



## **Macrophage Migration Inhibitory Factor in Vitiligo: Pathogenesis and Potential Therapeutic Aspects**

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### **Authors' contributions**

*This work was carried out in collaboration between all authors. Authors HMI, EEN and SAA and MHH designed the study. Authors EMH, MHH wrote the first draft of the manuscript. Authors HMI, EEN and MHH managed the literature searches. All authors read and approved the final manuscript.*

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### **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 are 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- $\alpha$ , nitric oxide and prostaglandin E<sub>2</sub>. 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.

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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; macrophage migration inhibitory factor; 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 (H<sub>2</sub>O<sub>2</sub>), 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, NACHT 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].

**Table1. Various pathogenic mechanisms**

	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	KumarandParsad [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 pernicious anemia 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 pernicious anemia, 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 inflammasome 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 leading 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. D-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, PI3K/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- $\alpha$ , IL-5, IFN- $\gamma$ , 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]**

<b>Chemotactic Functions</b>	
Monocytes	stimulation/
T lymphocytes	inhibition: is based on their
Vascular smooth muscle cells	concentration.
Fibroblasts	
Activities that cause angiogenesis	
Anti-apoptotic activities	
Cell proliferation	
Stimulation	
Mediators are induced	
Cytokines	TNF- $\alpha$ IL-1, 6, 8, 12 CCL2 VEGF
Growth factor	ICAM-1 VCAM-1 E-selectin P-selectin
Adhesion molecules	MMP-1, 3, 9, 13
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 (H<sub>2</sub>O<sub>2</sub>), 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 stimulators 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- $\alpha$ , IL-1, and IFN- $\gamma$  all of which have been linked to the pathogenesis of vitiligo [40]. Inflammatory cytokines TNF- $\alpha$  and IL-6 have anti-pigmentation effects. TNF- $\alpha$  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**

	References
TNF- $\alpha$ , IL-1, and IFN- $\gamma$ are examples of proinflammatory cytokines produced.	Ma et al. [40]
Inflammatory cytokines TNF- $\alpha$ and IL-6 have anti-pigmentation effects.	Moretti et al. [41]
TNF- $\alpha$ 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

	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 determine the treatment option (disease duration, impact, skin type, extent, sex, age, involved areas, social life, and cultural influences). Dermatologists must be mindful of their patients'

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 repigmentation [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, catalase superoxide dismutase combo and 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- $\alpha$  expression is significantly higher on the lesional site than on the perilesional, non-lesional and 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- $\alpha$  [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 repigmentation 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 day 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 anti-idiotypic interactions, Fc receptor regulation, cytokine synthesis modulation, cytokine antagonists and acceleration of IgG catabolism are thought to be involved [76].

### 5.3.10 Other systemic medications

By attaching to the melanocortin-1 receptor, a melanocyte stimulator is a longer-acting synthetic analogue of  $\alpha$ -MSH that increases melanocyte proliferation and melanogenesis [77]. As a side effect of glaucoma medication, latanoprost (LT) is a prostaglandin F<sub>2</sub>α 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- $\alpha$ ) 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- $\beta$  [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 photoaging are 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 NB UVB 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 and 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 photoactivated, 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 cure 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 tautomerization. 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.

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