	-	Barahmani et al., 2010 (269)
IL-12	Barahmani et al., 2010 (269), Gong et al., 2020 (33)	-	-
IL-18	Lee et al., 2010 (21)	-	Chodorowska et al., 2007 (14), Barahmani et al., 2010 (269), Gong et al., 2020 (33)

2. Interleukin 2 (IL-2)

IL-2, discovered in 1976, is an interleukin produced by activated T cells [1]. It is an important mediator in the growth, development, and activity of T and B lymphocytes, natural killer cells, and lymphokine-activated killer cells [2]. IL-2 mediates antigen-specific T-lymphocyte proliferation and modulates the expression of IFN-γ and major histocompatibility antigens [2].

Numerous studies described an increased serum level of IL-2 in patients with alopecia areata in comparison with healthy controls [2][1][3][4][5][6][7]. Moreover, higher levels of IL-2 mRNA were detected in peripheral blood mononuclear cells in patients with alopecia areata compared to control subjects [4]. In the study of Teraki et al. [3], an elevated serum level of IL-2 was observed only in patients with alopecia universalis in comparison with healthy individuals and patients with localized alopecia areata. Conversely, no significant difference was present in the serum level of IL-2 between patients with localized alopecia areata and healthy controls. In contrast to other studies, Loh et al. [8] showed a decreased serum level of IL-2 in patients with alopecia areata compared to the control group.

A study performed by Gautam et al. [5] revealed a positive correlation between the serum level of IL-2 and the severity of hair loss. Tembhre et al. [1] showed a positive correlation of serum IL-2 level with the total disease duration and the number of hairless patches on the scalp.

Askin et al. [7] reported a decrease in the serum level of IL-2 in patients with alopecia areata after tofacitinib treatment. However, no significant relationship between the change in interleukin level and the change in the Severity of Alopecia Tool (SALT) scores was observed.

IL-15 is structurally similar to IL-2. Both cytokines signal through two shared receptor subunits, the IL-2/15β chain (CD122) and the common γ chain (γC) [9]. In patients with alopecia areata, an increased serum level of IL-15 compared to healthy controls was described [7][10][11][12].

3. Interferon Gamma (IFN-γ)

IFN-γ is an activator of macrophages and inducer of class II MHC molecule expression. It is produced predominantly by natural killer and natural killer T cells as part of the innate immune response, and by CD4+ Th1 and CD8+ cytotoxic T lymphocyte once antigen-specific immunity develops [11].

According to the majority of previously published studies, an increased serum level of IFN-γ was observed in patients with alopecia areata compared to healthy controls [1][3][5][6][11][12][13][14][15][16][17][18][19][20][21]. Higher IFN-γ expression was also detected in peripheral blood mononuclear cells in patients with alopecia areata in comparison with the control group [22][23]. Teraki et al. [3] reported an elevated serum level of IFN-γ only in patients with alopecia universalis in comparison with the controls. No significant difference in the serum level of IFN-γ was observed between patients with localized alopecia areata and the control group. In contrast to other studies, an analysis performed by Katagiri et al. [24] revealed a decreased level of IFN-γ mRNA in the peripheral blood mononuclear cells of patients with alopecia areata in comparison with healthy individuals.

Kasumagic-Halilovic et al. [19] reported a higher serum level of IFN-γ in patients with alopecia totalis/universalis compared to patients with localized alopecia areata. Ma et al. [17] reported an increased serum level of IFN-γ in patients with active alopecia areata in comparison with patients with stable alopecia areata and control subjects.

A significant decrease in the serum level of IFN-γ was observed in the group of patients with alopecia areata responding to DPCP therapy. However, no difference was observed in the serum level of IFN-γ before and after DPCP treatment in the non-responder group [14][16][18].

4. Tumor Necrosis Factor (TNF)

TNF is an inflammatory cytokine produced by macrophages/monocytes and T and B lymphocytes during acute inflammation. It is responsible for a diverse range of signaling events within cells, leading to necrosis or apoptosis [25].

Numerous studies demonstrated an increased serum level of TNF in patients with alopecia areata compared to healthy controls [4][8][20][26][27][28][29]. Moreover, an increased expression of TNF mRNA was reported in peripheral blood mononuclear cells in patients with alopecia areata compared to healthy individuals [4][23].

A positive correlation between the serum level of TNF and disease severity was reported in the literature [20][27]. Indeed, a study performed by Alzolibani et al. [4] showed the serum level of TNF to be higher in patients with alopecia areata with the severity SALT score ≥ 25% compared to patients with the SALT score < 25%. Moreover, Rossi et al. [30] described a positive correlation between the expression of TNF level in peripheral blood mononuclear cells and the duration of the disease. According to Barahmani et al. [6] higher serum levels of TNF occurred in patients with alopecia areata and atopy compared to patients with alopecia areata without atopy.

5. Interleukin 12 (IL-12)

IL-12 is a pro-inflammatory cytokine produced by dendritic cells, macrophages, and B cells in response to microbial pathogens [31]. It induces the production of IFN-γ by T and natural killer cells.

Some authors observed an increased serum level of IL-12 in patients with alopecia areata compared to healthy controls [6][14]. Moreover, others reported a higher expression of IL-12 mRNA in peripheral blood mononuclear cells in patients with alopecia areata compared to healthy controls [23].

Rossi et al. [30] demonstrated a positive correlation between IL-12 levels in peripheral blood mononuclear cells and the severity and duration of hair loss [32].

A study conducted by Gong et al. [14] revealed higher serum levels of IL-12 in responders compared to non-responders at baseline. A significant decrease in serum IL-12 level was detected in the responders after DPCP treatment, while in the non-responders the serum level of IL-12 increased.

6. Interleukin 18 (IL-18)

IL-18 is a pleiotropic cytokine involved in the regulation of the innate and acquired immune response. It is produced by various hematopoietic and nonhematopoietic cells, including dendritic cells and macrophages. IL-18 is a potent inducer of IFN- γ in natural killer cells and CD4+ Th1 lymphocytes. It also modulates Th2 and Th17 cell responses, as well as the activity of CD8+ cytotoxic cells and neutrophils [33].

The majority of previously reported studies described no significant difference in the serum level of IL-18 between patients with alopecia areata and healthy controls [6][14][34]. However, Lee et al. [34] detected higher serum levels of IL-18 in patients with >50% of scalp hair loss compared to healthy controls and patients with ≤50% of scalp hair loss.

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