ABSTRACT

Vitiligo is an acquired skin disorder that is characterized by a gradual loss of skin pigmentation when melanocytes, the skin’s pigment-producing cells is lost. Pathogenic mechanisms are not well understood. Genetic, abnormal biochemical pathways, autoimmune, melanocyte adhesion deficits and nervous system imbalances are among the pathogenic triggers. Vitiligo lesions have also been shown to have macrophage infiltration. Macrophage migration inhibitory factor (MIF) is a lymphokine that concentrates macrophages at inflammatory sites and is involved in cell-mediated immunity. MIF enhances chemotaxis and macrophage infiltration and upregulates inflammatory responses by inducing the expression of proinflammatory mediators such as TNF-α, nitric oxide and prostaglandin E2. Therapy for vitiligo includes corticosteroids, immunomodulatory agents, vitamin D analogues, antioxidants, phototherapy, laser and surgical therapy. However, no single treatment for vitiligo produces consistently good results and treatment response is variable. Narrow-band ultraviolet (NB-UVB, 311–313nm) phototherapy is viewed as backbone of treatment.
Systemic therapies such as systemic corticosteroids and methotrexate were previously used to treat vitiligo which was assumed to be auto-immune nature. Pathogenic mechanisms, role of MIF and various treatment guidelines are discussed in this review.

Keywords: Vitiligo; pathogenesis; macrophagemigration inhibitoryfactor; therapy.

1. INTRODUCTION

Vitiligo is a depigmenting skin disorder described by the deficiency of melanocytes in explicit spaces of the skin bringing about color weakening in the influenced regions. A totally amelanotic, non-textured, white macule with particular edges is the average lesion [1]. Vitiligo is described by depigmentation of the skin and hair follicles and the degree of the patches permits us to recognize localized or segmental vitiligo and non-segmental vitiligo (NSV) [2]. The Vitiligo Global Issues Consensus Conference defines NSV as an acquired chronic pigmentation disorder characterized by white patches that are usually symmetrical and grow in size over time, corresponding histologically to a significant loss of functioning epidermal pigment cells and hair follicle melanocytes [3]. Vitiligo is now recognized as an autoimmune illness including hereditary and environmental variables as well as problems in metabolism, oxidative stress and cell detachment. The innate immune response and subsequently, adaptive immunity are triggered by inherent abnormalities in melanocytes and keratinocytes which induce the immunopathogenesis of vitiligo [1]. The pro-inflammatory cytokine Macrophage migration inhibitory factor has recently been linked to an increased incidence of vitiligo (MIF) [4]. It has been shown to play a role in a number of immunological and autoimmune diseases. Lipopolysaccharide (LPS), tumor necrosis factor (TNF), hypoxia, hydrogen peroxide (H2O2), thrombin and angiotensin II are all examples of triggers that cause MIF to be produced [5].

2. EPIDEMIOLOGY OF VITILIGO

Vitiligo is the most frequent depigmenting skin condition affecting 0.5–2% of the population worldwide, including both adults and children [6]. Vitiligo affects people of all races and skin types in the same way [7]. Males and females are both impacted, although women and girls seek help more frequently than boys and men, probably because of the greater negative social impact [8]. Vitiligo affects 25% of patients under the age of ten, almost half of those under the age of twenty and about 70%–80% of those under the age of thirty [9].

3. ETIOPATHOGENESIS OF VITILIGO

Vitiligo is a multifactorial disease characterized by the loss of functioning melanocytes [10]. Melanocyte loss has been linked to a number of processes in vitiligo. Genetics, immunological reactions, oxidative stress, the creation of inflammatory mediators and processes of melanocyte separation are among them. Both the innate and adaptive components of the immune system appear to be engaged. None of these theories are sufficient to explain the diverse vitiligo phenotypes and the relative importance of each of these mechanisms is still a source of debate. According to the convergence theory, multiple mechanisms may interact in vitiligo to contribute to the loss of melanocytes [11].

3.1 Genetics

Familial clustering is a feature of vitiligo. According to numerous research, the prevalence of vitiligo among first-degree relatives ranges from 0.14% to 20%. vitiligo is a polygenic disease, several candidate genes have been identified including major histocompatibility complex (MHC), catalase (CAT), angiotensin-converting enzyme (ACE), cytotoxic T lymphocyte antigen-4 (CTLA-4), non-receptor type 22 (PTPN22), catechol-O-methyltransferase (COMT), protein tyrosine phosphatase, NACH leucine-rich repeat protein 1 (NALP1), X-box binding protein 1 (XBP1), forkhead box P1 (FOXP1), interleukin-2 receptor A (IL-2RA) and human leukocyte antigen (HLA) that are involved in the immunity regulation for genetic association with vitiligo [12].
Table 1. Various pathogenic mechanisms

| Pathogenic Mechanism               | References                        |
|------------------------------------|-----------------------------------|
| Genetics                           | Spritz [12]                       |
| Autoimmune                         | Alkhateeb et al. [13]             |
| Humoral response                   | Zhu et al. [14]                   |
| Cell-mediated response             | Sabat et al. [15]                 |
| Oxidative Stress                   | Sastry et al. [16]                |
| Melanocytorrhagy                   | Kumar and Parsad [17]             |
| Neurohumoral                       | Lotti et al. [18]                 |
| Autocytotoxicity                   | Hann and Chun [19]                |
| Deficiency of survival signals     | Kitamura et al. [20]              |
| Convergence theory                 | Kundu et al. [21]                 |

3.2 Autoimmune Hypothesis

Other autoimmune illnesses are frequently associated to vitiligo. In a recent study of unselected vitiligo patients, increased rates of autoimmune thyroid disease, Addison’s disease, systemic lupus erythematosus, and psoriasis were found with roughly 30% of people having at least one additional autoimmune illness [13]. Furthermore, these autoimmune illnesses were found to be more common among first-degree relatives of the patients. In addition to autoimmune thyroid disease, Addison’s disease, systemic lupus erythematosus, and psoriasis, multiplex generalized vitiligo families had higher rates of psoriasis, rheumatoid arthritis, and type 1 diabetes mellitus [22]. This shows that a subset of autoimmune diseases, such as widespread vitiligo, may be predisposed by genetics. Vitiligo patients on the other hand, were found to have thyroid dysfunction but no other autoimmune disease [23].

3.3 Role of Humoral Response

Antibodies against melanocytes have been found in patients with vitiligo that is not stable [24]. In the cytoplasm of melanocytes, anti-melanocyte antibodies have been found. Patients with vitiligo had antibodies against membrane and cytoplasmic antigens and these membrane antigens were identified as Lamin A/C and vimentin X using protein mass spectrometry [14].

3.4 Role of Cell-mediated Response

The immune system can be stimulated by inflamma-mosome activation and the release of pro-inflammatory cytokines including IL-1, IL-6 and IL-8 [25]. CD4+ T lymphocytes receive melanocyte autoantigens from dendritic cells (DCs) activated by pro-inflammatory cytokines [26]. After producing numerous cytokines, CD4+ T cells evolve into Th1/Th17 lymphocytes [27]. Th17, which is activated by IL-23 and IL-6, plays a key role in the progression of vitiligo by secreting IL-17, IL-21, and IL-22. IL-17, the most important immunological feature of vitiligo, impacts melanocyte death in a variety of ways [15].

3.5 Oxidative Stress

There is significant evidence that the melanocytes of vitiligo patients have inherent issues that restrict their ability to deal with cellular stress [28]. Oxidative stress hypersensitivity has been linked to melanocyte degeneration in numerous studies. Oxidative stress changes the expression of genes that affect apoptosis, melanogenesis, cell cycle, stress response and immunology [16]. Extrinsic stimuli and intrinsic deficits in vitiligo melanocytes both lead to increased oxidative stress and overproduction of reactive oxygen species (ROS) resulting in altered gene expression. Trauma, stress, and ultraviolet light as well as serious infections, malignancies, neurological disorders, pregnancy, calcium imbalance, and other stimulants, all contribute to the overproduction of ROS in vitiligo [29].

3.6 Melanocytorrhagy Hypothesis

Non-segmental vitiligo is a primary melanocytorrhagic illness defined by altered melanocyte responses to friction resulting in detachment, apoptosis, and transepidermal loss according to the theory of melanocytorrhagic disorders [17].

3.7 Neurohumoral Hypothesis

According to scientific research, psychological stress and neurological pathways regulate the release of neuropeptides (NPs), various cell
behaviors, and expression of innate and adaptive immunity in the skin. The neurohumoral pathogenesis of vitiligo is supported by the common origin of both melanocytes and nerves from neural crest cells, the normal presence of SV in a dermatomal manner, changes in perspiration and nerve structure in vitiliginous skin and expression of specific neuropeptides in patients with vitiligo [18].

3.8 Autocytotoxicity

Toxic metabolites both intracellular and extracellular such as phenols or quinones can build up and harm melanocytes in genetically predisposed people causing autocytotoxic injury. When tyrosine enters melaninogenic pathways, it produces electrically unstable by-products that have the ability to damage other cellular substrates ending in melanocyte death [19].

3.9 Deficiency of Survival Signals

According to this hypothesis, the lack of survival signals in vitiliginous skin causes melanocyte death. Stem cell factors generated by neighboring keratinocytes govern melanocyte development and survival through binding to the membrane tyrosine kinase receptor c-kit in the normal epidermis. As a result, the perilesional melanocytes may have a significantly smaller amount of c-kit receptors [20]. A decrease in stem cell factor expression from the surrounding keratinocytes may aid in the death of melanocytes [30].

3.10 Convergence Theory

The search for aetiologic factors has led to the development of biochemical, neurologic, and autoimmune theories. The convergence theory was proposed several years ago to unite earlier views on vitiligo development into a comprehensive picture of vitiligo aetiology. The hypothesis that vitiligo is caused by a combination of aetiologic factors that affect melanocyte survival, rather than just predisposing mutations, melanocytes responding to chemical/radiation exposure, or hyperreactive T cells, has obviously changed over time [21].

4. MIF

Macrophage migration inhibitory factor was one of the earliest cytokines discovered in the early 1960s. It has a wide range of immunologic effects and is expressed by a variety of cells, indicating that it is important in immune response modulation. It gets its name from the protein's initial well-known function, which is to stop macrophages from migrating [31]. MIF is a T-lymphocyte cytokine that stops macrophages from moving randomly. It was discovered as a T-lymphocyte cytokine produced in delayed-type hypersensitivity reactions. Macrophages, monocytes, pituitary cells, and vascular endothelial cells have all been investigated as potential sources of MIF as an immunoneuroendocrine mediator. Dopachrome, phenylpyruvate tautomerase and thiol-protein oxidoreductase are all enzymes found in MIF [32]. MIF is a pleiotropic protein with biological properties similar to cytokines and hormones. MIF recruits the glycoprotein CD44 when it binds to the CD74 receptor, activating intracellular signaling pathways such as MAPK/ERK, Src, P13K/Akt and nuclear factor kappa B. When the chemokine receptors CXCR2, CXCR4 and CXCR7 link to one other, MIF signaling is activated [5]. In addition to its role in immunoinflammatory reactions, MIF is a hormone produced by the anterior pituitary and adrenal gland during hypothalamic pituitary axis activation. Thus, glucocorticoids regulate MIF secretion in T cells and macrophages in a biphasic and concentration-dependent manner, with "low" levels boosting MIF secretion and "high" levels inhibiting MIF secretion in T cells and macrophages [33].

4.1 Induction of MIF

Proinflammatory substances including as TNF-α, IL-5, IFN-γ, transforming growth factor and lipopolysaccharide (LPS) have been demonstrated to enhance MIF mRNA expression and protein production [34]. C5a, a complement-activated substance, has also been demonstrated to help polymorphonuclear leukocytes release MIF [35]. Furthermore, TLR4 ligand stimulation of mature DC evoked larger levels of MIF production than TLR4 ligand stimulation of immature DC [36]. Finally, macrophages produce MIF when they recognize an immune complex, which works as an autocrine/paracrine stimulator of TNF production [37].
4.2 Biological activities of MIF

Table 2. Kasama et al. [32]

| Chemotactic Functions                        | stimulation/inhibition: is based on their concentration. |
|---------------------------------------------|----------------------------------------------------------|
| Monocytes                                   |                                                          |
| T lymphocytes                               |                                                          |
| Vascular smooth muscle cells                |                                                          |
| Fibroblasts                                 |                                                          |
| Activities that cause angiogenesis          |                                                          |

| Anti-apoptotic activities                   |                                                          |
| Cell proliferation                          |                                                          |
| Stimulation                                 |                                                          |
| Mediators are induced                       |                                                          |
| Cytokines                                   | TNF-α                                                   |
|                                             | IL-1, 6, 8, 12                                          |
|                                             | CCL2                                                    |
|                                             | VEGF                                                    |
|                                             | ICAM-1                                                  |
|                                             | VCAM-1                                                  |
|                                             | E-selectin                                              |
|                                             | P-selectin                                              |
|                                             | MMP-1, 3, 9, 13                                         |

| Growth factor                               |                                                          |
| Adhesion molecules                          |                                                          |

| Proteinases                                 |                                                          |
| Nitric oxide                                |                                                          |
| Superoxide                                  |                                                          |

4.3 Role OF MIF In autoimmune Disorders

MIF affects the progression and outcome of autoimmune disorders through one or more of the pathways listed below: a) inhibiting the immunosuppressive effects of glucocorticoids. b) Effector functions of immune cells, such as cytokine production are stimulated. c) Upregulation of adhesion molecules and chemokines promotes immune cell migration and homing. d) The increase of adhesion molecules and chemokines inhibits immune cell recruitment and homing. MIF is unique among cytokines in that it has anti-glucocorticoid characteristics that affect immune cell effector functions such as cellular proliferation and cytokine generation [38].

4.4 MIF As a Vitiligo Incriminating Agent

MIF is a pro-inflammatory cytokine that has been connected to the development of vitiligo [4]. It has been shown to play a role in a number of immunological and autoimmune diseases. Lipopolysaccharide (LPS), tumor necrosis factor (TNF), hypoxia, hydrogen peroxide (H2O2), thrombin and angiotensin II are all examples of triggers that cause MIF to be produced [5]. Oxidative stress and DNA damage, two common mediators of MIF secretion, also enhanced MIF secretion [39]. It is also notable for allowing immune cells to get activated and the generation of proinflammatory cytokines such as TNF-α, IL-1, and IFN-γ, all of which have been linked to the pathogenesis of vitiligo [40]. Inflammatory cytokines TNF-α and IL-6 have anti-pigmentation effects. TNF-α and IL-6 mRNA levels were found to be higher in the epidermis of vitiligo tissue samples. [41]. MIF has been shown to inhibit macrophage spontaneous mobility, concentrate macrophages in sites of inflammation and perform a number of biological functions including macrophage activation, adhesion enhancement, phagocytosis and tumoricidal action. Macrophages, in fact, are a major source of MIF. As a result, the MIF and macrophage loop may have a role in the aetiology of vitiligo [40].
### Table 3. Role of Macrophage migration inhibitory factor in vitiligo

| Role of Macrophage migration inhibitory factor in vitiligo                                                                 | References |
|-----------------------------------------------------------------------------------------------------------------------------|------------|
| TNF-α, IL-1, and IFN-γ are examples of proinflammatory cytokines produced.                                                   | Ma et al. [40] |
| Inflammatory cytokines TNF-α and IL-6 have anti-pigmentation effects.                                                        | Moretti et al. [41] |
| TNF-α and IL-6 mRNA levels were higher in the epidermis of vitiligo samples.                                                   | Moretti et al. [41] |
| Limit macrophage movement, concentrate macrophages and conduct a variety of biological duties such as macrophage activation, adhesion enhancement, phagocytosis, tumoricidal activity, and melanocyte clearance. | Ma et al. [40] |

#### 4.5 Serum Concentrations of MIF in vitiligo

| Serum Concentrations of MIF in vitiligo                                                                                     | References |
|-----------------------------------------------------------------------------------------------------------------------------|------------|
| MIF levels in the blood were higher in patients with active NSV and were negatively correlated with evolution years. MIF polymorphisms were found to be connected to NSV susceptibility. | Garcia-Orozco et al. [42] |
| MIF serum levels and mRNA were significantly higher in patients' peripheral blood mononuclear cells (PBMCs) than in controls. The vitiligo area severity index score (VASI) was connected to variations in serum MIF concentrations and mRNA levels, and there was a significant difference between individuals who were progressing and those who were stable. | Ma et al. [40] |
| The mean serum MIF level in vitiligo patients was higher than in controls. Despite the fact that there was a significant difference between patients with generalized and localized vitiligo, no link was found between MIF levels and disease activity. | Serarslan et al. [43] |
| MIF mRNA levels and blood MIF concentrations were significantly greater in patients with vitiligo vulgaris compared to controls and in generalized vitiligo compared to localized vitiligo with a positive relationship between vitiligo type, duration, and severity. | Farag et al. [44] |
| Patients with vitiligo had a slightly higher MIF than controls, but there was no noticeable difference between those who progressed and those who remained stable. In all patient groups, both were positively related to the extent and severity of the illness. | Sorouret al. [45] |

### 5. VITILIGO TREATMENT

Vitiligo is still one of the most difficult skin diseases to treat. Recognizing that vitiligo is more than a cosmetic condition with safe and effective therapies is an important first step in controlling it [7]. Vitiligo therapy demands a specific method and a variety of circumstances determine the treatment option (disease duration, impact, skin type, extent, sex, age, involved areas, social life). Vitiligo therapy demands a specific method and a variety of circumstances.
expectations and provide detailed explanations on what to expect [46]. The treatments have been demonstrated to help in repigmentation, lowering the risk of relapses, and slowing the progression of the disease. Despite the difficulties and limitations of the treatments, vitiligo typically causes a significant deterioration in quality of life and the risk-benefit ratio in most cases favors an active approach. Systemic and topical drugs that target the pathways that cause melanocyte loss and melanocyte stem cell differentiation should provide more effective treatments in the near future [47]. Phototherapy, topical and systemic immunosuppressants and surgical procedures are some of the treatments that may help to slow the progression of the disease, stabilize depigmented lesions and encourage regimentation [2].

5.1 Camouflage

Camouflage can help alleviate this stress by concealing vitiligo lesions, hence improving vitiligo patients' psycho-social well-being and guaranteeing treatment adherence [48]. Color matching, stability, simplicity of application and removal are all aspects of a fantastic temporary camouflage. Waterproof, sweat-proof, noncomedogenic, nonallergenic, non-photolabile and UV-protective are all desirable qualities. The most significant drawbacks of temporary camouflage are improper application and inconsistency in color [50].

5.2 Topical Immunosuppressants

5.2.1 Corticosteroids

Corticosteroids aid to suppress cellular immune responses, melanocyte destruction and melanocyte regeneration as well as melanin formation [51]. Topical corticosteroids can be used alone (for example, in localized vitiligo) or in combination with phototherapy or other topical medications as a first-line treatment (e.g. in generalized vitiligo) [52].

5.2.2 Calcineurin inhibitors

When administered alone or in combination with phototherapy, tacrolimus and pimecrolimus are as effective as topical steroids but have a lower risk of side effects [53]. They inhibit the production of pro-inflammatory cytokines, allowing melanocytes and melanoblasts to proliferate. When applied twice daily for a minimum of 6 months, they are especially beneficial on the face and neck [54].

5.2.3 Vitamin D3 analogues

In vitiligo, the expression of proinflammatory and proapoptotic cytokines like IL6, IL8, IL10, IL12, INF and TNF is elevated. Vitamin D can have immunomodulatory effects by reducing the expression of IL6, IL8 and TNF, thereby limiting dendritic cell maturation, differentiation and activation via a VDR-dependent route [55].

5.2.4 Prostaglandin F2 alpha analogue

Latanoprost and bimatoprost, two analogues of prostaglandin F2 alpha (PGF2), have recently been employed. PGF2, on the other hand, has an indirect effect via activating COX-2 and PGE2, making it a feasible therapeutic option with improved efficacy when combined with phototherapy [56].

5.2.6 Fluorouracil

The darkening that occurs as a side effect of 5-FU treatment in people with skin cancer is the fundamental justification for using it as a vitiligo treatment. After microneedling, 5-FU activates the amelanotic (inactive) melanocytes in the bottom portion of the hair follicle, prompting them to multiply and migrate upward to the infundibulum where they start actively generating melanin and then migrate higher until they reach the skin's surface [57].

Table 4. Various lines of treatment of vitiligo

| References |
|---------------------------------|
| Camouflage | Tanioka et al. [48] |
| Topical immunosuppressants | Rodrigues et al. [2] |
| Systemic immunosuppressants | Rodrigues et al. [2] |
| Phototherapy | Rodrigues et al. [2] |
| Surgical procedures | Rodrigues et al. [2] |
| Depigmentation techniques | Alghamdi and Kumar [49] |
5.2.7 Basic fibroblast growth derived peptide

In the treatment of vitiligo, the use of basic fibroblast growth factor (bFGF) and peptides derived from it has given conflicting results. The level of bFGF mRNA in lesional skin is very low, which could be associated to depigmentation [58].

5.2.8 Antioxidants

Oxidative stress and free radicals are hypothesized to play a role in the pathophysiology of vitiligo, with higher amounts of hydrogen peroxide in the epidermis of vitiliginous skin [59]. The scientists looked examined superoxide dismutase with and without catalase as well as other compounds (vitamin B12, calcium pantothenate, copper and zinc). Excimer light with (SOD, copper–zinc, vitamin B12, calcium pantothenate) promotes increased repigmentation after 3 months of therapy, while the results of another research involving (SOD, CAT) were negative [60].

5.3 Systemic Immunosuppressants

5.3.1 Antioxidants

In open trials, oral administration of single or several antioxidants was proven to decrease the progression of vitiligo and promote repigmentation [61]. Pseudocatalase, vitamin E, vitamin C, ubiquinone, lipoic acid, Polypodium leucotomos, catalasesuperoxide dismutase comboand Ginkgo biloba have all been used alone or in conjunction with phototherapy [62].

5.3.2 Oral mini-pulse steroid

Systemic corticosteroids are the first-line treatment for vitiligo that is quickly progressing. It not only slows disease progression, but it also promotes repigmentation by allowing normal melanocytes to migrate from the lesions’ peripheral or the perifollicular region. The time it takes for sickness to stop reoccurring can range from a few weeks to months [63]. Patients with vitiligo that is rapidly advancing may benefit from oral mini-pulse (OMP) therapy, as they may have a poor response to other treatments [64]. The administration of cyclical pulsed dose corticosteroids in substantially lower doses than typical pulsed therapy is referred to as OMP therapy. The two most commonly used corticosteroids are betamethasone and dexamethasone [62]. It is effective in preventing development and producing rapid repigmentation when paired with NB-UVB, so, long-term side effects can be avoided [65].

5.3.3 Methotrexate

Methotrexate is a folic acid derivative that exhibits antiproliferative, antineoplastic, cytotoxic, immunosuppressive and anti-inflammatory characteristics. It has been used to treat a variety of dermatological conditions [66]. In vitiligo, TNF-α expression is significantly higher on the lesional site than on the perilesional, non-lesionaland healthy skin. Oral and topical steroids have been used to treat vitiligo since the beginning of time, but they come with their own set of side effects when taken for a lengthy period of time. Methotrexate has so been utilized in the treatment of vitiligo as a steroid-free alternative. It helps to treat vitiligo by lowering the number of T cells capable of generating TNF-α [67]. In the treatment of vitiligo, an up-titrating dose of 12.5–25 mg/week can be employed. There have been no serious side effects reported [68].

5.3.4 Azathioprine

Azathioprine is an immunomodulator that has been used to treat a variety of dermatological conditions, but not vitiligo. Various trials have employed azathioprine in the treatment of vitiligo at doses of 100 mg/day or 0.6–0.75 mg/kg. When compared to oral betamethasone pulse therapy, azathioprine has demonstrated good efficacy in preventing vitiligo development and repigmentation [69].

5.3.5 Cyclophosphamide

Because of its suppressive effect on lymphocytes and antibody production, cyclophosphamide is often used in many autoimmune dermatoses, including vitiligo. It has not been approved for vitiligo therapy. It comes in a 1–1.5 mg per kilogramme of body weight dosage. Some of the more serious adverse effects include hemorrhagic cystitis, myelosuppression, amenorrhoea, azoospermia and nail and teeth discoloration [70].

5.3.6 Cyclosporine

The phosphorylation of nuclear factor of activated T cells (NFAT), a transcription factor essential for the production of interleukin 2
genes, is inhibited by cyclosporine (IL 2). This interleukin is a master cytokine that is necessary to fully activate the T cell pathway [71]. Cyclosporine may produce regimentation in lesions that are already present as well as slowing disease progression. Cyclosporine, in addition to having an immunomodulatory effect, is likely to have a direct effect on melanogenesis [72].

5.3.7 JAK STAT Inhibitors

JAK STAT inhibitors, also known as jakinibs, work by blocking the JAK family of enzymes (JAK1, JAK2, JAK3, and TYK2) and can thus be used to treat a variety of disorders involving the JAK–STAT pathway. Many proinflammatory pathways’ downstream signaling is regulated by the intracellular pathway Janus kinase signal transducer and activator of transcription (JAK/STAT). JAK STAT inhibitors are intracellular small molecular medicines that are accessible in oral and topical formulations. Tofacitinib is a promising therapy option because it suppresses interferon gamma signaling, which is important in CD8 lymphocyte-mediated melanocyte death in vitiligo. Tofacitinib, at a dose of 5–10 mg twice daily orally, causes sufficient repigmentation in vitiligo patients. Because oral formulations cause the bulk of these side effects, a topical formulation of 2% tofacitinib with or without penetration enhancers has been developed as a safer option [73].

5.3.8 Biologics

Increased cytokines in vitiligo are paracrine inhibitors of melanocyte proliferation, impair melanocyte tyrosinase activity and contribute to melanocyte apoptosis. TNF inhibitors have been shown to reduce melanocyte death while also encouraging the growth of melanocyte stem cells. TNF inhibitors like as infliximab, adalimumab and etanercept have been used to treat vitiligo. Etanercept 50 mg twice a week was given subcutaneously for 12 weeks, then 50 mg once a week. Adalimumab (40 mg) was given subcutaneously every other week. At 0, 2, 6, and 8 weeks, infliximab is given intravenously at a dose of 5 mg/kg body weight [74]. Rituximab is a chimeric monoclonal antibody that specifically targets the CD20 protein on the surface of B cells. It's also used to treat autoimmune illnesses like bullous diseases. It's vitiligo treatment that isn't approved by the FDA. In vitiligo, antibodies against melanocyte-associated antigens cause melanocyte apoptosis. Rituximab increases melanocytes, decreases lymphoid infiltrates and lowers apoptotic markers in melanocytes. Using a single intravenous infusion of 1 g of rituximab for a 6-month follow-up period revealed good results. Some of the negative effects of rituximab include nephrotoxicity, tumor lysis syndrome, infection reactivation and late onset neutropenia [75].

5.3.9 Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) is a sterile, highly concentrated IgG preparation prepared from pooled human plasma that includes over 95% unaltered IgG and very little IgA or IgM. The specific mechanism of action of IVIG is uncertain, however antiidiotypic interactions, fc receptor regulation, cytokine synthesis modulation, cytokine antagonists and acceleration of IgG catalysis are thought to be involved [76].

5.3.10 Other systemic medications

By attaching to the melanocortin-1 receptor, afamelanotide is a longer-acting synthetic analogue of α-MSH that increases melanocyte proliferation and melanogenesis [77]. As a side effect of glaucoma medication, latanoprost (LT) is a prostaglandin F2alpha analogue that has been linked to skin pigmentation. It promotes melanocyte growth by increasing tyrosinase activity [56]. Because of their immunomodulatory effects, statins which are best known for combating atherosclerosis have spurred interest in vitiligo treatment. Statins inhibit the expression of a number of adhesion molecules involved in the cellular immune response including MHC II in antigen presenting cells (APCs), T cell chemokine receptors and inflammatory cytokines like tumour necrosis factor (TNF-α) in antigen presenting cells, interleukin IL-6 and IL-2 in antigen presenting cells. They are also antioxidants since they inhibit nitric oxide synthase and promote the production of regulatory proteins like IL-12 and TGF-β [78]. Levamisole is an antihelminthic agent that acts as a nicotinic acetylcholine receptor agonist. It possesses a wide spectrum of immunomodulatory effects in macrophages and T lymphocytes, primarily impacting phagocytosis, chemotaxis, adhesion and intracellular killing. Increased B-cell activity is likewise inhibited by levamisole. In the treatment of vitiligo, 150 mg twice a day for two days is administered orally. It has been demonstrated to both control and facilitate skin repigmentation. Nausea, vomiting, diarrhea, hunger, weakness and dizziness are all
potential adverse effects [79]. Minocycline is a semi-synthetic tetracycline antibiotic. In addition to its antibacterial activity, minocycline provides a number of non-antibiotic benefits, including antioxidative activity. Long-term usage of minocycline, on the other hand may result in hyperpigmentation of the skin. Cell growth was inhibited, thiol levels were lowered, and superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase activities were boosted (GPx) [80].

5.4 Phototherapy

5.4.1 Narrow-band ultraviolet -B

Narrowband ultraviolet B (NB-UVB) therapy for vitiligo is considered an effective and safe treatment option with outstanding results [81]. Phototherapy with a peak wavelength of 311 nm has been used to treat vitiligo for decades. In vitiligo patients, NB-UVB phototherapy is performed two to three times per week over several months to years to generate considerable repigmentation [64]. The efficacy of NB-therapeutic UVB is due in part to its immunomodulating qualities which prevent melanocyte death and as a result, depigmentation. The main mechanism of action, however, is to induce repigmentation by encouraging melanocyte differentiation, migration and proliferation, most likely through increased melanocyte growth factors such as basic fibroblast growth factor (bFGF) and endothelin-1 (EN-1) [82]. Indeed, [83] in vitiligo skin, researchers discovered that NB-UVB causes amelanotic spindle cells to multiply and move as melanocyte precursors, repopulating the epidermis with new generations of melanocytes and restoring pigmentation. In terms of vitiligo repigmentation rates, NB-UVB has been shown to be superior to PUVA, especially in the case of unstable widespread vitiligo and achieving more cosmetically satisfactory results. [84]. Short-term side effects like erythema, blistering and hyperpigmentation, as well as long-term side effects like premature photoagingare well-known cutaneous side effects of NB-UVB phototherapy. However, the systemic effects of NB-UVB phototherapy on internal health have not been well investigated [85].

5.4.2 NB UVB in combination with systemic treatments

A number of studies have looked into combining these medications with NB UVB to speed up and increase the therapeutic response to phototherapy, in addition to their monotherapy use [86]. Combination therapy improves effectiveness and patient compliance while reducing recovery time [87]. According to [65] With minimal side effects, oral methyl prednisolone mini pulse therapy combined with NB UVB successfully produced repigmentation and prevented the progression of vitiligo. Methotrexate (MTX) in conjunction with NBUVB is an equally effective and low-side-effects treatment for vitiligo vulgaris progression, therefore it can be used as a steroid-free alternative in patients with active vitiligo when corticosteroids are not tolerated [88].

5.4.3 PUVA (Psoralen+UVA)

As part of photochemotherapy, the patient receives total body irradiation with UVA (320–400 nm) after taking a photosensitizer many times a week. The most popular photosensitizer is 8-methoxypsoralen (methoxsalen, 8-MOP). It's applied topically (creams, gels, solutions) or taken orally, then exposed to UVA [89]. The actual mechanism of action of methoxsalen is uncertain. The most well-known biological reaction of methoxsalen is with DNA. Methoxsalen conjugates and forms covalent bonds with DNA when photactivated, resulting in monofunctional and bifunctional adducts [90].

5.4.4 Laser

Facial vitiligo has profound psychological and emotional consequences. Excimer lasers with a wavelength of 308 nm have been widely used to treat vitiligo [91]. Its mechanism of action is thought to be similar to previous UVB therapies, as evidenced by treated vitiligo patches that repigment in the same patterns as those found with typical NB-UVB phototherapy [92]. The 632.8-nm helium neon (He-Ne) laser is used to treat patients with segmental vitiligo, which has a worse response to standard therapy than NSV. By changing the adrenergic dysregulation of cutaneous blood flow seen in SV, the He-Ne laser promotes melanogenesis, melanocyte production, migration and survival in the skin [93].

5.5 Surgical Procedures

A significant proportion of vitiligo lesions do not respond to medical treatment or respond with insufficient repigmentation. Such lesions are thought to be amenable to surgical therapy. In the treatment of recalcitrant vitiligo patients,
surgical intervention has proven to be a beneficial method [94]. All patients should be educated about the Koebner phenomenon before initiating vitiligo surgical therapies [95]. The two types of vitiligo surgery are tissue grafting and cellular grafting [96].

5.6 Depigmentation

Depigmentation may help patients with advanced or recalcitrant illness. Though there is no universal agreement on when to begin depigmentation, treatment is generally recommended if more than 60% of the body surface area is affected or noticeable parts such as the face and hands are impacted. Depigmenting therapies include monobenzyl ether of hydroquinone (MBEH), monomethyl ether of hydroquinone (MMEH), phenol, laser and cryotherapy [49].

5.7 Role of MIF as a therapeutic target

MIF is a multifunctional cytokine associated with the onset of autoimmune inflammatory disorders. Anti-MIF antibodies or specific MIF antagonists that target MIF selectively could provide new therapeutic alternatives for certain diseases. Because MIF and glucocorticoids have such a close regulatory relationship, pharmacological antagonism of MIF could be a steroid-free treatment option for people with refractory autoimmune diseases [97]. Using D-dopachrome-tautomerase activity and possible substrates with bio-inhibitory activity, the biological function of the substrate was studied, and a molecule with a clear structural similarity to the analgesic medication acetaminophen was found [98]. Acetaminophen has been discovered to be a mild inhibitor of dopachrome tautomeration. N-acetyl-p-benzoquinone imine, the first small molecule inhibitor, inactivates both the catalytic and biological functions of MIF, most likely by disrupting a physiologically important epitope through a conformational change in the protein structure following the enzymatic activity. Another chemical that has the ability to disrupt MIF's biological effects is isoxazolines [99]. Imine conjugates, amino acid-benzaldehyde analogue conjugates and amino acid-benzaldehyde analogue conjugates [100].

6. CONCLUSION

MIF may play a role in the progression of vitiligo, as well as its pathogenesis and as a disease severity marker. Furthermore, as a marker, MIF could be a therapeutic target in the aetiology and treatment of vitiligo.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Picardo M, Dell’Anna ML, Ezzedine, K, Hamzavi I, Harris JE, Parsad D, et al. Vitiligo. Nature Reviews Disease Primers. 2015;1:15011. DOI: 10.1038/nrdp.2015.11 PMID: 27189851
2. Rodrigues M, Ezzedine K, Hamzavi I, Pandya AG, Harris JE. Vitiligo Working Group. Current and emerging treatments for vitiligo. J Am Acad Dermatol. 2017;77(1):17–29. DOI: 10.1016/j.jaad.2016.11.010 PMID: 28619557
3. Boniface K, Seneschal J, Picardo M, Taïeb A. Vitiligo: Focus on clinical aspects, immunopathogenesis, and therapy. Clinical Reviews in Allergy Immunology. 2018;54(1), 52–67. DOI: 10.1007/s12016-017-8622-7 PMID: 28685247
4. Farag AG, Habib MS, Kamh ME, Hammam MA, Elnaidany NF. Macrophage migration inhibitory factor as an incriminating agent in vitiligo. Anais Brasileiros de Dermatologia. 2018;93(2):191–196. DOI: 10.1590/abd1806-4841.20186068 PMID: 29723363
5. Jankauskas SS, Wong DWL, Bucala R, Djudjaj S, Boor P. Evolving complexity of MIF signaling. Cellular Signalling. 2019;57:76–88. DOI: 10.1016/j.cellsig.2019.01.006 PMID: 30682543
6. Krüger C, Uta Schallreuter K. A review of the worldwide prevalence of vitiligo in children/adolescents and adults. Int J Dermatol. 2012;51(10):1206–12. DOI: 10.1111/j.1365-4632.2011.05377.x PMID: 22458952
7. Ezzedine K, Sheth V, Rodrigues M, Eleftheriadou V, Harris JE, Hamzavi IH, et al. Vitiligo Working Group. Vitiligo is not a cosmetic disease. J Am Acad Dermatol. 2015;73(5):883–5. DOI: 10.1016/j.jaad.2015.07.039 PMID: 26475548
8. Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their relatives. Pigment Cell Res. 2003;16(3):208–214. DOI: 10.1034/j.1600-0749.2003.00032.x 
PMID: 12753387

16. Zhu M, Ma H, Zhan Z, Liu C, Luo W, Zhao G. Detection of auto antibodies and transplantation of cultured autologous melanocytes for the treatment of vitiligo. Exp Ther Med. 2017;13(1):23-8. DOI: 10.3892/etm.2016.3949 
PMID: 28132462

9. Lee H, Lee M, Lee DY, Kang HY, Kim KH, Choi GS, et al. Prevalence of vitiligo and associated comorbidities in Korea. Yonsei Med J. 2015;56(3):719–25. DOI: 10.3349/ymj.2015.56.3.719 
PMID: 25837178

17. Zhu MC, Liu CG, Wang DX, Zhan Z. Detection of serum antimelanocyte antibodies and identification of related antigens in patients with vitiligo. Genet Mol Res. 2015;14(4)16060-73. DOI: 10.4238/2015.December.7.19 
PMID: 26662399

10. Ezzedine K, Lim HW, Suzuki T, Katayama I, Hamzavi I, Lan CCE, et al. Vitiligo Global Issue Consensus Panelists. Revised classification/nomenclature of vitiligo and related issues: the Vitiligo Global Issues Consensus Conference. Pigment Cell Melanoma Res. 2012;25(3):E1–13. DOI: 10.1111/j.1755-148X.2012.00997.x 
PMCID: PMC3511780

18. Marie J, Kovacs D, Pain C, Jouary T, Cota C, Vergier B, et al. Inflammasome activation and vitiligo/nonsegmental vitiligo progression. Br J Dermatol. 2014;170(4):816-823. DOI: 10.1111/bjd.12691 
PMID: 2473494

11. Strassner JP, Harris JE. Understanding mechanisms of autoimmunity through translational research in vitiligo. Curr Opin Immunol. 2016;43:81–8. DOI: 10.1016/j.coi.2016.09.008 
PMID: 27764715

19. Spritz RA. The genetics of generalized vitiligo: Autoimmune pathways and an inverse relationship with malignant melanoma. Genome Med. 2010;19;2(10):78. DOI: 10.1186/gm199 
PMID: 20959028

12. Spritz RA. The genetics of generalized vitiligo: Autoimmune pathways and an inverse relationship with malignant melanoma. Genome Med. 2010;19;2(10):78. DOI: 10.1186/gm199 
PMID: 20959028

20. Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their relatives. Pigment Cell Res. 2003;16(3):208–214. DOI: 10.1034/j.1600-0749.2003.00032.x 
PMID: 12753387

21. Sabat R, Wolk K, Loyal L, Döcke W-D, Ghoreschi KT cell pathology in skin inflammation. Semin Immunopathol. 2019;41(3):359-377. DOI: 10.1007/s00281-019-00742-7 
PMID: 31028434

13. Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their relatives. Pigment Cell Res. 2003;16(3):208–214. DOI: 10.1034/j.1600-0749.2003.00032.x 
PMID: 12753387

22. Harris JE. Cellular stress and innate inflammation in organ-specific autoimmunity. Lessons learned from vitiligo. Immunol Rev. 2016;269(1):11-25. DOI: 10.1111/imr.12369 
PMID: 26683142

14. Laberge G, Mailloux CM, Gowan K, Holland P, Bennett DC, Fain PR, et al. Early onset and increased risk of other autoimmune diseases in familial generalized vitiligo. Pigment Cell Res. 2005;18(4):300–305. DOI: 10.1111/j.1600-0749.2005.00242.x 
PMID: 16029422

23. Sastry KS, Naeem H, Mokrab Y, Chouchane A. RNA-seq reveals dysregulation of novel melanocyte genes upon oxidative stress: implications in true association. Dermatology 1994;188(4):269–275. DOI: 10.1159/000247164 
PMID: 8193398
vitiligo pathogenesis. Oxid Med Cell Longev. 2019;2841814.
DOI: 10.1155/2019/2841814
PMID: 31871544

24. Glassman SJ. Vitiligo, reactive oxygen species and T-cells. Clin Sci (Lond). 2011;120(3):99-120.
DOI: 10.1042/CS20090603
PMID: 20958268

25. Kumar R, Parsad D. Melanocytorrhagy and apoptosis in vitiligo: Connecting jigsaw pieces. Indian J Dermatol Venereol Leprol. 2012;78(1):19-23.
DOI: 10.4103/0378-6323.90942
PMID: 22199056

26. Lotti T, Zanardelli M, D'Erme AM. Vitiligo: What's new in the psycho-neuro-endocrine-immune connection and related treatments. Wien Med Wochenschr. 2014;164(13-14):278-85.
DOI: 10.1007/s10354-014-0288-7
PMID: 25059737

27. Hann SK, Chun W. Autocytotoxic hypothesis for the destruction of melanocytes as the cause of vitiligo. In: Hann SK, Nordlund J, Lerner A Beditors. Vitiligo. Oxford: Blackwell Science Ltd; 2000.

28. Kitamura R, Tsukamoto K, Harada K, Shimizu A, Shimada S, Kobayashi T, et al. Mechanisms underlying the dysfunction of melanocytes in vitiligo epidermis: Role of SCF/KIT protein interactions and the downstream effector, MITF-M. J Pathol. 2004;202(4):463-75.
DOI: 10.1002/path.1538
PMID: 15095274

29. Lee A, Kim N, Choi W, Youm Y. Lesskeratinocyte-derived factors related to more keratinocyte apoptosis in depigmented than normally pigmented suction-blistered epidermis may cause passive melanocyte death in vitiligo. J Invest Dermatol. 2005;124(5):976-83.
DOI: 10.1111/j.0022-202X.2005.23667.x
PMID: 1585403

30. Kundu RV, Mhlaba JM, Rangel SM, Le Poole IC. The convergence theory for vitiligo: A reappraisal. Exp Dermatol. 2019; 28(6):647-655.
DOI: 10.1111/exd.13677
PMID: 29704874

31. Bloom BR, Bennett B. Mechanisms of a reaction in vitro associated with delayed-type-hypersensitivity. Science.1968;153 (3731):80-82.
DOI: 10.1126/science.153.3731.80
PMID: 5938421

32. Kasama T, Ohtsuka K, Sato M, Takahashi R, Wakabayashi K, Kobayashi K. Macrophage Migration Inhibitory Factor: A Multifunctional Cytokine in Rheumatic Diseases. Arthritis. 2010;2010:106202.
DOI: 10.1155/2010/106202
PMID: 22046508

33. Aeberli D, Leech M, Morand EF. Macrophage migration inhibitory factor and glucocorticoid sensitivity. Rheumatology. 2006;45(8):937-943.
DOI: 10.1093/rheumatology/ke142
PMID: 16705047

34. Morand EF, Leech M, Bernhagen J. "MIF: a new cytokine link between rheumatoid arthritis and atherosclerosis," Nature Reviews Drug Discovery. 2006;5(5):399-410.
DOI: 10.1038/nrd2029
PMID: 16628200

35. Riedemann NC, Guo R, Gao H, Sun L, Hoesel M, Hollmann TJ, et al. Regulatory role of C5a on macrophage migration inhibitory factor release from neutrophils. Journal of Immunology. 2004;173(2):1355-1359.
DOI: 10.4049/jimmunol.173.2.1355
PMID: 15240730

36. Popa C, Van Lieshout AWT, Roelofs MF, Geurts-Moespot A, Van Riel PLCM, Calandra T, et al. MIF production by dendritic cells is differentially regulated by Toll-like receptors and increased during rheumatoid arthritis. Cytokine. 2006;36(1-2):51-56.
DOI: 10.1016/j.cyto.2006.10.011
PMID: 17166737

37. Paiva CN, Arras RH, Magalhães ES, Alves LS, Lessa LP, Silva MH, et al. "Migration inhibitory factor (MIF) released by macrophages upon recognition of immune complexes is critical to inflammation in Arthus reaction" Journal of Leukocyte Biology. 2009; 85(5): 855-61.
DOI: 10.1189/jlb.0108009
PMID: 19188484

38. Santos L, Hall P, Metz C, Bucala R, Morand EF. Role of macrophage migration inhibitory factor (MIF) in murine antigen-induced arthritis: interaction with glucocorticoids. Clinical Experimental Immunology. 2001;123(2):309-314.
DOI: 10.1046/j.1365-2249.2001.01423.x
PMID: 11207663
39. Gupta Y, Pasupuleti V, Du W, Welford SM. Macrophage migration inhibitory factor secretion is induced by ionizing radiation and oxidative stress in cancer cells. PLoS One. 2016; 11(1):1–11:e0146482. DOI: 10.1371/journal.pone.0146482 PMID: 26741693

40. Ma L, Xue H, Guan X, Shu C, Zhang Y, Zhang J, et al. Relationship of macrophage migration inhibitory factor levels in PBMCs, lesional skin and serum with disease severity and activity in vitiligo vulgaris. Braz J Med Biol Res. 2013; 46(5):460-4. DOI: 10.1590/S0100-879X201200500152 PMID: 23797494

41. Moretti S, Fabbri P, Baroni G, Berti S, Bani D, Berti E, et al. Keratinocyte dysfunction in vitiligo epidermis: cytokine microenvironment and correlation to keratinocyte apoptosis. Histol Histopathol. 2009;24(7):849-57. DOI: 10.14670/HH-24.849 PMID: 19475531

42. Garcia-Orozco A, Martinez-Magaña IA, Riera-Leal A, Muñoz-Valle JF, Martinez-Guzman MA, Quiñones-Venegas R, et al. Macrophage inhibitory factor (MIF) gene polymorphisms are associated with disease susceptibility and with circulating MIF levels in active non-segmental vitiligo in patients from western Mexico. Mol Genet Genomic Med. 2020;8(10):e1416. DOI: 10.1002/mgg3.1416 PMID: 32705792

43. Serarslan G, Yonden Z, Sogut S, Savas N, Celik E, Arpacı A. Macrophage migration inhibitory factor in patients with vitiligo and relationship between duration and clinical type of disease. Clin Exp Dermatol. 2010; 35(5): 487-490. DOI: 10.1111/j.1365-2230.2009.03617.x PMID: 19874371

44. Farag AGA, Hammam MA, Habib MSE, Elnaindy NF, Kamh ME. Macrophage migration inhibitory factor as an incriminating agent in vitiligo. An Bras Dermatol. 2018;93(2):191-196. DOI: 10.1590/abd1806-4841.20180608 PMID: 29723363

45. Sorour OS, Nassar ES, Eldin Ahmed SM, Farid CI. Serum levels of macrophage migration inhibitory factor and interleukin 17 in patients with nonsegmental vitiligo. Journal of Egyptian womens dermatologic society. 2020;17(1):13-18. DOI: 10.4103/GEWD.JEWD_39_19

46. Speeckaert R, Van GeelN. Vitiligo: An Update on Pathophysiology and Treatment Options. Am J Clin Dermatol. 2017; 18(6):733-744. DOI: 10.1007/s40257-017-0298-5 PMID: 28577207

47. Passeron T. Medical and Maintenance Treatments for Vitiligo.Dermatol Clin .2017; 35(2):163-170. DOI: 10.1016/j.det.2016.11.007 PMID: 28317526

48. Tanioka M, Yosuke Y, Mayumi K, Yoshiki M. Camouflage for patients with vitiligo vulgaris improved their quality of life. J Cosmet Dermatol. 2010; 9(1):72-75. DOI: 10.1111/j.1473-2165.2010.00479.x PMID: 20367677

49. Büyükbayraklar Z, Doruk C, Camci H. Camouflage treatment of a severe deep-bite and orthognathic surgery required case with en masse retraction. Turk J Orthod. 2017;30(4):126. DOI: 10.5152/TurkJOrthod.2017.17033 PMID: 30112504

50. Garg BJ, Saraswat A, Bhatia A, Katare O P. Topical treatment in vitiligo and the potential uses of new drug delivery systems. Indian Journal of Dermatology, Venereology and Leprology. 2010;76(3): 231-8. DOI: 10.4103/0378-6323.62961 PMID: 20445292

51. Wittal R. How I treat vitiligo. In: Lotti T, Hercogová J, Schwartz RA (eds) Vitiligo: What's New, What's True. Zurich World Health Academy and Vitiligo Research Foundation; 2013.

52. Ho N, Pope E, Weinstein M, Greenberg S, Webster C, Krafchik BR. A double-blind, randomized, placebo-controlled trial of topical tacrolimus 0.1% vs. clobetasol propionate 0.05% in childhood vitiligo. Br J Dermatol. 2011;165(3): 626–32. DOI: 10.1111/j.1365-2133.2011.10351.x PMID: 21457214

53. Daniel BS, Wittal R. Vitiligo treatment update. Australasian Journal of Dermatology. 2015; 56(2):85–92. DOI: 10.1111/ajd.12256 PMID: 25495880

54. AlGhamdi K, Kumar A, Moussa N. The role of vitamin D in melanogenesis with an emphasis on vitiligo. Indian Journal of Dermatology, Venereology and Leprology. 2013;79(6):750–8. DOI: 10.4103/0378-6323.120720 PMID: 24177606
55. Anbar TS, El-Ammaawi TS, Abdel-Rahman AT, Hanna MR. The effect of latanoprost on vitiligo: A preliminary comparative study. International Journal of Dermatology. 2015;54(5):587–593. DOI: 10.1111/jid.12631 PMID: 25545321

56. Mohamed HA, Mohammed GF, Gomaa AH A, Eyada MMK. Carbon dioxide laser plus topical 5-fluorouracil: a new combination therapeutic modality for acral vitiligo. J Cosmet Laser Ther. 2015;17(4):216–223. DOI: 10.3109/14764172.2014.1003241 PMID: 25549816

57. Seif El Nasr H, Shaker OG, Fawzi MMT, El-Hanafi G. Basic fibroblast growth factor and tumor necrosis factor alpha in vitiligo and other hypopigmented disorders: Suggestive possible therapeutic targets. Journal of the European Academy of Dermatology and Venereology. 2013; 27(1):103–108. DOI: 10.1111/j.1468-3083.2011.04368.x PMID: 22151832

58. Peluso I, Cavaliere A, Palmery M. Plasma total antioxidant capacity and peroxidation biomarkers in psoriasis. J Biomed Sci 2016; 23(1):52. DOI: 10.1186/s12929-016-0268-x PMID: 27377373

59. Soliman M, Samy NA, Eittah MA, Hegazy M. Comparative study between excimer light and topical antioxidant versus excimer light alone for treatment of vitiligo. J Cosmet Laser Ther. 2016;18(1):7–11. DOI: 10.3109/14764172.2015.1052510 PMID: 26052821

60. Picardo M, Dell’Anna ML. Vitamins and antioxidants: topical and systemic. In: Picardo M, Taieb A, editors. Vitiligo. Berlin: Springer. 2010:369–74.

61. Taieb A, Alomar A, Böhm M, Dell’anna ML, De Pase A, Eleftheriadou V, et al. Guidelines for the management of vitiligo: the European Dermatology Forum consensus. Br J Dermatol. 2013;168(1):5–10. DOI:10.1111/j.1365-2133.2012.11197.x PMID: 22860621

62. Lee D, Lee K, Choi S, Lee J. Segmental vitiligo treated by the combination of epidermal grafting and systemic corticosteroids. Dermatol Surg. 2010;36 (4):575-6. DOI: 10.1111/j.1524-4725.2010.01506.x PMID: 20402941
72. Sonthalia S, Aggarwal P. Oral tofacitinib: Contemporary appraisal of its role in dermatology. Indian Dermatology Online Journal. 2019;10(5):503-518. DOI: 10.4103/idoj.IDOJ_474_18 PMID: 31544068

73. Alghamdi KM, Khurrum H, Taieb A, Ezzedine K. Treatment of generalized vitiligo with anti-TNF-alpha agents. J Drugs Dermatol. 2012;11(4):534–9. PMID: 22453596

74. Ruiz-Argüelles A, García-Carrasco M, Jimenez-Brito G, Sánchez-Sosa S, Pérez-Romano B, Garcés-Eisele J, et al. Treatment of vitiligo with a chimeric monoclonal antibody to CD 20: A pilot study. Clinical Experimental Immunology. 2013;174(2):229–236. DOI: 10.1111/cei.12168 PMID: 23815517

75. Dhar S. Intravenous immunoglobulin in dermatology. Indian Journal of Dermatology. 2009;54(1):77-9. DOI: 10.4103/0019-5154.48996 PMID: 20049279

76. Lim HW, Grimes PE, Agbai O, Hamzavi I, Henderson M, Haddican M, et al. Afamelanotide and narrowband UV B phototherapy for the treatment of vitiligo: A randomized multicenter trial. JAMA Dermatol. 2015;151(1):42 50. DOI: 10.1001/jamadermatol.2014.1875 PMID: 25230094

77. Feily A, Baktash D, Mohhebbipour A, Feily A. Potential advantages of simvastatin as a novel anti-vitiligo arsenal. Eur Rev Med Pharmacol Sci. 2013;17(14):1982–1983. PMID: 23877867

78. Scheinfeld N, Rosenberg JD, Weinberg JM. Levamisole in dermatology. American Journal of Clinical Dermatology. 2004;5(2), 97–104. DOI: 10.2165/00128071-200405020-00004 PMID: 15109274

79. Rok J, Rzepka Z, Maszczyk M, Beberok A, Wrześniok D. Minocycline Impact on Redox Homeostasis of Normal Human Melanocytes HEMn-LP Exposed to UVA Radiation and Hydrogen Peroxide. Int J Mol Sci. 2021;22(4):1642. DOI: 10.3390/ijms22041642 PMID: 33561995

80. El-Zawahry BM, Bassiouny DA, Sobhi RM, Abdel-Aziz E, Zaki N S, Habib D F, et al. A comparative study on efficacy of UVA1 vs. narrow-band UVB phototherapy in the treatment of vitiligo. Photodermatol Photoimmunol Photomod. 2012;28(2):84-90. DOI: 10.1111/j.1600-0781.2011.00643.x PMID: 22409711

81. Abdel-Naser MB, El-Khateeb EA, Sallam TH, Habib MA. Endothelin-1 is significantly elevated in plasma of patients with vitiligo treated with psoralen plus ultraviolet a. Clin Exp Dermatol. 2006;31(4):571–575. DOI: 10.1111/j.1365-2230.2006.02148.x PMID: 16716165

82. Awad SS. New population of amelanotic spindle cells are clearly demonstrated in vitiliginous skin after ultraviolet radiation. J Eur Acad Dermatol Venereol. 2014; 28(12):1811-1815. DOI: 10.1111/jdv.12304 PMID: 24164170

83. Sapam R, Agrawal S, Dhali TK. Systemic PUVA vs. narrowband UVB in the treatment of vitiligo: a randomized controlled study. Int J Dermatol. 2012; 51:1107–15. DOI: 10.1111/j.1365-4632.2011.05454.x PMID: 22909369

84. Zhang P, Wu MX. A clinical review of phototherapy for psoriasis. Lasers Med Sci 2018; 33(1): 173–180. DOI: 10.1007/s10103-017-2360-1 PMID: 29067616

85. Middelkamp-Hup MA, Bos JD, Rius-Diaz F, Gonzalez S, Westerhof W. Treatment of vitiligo vulgaris with narrow-band UVB and oral Polypodium leucotomos extract: a randomized double-blind placebo-controlled study. J Eur Acad Dermatol Venereol. 2007; 21(7): 942–950. DOI: 10.1111/j.1468-3083.2006.02132.x PMID: 17659004

86. Namazi MR, Shotorbani AK. Evaluation of the efficacy of topical ethyl vanillate in enhancing the effect of narrow band ultraviolet B against vitiligo: A double blind randomized, placebo controlled clinical trial. Iran J Med Sci. 2015;40(6):478-84. PMID: 26538775

87. Deshmukh A, Khurana G. A randomized controlled study to compare the efficacy of methotrexate vs. oral minipulse (betamethasone) along with NB-UVB in patients with vitiligo vulgaris. Pigment international. 2020;7 (1):32-38. DOI: 10.4103 PMID: 2002;19(1):19–25.
Canton M, Caffieri S, Dall'Acqua F, Lisa FD. PUVA-induced apoptosis involves mitochondrial dysfunction caused by the opening of the permeability transition pore. FEBS Lett. 2002; 522(1-3):168–172.

DOI: 10.1016/s0014-5793(02)02926-5
PMID: 12095639

Juntongjin P, Toncharoenphong N. Effectiveness of a combined 308-nm excimer lamp and topical mid-potent steroid treatment for facial vitiligo: a preliminary, randomized double-blinded controlled study. Lasers Med Sci. 2020; 35(9):2023–2029
DOI: 10.1007/s10103-020-03048-5
PMID: 32458080

Yang Y, Cho H, Ryou J, Lee M. Clinical study of repigmentation patterns with either narrow-band ultraviolet B (NBUVB) or 308 nm excimer laser treatment in Korean vitiligo patients. Int J Dermatol. 2010; 49(3):317-323.
DOI: 10.1111/j.1365-4632.2009.04332.x
PMID: 20465673

Lan CE, Wu C, Chiou M, Hsieh P, Yu H. Low-energy helium-neon laser induces locomotion of the immature melanoblasts and promotes melanogenesis of the more differentiated melanoblasts: recapitulation of vitiligo repigmentation in vitro. J Invest Dermatol. 2006;126(9):2119-26.
DOI: 10.1038/sj.jd.5700372
PMID: 16691191

Ashwini PK, Sushmitha DJ, Veeranna S. Vitiligo with special emphasis on vitiligo surgery. Archives of medicine, health sciences. 2020; 8(1):140-146.
DOI: 10.4103

Van Geel N, Speeckaert R, Taieb A, Picardo M, BöhmM, Gawrkodger DJ, et al. VETF members. Koebner's phenomenon in vitiligo: European position paper. Pigment Cell Melanoma Res. 2011;24(3): 564–73.

DOI: 10.1016/j.1755-148X.2011.00838.x
PMID: 21324101

Mysore V, Koushik L. Overview of vitiligo surgery. In: Mysore V, editor. ACS(I) Textbook on Cutaneous and Aesthetic Surgery. Ch. 24A. New Delhi: Jaypee Brothers. 2017:327-33.

Alghamdi KM, Kumar A. Depigmentation therapies for normal skin in vitiligo universalis. J Eur Acad Dermatol Venereol. 2011;25(7): 749–57.
DOI: 10.1111/j.1468-3083.2010.03876.x
PMID: 21054565

Greven D, Leng L, Bucala R. Autoimmune diseases: MIF as a therapeutic target. Expert OpinTher Targets. 2010;14(3):253-64.
DOI:10.1517/14728220903551304
PMID: 20148714

Senter PD, Al-Abed Y, Metz CN, Benigni F, Mitchell RA, Chesney J, Han J, Gartner CG, Nelson SD, Todaro GJ, Bucala R. Inhibition of macrophage migration inhibitory factor (MIF) tautomerase and biological activities by acetaminophen metabolites. Proc Natl Acad Sci USA. 2002;99(1): 144–149.
DOI: 10.1073/pnas.011569399
PMID: 11773615

Lubetsky JB, Dios A, Han J, Aljabari B, Ruzsicska B, Mitchell R, et al. The tautomerase active site of macrophage migration inhibitory factor is a potential target for discovery of novel anti-inflammatory agents. J Biol Chem. 2002; 277(28):24976–24982.
DOI: 10.1074/jbc.M203220200
PMID: 11997397

Dios A, Mitchell RA, Aljabari B, Lubetsky J, O'Connor K, Liao H, et al. Inhibition of MIF bioactivity by rational design of pharmacological inhibitors of MIF tautomerase activity. J Med Chem. 2002; 45(12): 2410–2416.
DOI: 10.1021/jm010534q
PMID: 12036350

© 2021 Ibrahim et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/70397