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Evaluation of Serum Level of Interleukin-15 in Patients with Vitiligo

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ABSTRACT

The purpose of this study is to examine the correlation between IL-15 levels in the blood of vitiligo patients and those of healthy controls. Although interleukin-15 (IL-15) has been demonstrated to have an important role in the pathophysiology of numerous autoimmune illnesses, its impact in vitiligo patients has not been well studied. Medline databases (Pub Med and Medscape) were searched for and reviewed for information on IL-15's involvement in vitiligo patients up till 2022. The papers that were included in the meta-analysis were chosen based on a strict set of criteria. The following requirements were met for inclusion: To begin with, it is written in English. 2. Appear in publications with strict peer review. Provide an update on the function of IL-15 in vitiligo patients who will have access to this therapy between now and 2023. Information Extraction: Studies were not included if they did not meet the inclusion criteria. Ethical permission, eligibility criteria, controls, information, and established assessment measures were all considered as part of a comprehensive evaluation of the study's quality. All of the studies that met the criteria were analyzed, and data were abstracted using a standardized method to identify any relevant information about the studies' results that we were interested in. This research leads us to the conclusion that IL-15 is likely involved in the immunological etiology of vitiligo.Interleukin-15 and vitiligo are both important terms.

Keywords: Dermatology, Venereology, Andrology.

1. Introduction

Vitiligo, which affects between half a percent and one percent of the world's population, is the most common DE pigmentary condition [1].

Its pathophysiology is unknown, however it is believed that a number of etiological factors lead to the death of melanocytes. Many researchers believe that a combination of cellular immunity, humoral immunity, and cytokine activity is responsible for the loss of melanocytes in autoimmune disease [2].

There was CD8+ cT cell infiltration in the skin biopsies taken from people with vitiligo in the perilesional sites, suggesting a cytotoxic assault on melanocytes. A Th1 cell response was also suggested by the increased production of TNF- and IFN- [3].

The cytokine interleukin-15 (IL-15) belongs to the interleukin-2 (IL-2) family. Different cell types, such as epithelial cells, nerve cells, monocytes, and dendritic cells, all express it (DCs). By secreting IL-15, neighboring cells may be stimulated by a process called trans-presentation. NK cells, neutrophils, and DCs all benefit from IL-15's ability to stay alive and develop [4].

It also increases macrophage and neutrophil phagocytic activity, as well as NK cell cytotoxicity and the production of cytokines including interferon-gamma and tumor necrosis factor-alpha 5. More so, DCs effectively control the maturation and maintenance of memory cT cells by IL-15 trans-presentation [5].

The Components and Procedures:

Medline databases (Pub Med and Medscape) were combed for information on IL-15's function in the etiology of vitiligo and other relevant topics until the year 2022.

The papers that were included in the meta-analysis were chosen based on a strict set of criteria. The following requirements were met for inclusion: To begin with, it is written in English. 2. Appear in publications with strict peer review. Provide an update on the function of IL-15 in vitiligo patients who will have access to this therapy between now and 2023.

Information Extraction: Studies were not included if they did not meet the inclusion criteria. Ethical permission, eligibility criteria, controls, information, and established assessment measures were all considered as part of a comprehensive evaluation of the study's quality. All of the studies that met the criteria were analyzed, and data were abstracted using a standardized method to identify any relevant information about the studies' results that we were interested in.

A Literature Review on Vitiligo

Vitiligo is a persistent skin condition that causes a person's pigmentation to fade. Destruction of cutaneous melanocytes leads to hypopigmented, asymptomatic macules with well-defined borders [6].

There seems to be no variation in prevalence between sexes or between races or phototypes. In pediatric series, the average onset age is 4.8 years; however, in 25% of instances, the illness manifests itself in children younger than 10. [7].

Vitiligo's etiological and causative factors

Genetics, autoimmunity, oxidative stress, the production of inflammatory mediators, melanocyte detachment, and other factors all have a role in the development of vitiligo. Somehow, the immune system's innate and adaptive components are both playing a role [8]. According to the "convergence hypothesis" or "integrated theory," the death of melanocytes may result from a combination of several processes [9].

Segmental and nonsegmental vitiligo (SV and NSV, respectively) have a same inflammatory etiology characterized by the first release of pro-inflammatory cytokines and neuropeptides in response to an external or internal damage, followed by vascular dilatation and an immunological response [10].

The "neural hypothesis" proposes that the nerve system has a role in the development of vitiligo. [11].

Similarly, similar T-cell infiltrations into melanocytes were seen in SV as in NSV, providing additional evidence that SV is also caused by autoimmunity [12].

It's possible that oxidative stress is the first step in the death of melanocytes. Melanocytes from vitiligo patients were shown to be more fragile and harder to cultivate ex vivo than those from healthy controls, suggesting that they are more vulnerable to oxidative stress [13].

Incidence of Common Vitiligo

Milky white macules appear on different regions of the body, usually in a symmetrical distribution. While most people with hypopigmentation have no symptoms, some have reported slight itching in the days leading up to their diagnosis. It may begin anywhere on the body, but often manifests first in the extremities [14]. The pediatric variant of mixed vitiligo is characterized by segmental involvement prior to the development of classic widespread vitiligo. Patients with SV who have leukotrichia or halo nevi are more likely to progress to mixed vitiligo [15].

Acrofacial Vitiligo

Typically, just the face, head, hands, and feet are affected. Distinctive features include a lack of pigmentation around the mouth and fingers. It may spread to other areas of the body and develop into the more common form of vitiligo [16].

Universal Vitiligo

It typically manifests in mature individuals. Although the term "universalis" is often reserved for cases in which depigmentation affects the majority of the body's surface (80% to 90%), some patches of pigmentation and unscathed hairs are still present in these cases [17].

Symptoms of Vitiligo that Appear in Patches

The most frequent kind of SV is called mono-segmental vitiligo and is characterized by the development of one or more white depigmented macules scattered on one side of the body, with early follicular involvement (leukotrichia) [18].

Lesions in vitiligo ponctué/punctate appear as depigmented, punctiform, 1- to 1.5-mm macules and may appear anywhere on the body. There is no melanocyte loss, hence this condition is rather common, even on areas that get a lot of sun, such the face, neck, hands, and feet [19].

Hypochromic or Mild Vitiligo: To my knowledge, only those with dark complexion are affected. The term "minor" is used to describe a mild pigmentation problem. Pathology and the presence of more typical vitiligo macules establish a connection to real vitiligo [20].

Vitiligo of the follicles, or follicular vitiligo, is a subtype of generalized vitiligo first reported in a young black patient. Unlike the widespread whitening of the skin, the hair is affected only in the follicles [21].

Interleukins

Once assumed to be expressed only by leukocytes, it was subsequently discovered that many other bodily cells also generate interleukins, a kind of cytokine. They're crucial for immune cell proliferation, maturation, migration, and adhesion, as well as activation and differentiation. Additionally, they both contribute to and inhibit inflammation. Therefore, interleukins' major role is to control growth, differentiation, and activation in response to inflammation and immunity. Interleukins are a superfamily of proteins that bind to high-affinity receptors on cell surfaces and trigger a wide variety of cellular and tissue responses. They may act as either a paracrine or autocrine factor. Animal experiments using interleukins are also employed to explore aspects of clinical medicine [22].

There are fifteen distinct varieties of interleukins, which have been given the numbers 1 through 15 to indicate their uniqueness. Most of the interleukins' immunological roles have been well elucidated. T and B lymphocytes (white blood cells crucial to triggering the acquired immune response) are activated predominantly by IL-1 and IL-2, with IL-2 acting as a stimulant of T- and B-cell proliferation and maturation. Not only is IL-1 a mediator of inflammation, but so is IL-6. Cytotoxic T cells and natural killer cells proliferate in response to IL-12, whereas IL-4 stimulates antibody release by B lymphocytes. Which cells will react to an infection and how the sickness manifests itself are both affected by the interleukins that are triggered by a certain infectious agent [23].

Interleukins Have These Common Characteristics

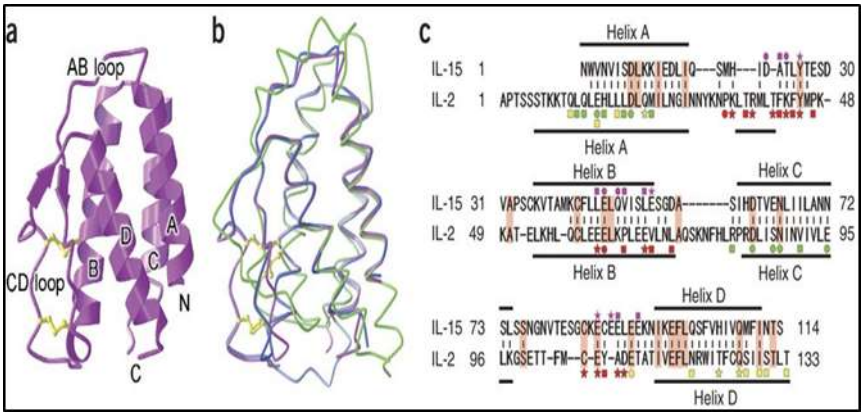
The body naturally regulates the rate at which it produces interleukins. Most interleukins are encoded by mRNA that is unstable, leading to temporary synthesis. Upon completion of synthesis, these compounds are quickly excreted. Interleukin (IL) responses at the cellular level include up- and down-regulatory processes, the activation of genes encoding inhibitors of cytokine receptors, and the involvement of these inhibitory genes. The roles they play are overlapping. To provide just a few examples, the cytokines interleukin-4 (IL-4), IL-5, and IL-13 all play a role in B-cell differentiation and proliferation [24].

External signals or high-affinity receptors activate and control cellular responses to cytokines. One way in which infections might cause an increase in cytokine receptor expression is by activating B-cells [25].

Interleukin-15

The c cytokine interleukin-15 is produced by many different types of cells. This cytokine bridges the gap between the innate and adaptive immune systems and has several targets and functions [26]. Numerous cell types and tissues, such as monocytes, macrophages, keratinocytes, fibroblasts, myocytes, dendritic cells (DCs), and nerve cells, express it constantly [27].

Interleukin-15, like the other short-chain helical cytokines, has a 'up-up-down-down' topology for its four helices (Fig. 1a). IL-2 (Protein Data Bank accession code, 3ink; r.m.s. departure of 2.7 for 98 residues; Fig. 1b) is the closest homolog, followed by IL-4 (Protein Data Bank accession code, 1rcb; r.m.s. deviation of 2.7 for 99 residues). Alignments of their structures showed that IL-15 and IL-2 are 20.2% similar and 39.5% identical in sequence (Fig. 1c). The A, C, and D helices, which interact with the IL-2R and IL-2Rc subunits in IL-2R complexes, are highly conserved across IL-15 and IL-2 [28].



The structure of interleukin-15 is shown in **Fig. (1).** In (a), IL-15, the two disulfide bridges are shown in yellow at their respective places. The N-terminus is the amino end, while the C-terminus is the carboxy end. (b) A combination of IL-2 and the two IL-15 copies (magenta and blue) in the P21212 crystal (green). (c) Alignment of the IL-15 and IL-2 amino acid sequences based on their structures. Colored in pink are residues that are identical in sequence. Circles above and below sequences represent hydrogen bonds; squares above and below sequences represent van der Waals contacts; stars above and below sequences represent both hydrogen bonds and van der Waals contacts; magenta represents binding to IL-15R; red represents binding to IL-2R; green represents binding to IL-2R; and yellow represents binding to c. The residues having an r.m.s. variation in the C position of less than 3.0 are denoted by lines between the IL-15 and IL-2 sequences [28].

There are two IL-15 isoforms, one with a shorter signal peptide (SSP) of 21 amino acids and the other with a larger SSP of 48 amino acids (LSP). However, whereas the LSP-IL-15 is secreted and functions as an immune modulator, the SSP-IL-15 isoform is effectively translated but is not secreted, restricting it to the cytoplasm and nucleus. We still don't know how SSP-IL-15 works biologically. SSP-IL-15, however, is secreted as a complex with IL-15R, and this form has a relatively brief half-life [29].

Multiple human tissues, including epithelial cells and fibroblasts, as well as the heart, lung, liver, kidney, placenta, and skeletal muscle, express interleukin-15. Consistent with IL-15's function during hematopoiesis, it is also generated by bone marrow stromal cell lines, thymic epithelium, and foetal intestinal epithelium [30]. Epidermal skin cells and keratinocytes, foetal skin, retinal pigment epithelium, and intestinal epithelial cells are only few of the epithelial and fibroblast cells that have been shown to generate IL-15 mRNA and/or protein [31].

Vitiligo and interleukin-15 Interleukin-15 helps NK cells, neutrophils, and dendritic cells survive and develop. In addition, it enhances the phagocytic activity of macrophages and neutrophils and the cytotoxic activity of natural killer (NK) cells by increasing the production of cytokines such as interferon gamma (IFN-) and tumor necrosis factor-alpha (TNF-). In addition, IL-15 trans-presentation by DCs effectively controls the maturation and maintenance of memory cT cells. Also, IL-15 promotes Th17 cell proliferation through the T-cell receptor [32].

Both rodent models of the illness and human patients with vitiligo have had CD8+ T cells with a Trm cell phenotype discovered inside lesions. Lesions from vitiligo have an increased number of cells that express the CD69, CD103, and CD49a markers. In response to stimulation, they also secrete IFN- and TNF- and display high amounts of CXCR3. Autoreactive Trm cells were identified by their specificity for melanocyte antigen-specific pentamers (33).

Given that Trm cells seem to be responsible for vitiligo recurrence after quitting existing therapies, they have been identified as possible therapy targets to create sustainable, long-lasting reversal of illness. Although IL-15, IL-7, and TGF- are all necessary for the development of CD8+ Trm cells, only IL-15 has been shown to be necessary for their survival. Complex signaling is involved in the production of IL-15, which is continuously produced by myeloid and stromal cells in a wide variety of peripheral organs [34].

Lymphocytes may express CD215, CD122, and CD132 (the common gamma chain), which all bind IL-15 as a soluble cytokine. Myeloid and stromal cells expressing CD215 are primarily responsible for trans-presenting IL-15 to lymphocytes, a process that serves to bind the cytokine to the cell surface membrane and limit its systemic distribution. By attaching to CD122 and CD132, lymphocytes get the IL-15 signal, which may promote antigen-independent proliferation and cell survival [35].

High levels of CD122 expression by autoreactive Trm cells in mouse and human vitiligo blood and lesion skin, as well as CD215 induction by keratinocytes in vitiligo lesions, suggested that this pathway was functional. Interestingly, in both mouse and human vitiligo, CD122 expression was much greater on melanocyte-specific T cells compared to endogenous memory T cells, indicating that autoreactive T cells were more reliant on this cytokine than non-autoreactive T cells [34].

The anti-CD122 blocking antibody also suppressed IL-15-mediated T cell survival in vitro, but not IL-2-mediated proliferation. This is in line with IL-15 playing a crucial role in modulating T cell survival, but not proliferation, which seems to be mediated by IL-2. Vitiligo was cured and autoreactive, melanocyte-specific Trm cells were eliminated from the body with a systemic therapy with an anti-CD122 blocking antibody, with no effect on

endogenous memory T cells. Therefore, autoreactive T cells were the target of the anti-CD122 inhibiting antibody. The results of a short course of therapy lasted for a long time, and injections into the skin were also successful. These findings corroborate the hypothesis that IL-15 plays a crucial role in the maintenance of autoreactive Trm cells in vitiligo and imply that blocking IL-15 may be a useful targeted therapy approach for vitiligo [34].

Based on the findings of this investigation, IL-15 is hypothesized to have a part in the immunological pathogenesis of vitiligo.

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