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VITILIGO: A COMPREHENSIVE REVIEW OF PATHOGENESIS, TYPES AND MANAGEMENT

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ABSTRACT

Vitiligo is a chronic, multifactorial autoimmune disorder characterized by progressive loss of functional melanocytes, leading to depigmented macules and patches on the skin and mucosa. Affecting approximately 0.5–1% of the global population, vitiligo imposes significant psychosocial distress and remains a therapeutic challenge due to its complex and incompletely understood pathogenesis. Current evidence indicates that vitiligo arises from an intricate interplay of genetic predisposition, oxidative stress, immune dysregulation, and environmental triggers. Mitochondrial dysfunction, excessive oxidative stress, and impaired antioxidant defence initiate melanocyte damage, while autoreactive $CD8^+$ T cells, altered $CD4^+/CD8^+$ ratios, and reduced regulatory T-cell (Treg) activity drive autoimmune destruction. Heat shock protein 70 (HSP70i) and proinflammatory cytokines such as IFN-γ and IL-17 amplify this immune cascade, culminating in melanocyte loss. Clinically, vitiligo presents in diverse forms—focal, segmental, acrofacial, generalized, universal, and mucosal—each with distinct distribution and prognostic implications. Diagnosis is primarily clinical but may be supported by laboratory and imaging modalities such as Wood's lamp examination, digital photography, and point-counting techniques for disease assessment. Therapeutic approaches include topical corticosteroids, calcineurin inhibitors, vitamin D analogues, and phototherapy (NB-UVB, PUVA), with emerging options like Janus kinase (JAK) inhibitors, HSP70i gene therapy, and melanocyte-stimulating agents offering new hope. Despite recent advances, complete and sustained repigmentation remains elusive. Future directions emphasize the need for personalized, multimodal regimens targeting immune modulation, oxidative balance, and melanocyte regeneration. This comprehensive review explores the current understanding of vitiligo's pathogenesis, classification, diagnostic strategies, and evolving management paradigms, highlighting promising innovations that may transform patient outcomes.

KEYWORDS: Vitiligo, autoimmune disease, melanocyte destruction, oxidative stress, JAK inhibitors, phototherapy, immunopathogenesis, novel therapies.

INTRODUCTION

Vitiligo is an autoimmune disease. Melanocytes are gradually killed in vitiligo, an autoimmune disorder that causes pale, white areas of skin. Vitiligo is a condition that affects 0.5–1% of people and is linked to social stigma, psychological stress, and low self-esteem. There is a genuine need for novel treatment approaches because the therapies now available for vitiligo are not very effective.

There is a genuine need for novel treatment approaches because the therapies now available for vitiligo are not very effective. Numerous studies conducted over the years have demonstrated that vitiligo is caused by a complex interplay of genetic, environmental, metabolic, and immunological variables that create a microenvironment that favours melanocyte loss. Patients with vitiligo have been found to accumulate oxidative stress as a result of impaired mitochondrial function, a weakened antioxidant system, and improper

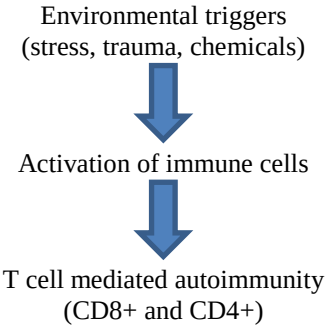
tetrahydrobiopterin recycling. DNA damage, lipid and protein peroxidation, neoantigen development, and disruption of normal melanogenesis in melanocytes are all possible outcomes of this cumulative oxidative stress. Furthermore, vitiligo pathogenesis has been linked to humoral and cellular autoimmunity, a change in the ratio of CD4+ to CD8+ T cells, a reduction in the function of regulatory T cells (Tregs), the presence of autoreactive anti-melanocyte CD8+ T cells in the skin and blood, and an imbalance in pro- and anti-inflammatory cytokine levels.

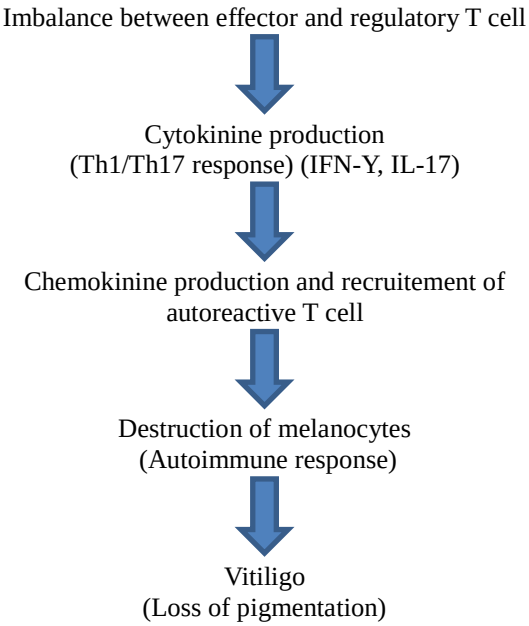
Vitiligo's pathophysiology is influenced by several variables. Inducible heat shock protein 70 (HSP70i) can be released by melanocytes under oxidative stress. Innate immune cells and melanocyte antigens can be directly activated by HSP70i and then introduced to antigen-presenting cells (APCs). Auto-reactive T lymphocytes are then enlisted by these innate immune cells and APCs to facilitate the targeted destruction of melanocytes in vitiligo. Reduced cutaneous regulatory T cell (Treg) activity is another factor contributing to the loss of tolerance to self-antigens. Tregs are T cell subsets that suppress immune cells, including cytotoxic, self-reactive T cells, to preserve immunological homeostasis and promote peripheral tolerance. Numerous autoimmune diseases have been linked to Treg deficiencies and scarcity. Within lesional, non-lesional, and perilesional sections of vitiligo skin, a local Treg deficiency was discovered, indicating a diminished capacity of vitiligo patients to preserve peripheral immune homeostasis. According to other reports, there may be fewer Tregs in circulation or they may be less active. Because there is less Treg activity in vitiligo skin, autoreactive, cytotoxic T cells can proliferate and remove melanocytes from the skin, which promotes gradual depigmentation.

METHODOLOGY

Extensive literature and information investigation were done, and internet search engines were used to complete the review. The research includes articles that were found through a search in the PubMed database. The following keywords were used in the search: "depigmentation," "hypopigmentation," "vitiligo," "types of vitiligo," "types of hypopigmentation," and "types of depigmentation." Thirty of the 210 articles that were located were used to write this narrative evaluation.

Immunopathogenesis of vitiligo





Description of immunopathogenesis of vitiligo

The immune Patho mechanisms involved in vitiligo are still unknown. Cellular immunity is suggested by CD8+ and CD4+ cell infiltrations of the depigmented area. Circulating melanocyte-specific CD8+ cells and alterations in T cell subtypes have been detected. A dysfunction of CD4+ seems to enhance autoimmune mechanisms. It is probable that different cells, including macrophages, dendritic cells and Langerhans cells are involved. Different inflammatory cytokines with an effect on pigmentation have been found. A humoral immune reaction has been implicated through the detection of circulating antibodies. However, these antibodies lack specificity, although they have shown melanocytotoxic and apoptosis induction capacities. Further studies of local skin and peripheral blood are needed to clarify the role of autoimmunity in melanocyte destruction.

Figure of vitiligo

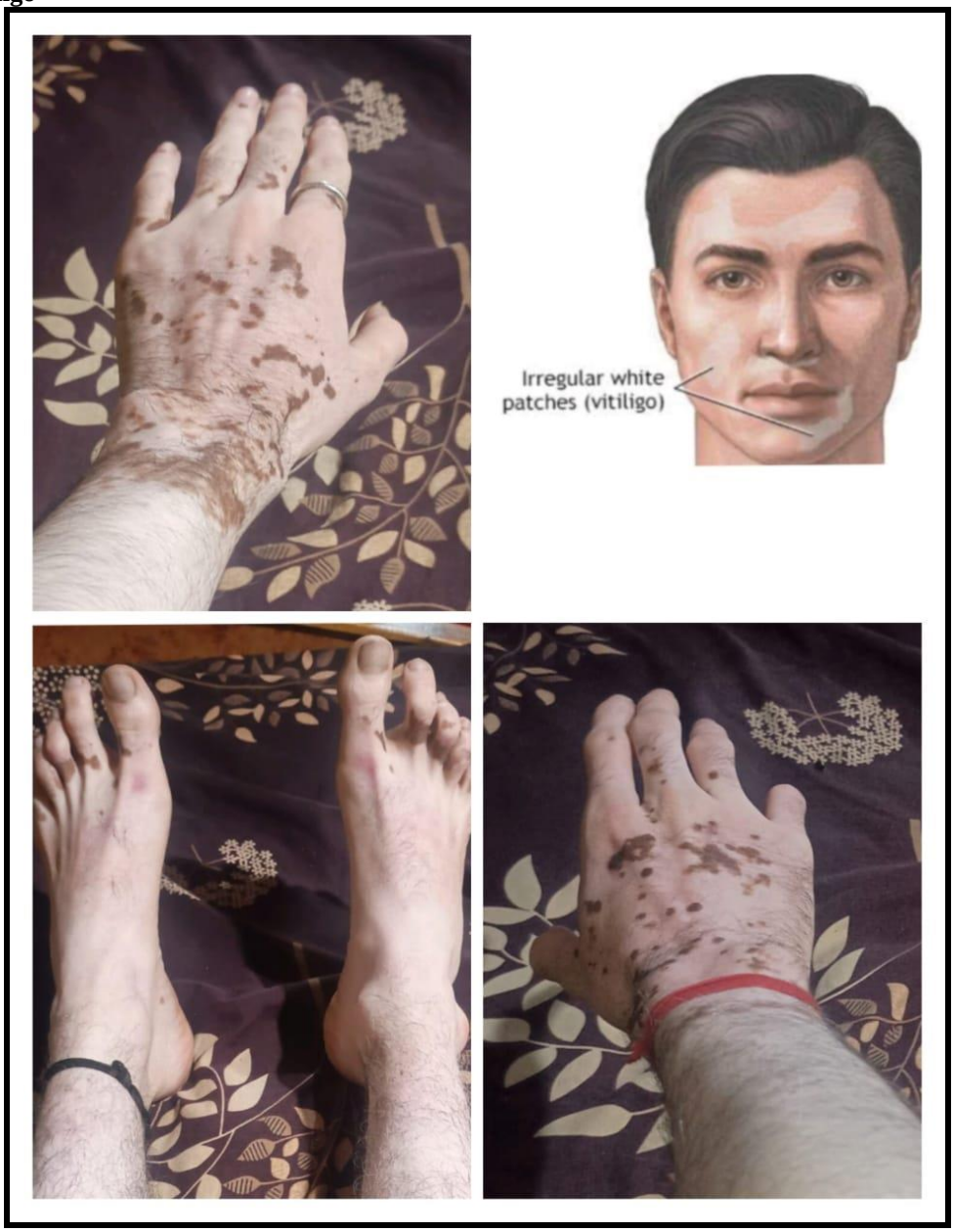
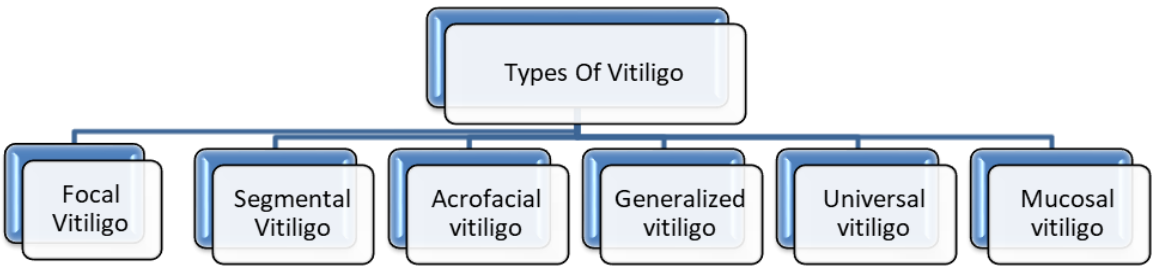


Figure no. 1: Visual Image of Vitiligo).

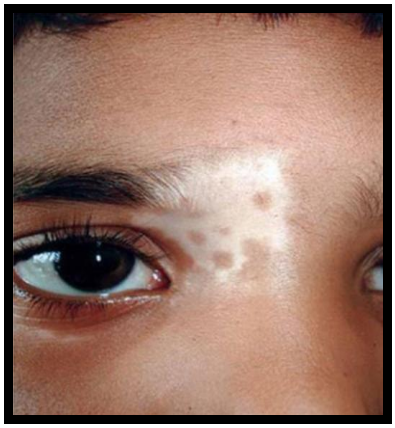
Types of vitiligo

Table no. 1: Types of vitiligo).



● **Focal vitiligo**

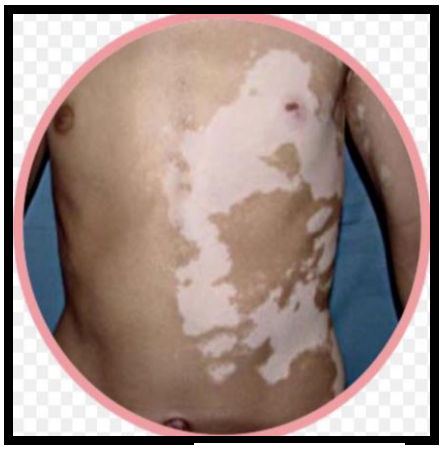
Focal vitiligo typically presents as a single macule or several dispersed macules in a particular region, most often following the distribution of a nerve, although the neck and trunk are also frequently affected. This type is more prevalent in children.



(Figure no. 2:- Focal vitiligo).

● Segmental vitiligo

Segmental vitiligo appears as unilateral macules following a dermatomal or quasi-dermatomal pattern. This type usually emerges early in life and, in contrast to other forms, is not linked with thyroid disorders or other autoimmune conditions. Changes in neural peptides have been suggested to play a role in its development. Over half of individuals with segmental vitiligo also experience poliosis.



(Figure no. 3: - Segmental vitiligo).

● Acrofacial vitiligo

Acrofacial vitiligo manifests as loss of pigment in the tips of the fingers and around the mouth and other facial openings.

(Figure no. 4:- Acrofacial vitiligo).

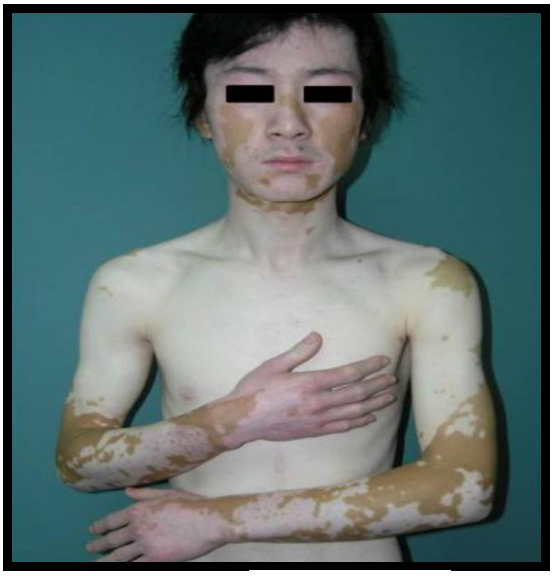
● Generalized vitiligo

Generalized vitiligo, commonly referred to as vitiligo vulgaris, is the most prevalent form. Depigmented spots are distributed extensively and are typically symmetrical.

(Figure no. 5:- Generalized vitiligo).

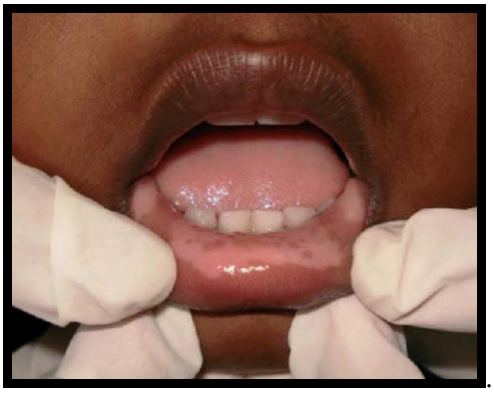
● Universal vitiligo

Universal vitiligo is characterized by depigmented macules and patches on the majority of the body and may be associated with multiple endocrine disorders.



(Figure no. 6:- Universal vitiligo).

● Mucosal vitiligo: Mucosal vitiligo appears only on the mucous membranes.

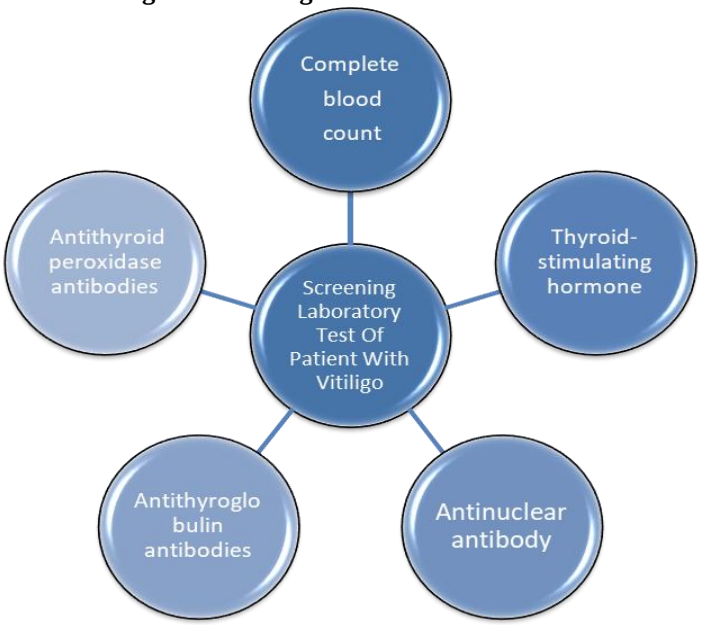


(Figure no. 7:- Mucosal vitiligo).

Screening laboratory test of patient with vitiligo

Laboratory Tests The diagnosis of vitiligo is based primarily on clinical findings. However, given the association between vitiligo and other autoimmune diseases (a history of autoimmune disease in a family member is obtained in 32% of patients), several screening laboratory tests are helpful, including thyroid stimulating hormone, antinuclear antibody, and complete blood count. Clinicians should also consider testing for se rum antithyroglobulin and antithyroid peroxidase antibodies, especially if patient and family history indicates so. Antithyroid peroxidase antibodies, in particular, are regarded as a sensitive and specific marker of autoimmune thyroid disorders.

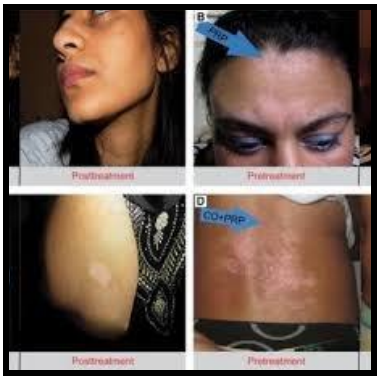
Table no 2:- Laboratory Tests The diagnosis of vitiligo.



Assessment methods for evaluation of vitiligo

Table no. 3: Assessment methods for evaluation of vitiligo.

Sr.no	Name Of Methods	Description	Images
1)	**Visible light photography**	Images can illustrate a patient's condition at a specific time, and a series of photographs taken over time can offer insights into the disease's progression or the effectiveness of treatment. Traditional photography using standard 35-mm film has been a popular method for capturing images of the skin for medical documentation and educational purposes. However, it can be challenging to differentiate between hypomelanosis and amelanosis in very light-skinned patients when using photography under visible light.	
2)	**Ultraviolet light photography**	The foundation of UV light photography is the idea that melanin in the epidermis selectively absorbs UV rays more than visible light. By applying UV light to the patient's skin, Wood's lamp is used to diagnose skin conditions. After passing through the epidermis, where melanin attenuates the UV rays, they enter the dermis and cause collagen bundles to emit fluorescence. Haemoglobin in the capillaries and epidermal melanin attenuate some of the fluorescence that is released, which is directed toward the skin's surface. This process facilitates the evaluation of the degree of pigment irregularities and highlights differences in epidermal pigmentation that are not evident to the naked eye. With UV photography, the outcomes of Wood's light analysis can be captured. The contrast between skin with low or no pigment and skin with high levels of melanin is accentuated by Wood's lamp. Utilizing Wood's light and assessing its outcome require experience.	

3)	**Digital photography**	Digital photography is a potent tool that may improve our online and email communication with patients, colleagues, and the general public. The technology, which needs a computer, printer, and computer software, is affordable and easy to use. Digital cameras with pixel resolutions more than 1556 x 1024 can produce high-quality skin photographs. The brightness of each pixel in the picture is measured and quantified once it has been sampled separately. The corresponding pixel of the computer's bitmap image contains this integer value. Using the Image-Pro Plus 4.5 application (Media Cybernetics, Silver Spring, MD, USA), the area that defines the object's contour is measured and reported as a polygonal area. The ability to create a lasting visual record of the lesion is one of the main benefits of photographic measuring. However, a number of technological issues could make digital photography less useful for assessing vitiligo.	
4)	**Point-counting method**	To determine the volumes of organs or structures, the irregularly shaped sectional surface area is estimated using the point-counting method. After marking the edges of the lesion with a regular ballpoint pen, a piece of paper is quickly placed over the lesion. The projection regions' copy borders were improved for every lesion by redrawing the outlines with a pen. A translucent sheet with a point (+) written on it is randomly placed on the lesion projection region to estimate the number of points. It counts the number of junctions that strike the area of interest. The representative area of a point on a grid is multiplied by the total number of points counted for the lesion to determine the total size of each lesion. On the grid, each + sign has an area of 0.1 cm^2. The point-counting method's reliability for measuring surface areas has been tested against image analysis and found to be statistically significant.	

Pharmacological management

1. Topical Treatment Corticosteroids

Corticosteroids play a crucial role in treating vitiligo by managing and lowering the inflammatory response. Topical corticosteroids serve as the primary treatment for vitiligo, whether they are potent (such as betamethasone valerate) or highly potent (like clobetasol propionate). The therapeutic effects are generally more pronounced in areas exposed to the sun, while results in acral regions tend to be less favorable.

2. Vitamin D3 Analogues (D3A)

Topical vitamin D3 analogues (D3A) are not effective on their own for treating vitiligo because their immune-modulating effects reduce T cell activity, encourage the formation of melanocytes, and stimulate melanogenesis. However, they can be beneficial as adjuncts to other therapies. The ideal weekly dosage for the ointment is 100 g applied over 30% of the body area for four weeks, and for the cream, it is also 100 g weekly for eight weeks, combined with calcipotriol at 0.005% and betamethasone at 0.05%.

Other potential pharmacological treatments include 5-Fluorouracil (5-FU), methotrexate (MTX), prostaglandin F2 alpha analogues, a peptide from basic fibroblast growth factor (bFGF), Janus kinase (JAK) inhibitors, systemic corticosteroids, apremilast, among others, including the use of the antibiotic minocycline.

3. Sunscreens

Sunscreens play a crucial role in preventing sunburn and reducing photo damage, which in turn lowers the likelihood of triggering an isomorphic response of Koebner. Furthermore, sunscreens can diminish tanning of unaffected skin, thereby lessening the visual contrast with vitiliginous areas.

4. Cosmetics

Many patients view cosmetic cover-ups as a beneficial treatment alternative. Areas that lack pigmentation, particularly on the face, neck, or hands, can be concealed using standard makeup, self-tanning products, or various topical dyes. The benefits of cosmetics include their relatively low cost, minimal side effects, and ease of application. For children and adults with skin types I and II, it may be wise to initially focus solely on cosmetics and sunscreen without implementing other active treatments.

5. Physical therapy

Narrow-Band UVB Phototherapy: UV irradiation appears to have several systemic effects, including stimulation of the central hypothalamic pituitary-adrenal

axis, initiation of the proopiomelanocortin route in the hypothalamic arcuate nucleus, immunosuppressive effects, and opioid genic outcomes. UVB (wavelength of 280-320 nm) irradiance is more prominent than UVA (wavelength of 320-400 nm). NB-UVB photodynamic therapy (wavelength of 311 nm) suppresses the immune system, induces melanocyte separation, increases melanin synthesis, and causes melanocyte emigration from perilesional skin to treat vitiligo.

6. PUVA

PUVA irradiation (wavelength of 320-340 nm) causes melanin production by suppressing the immune system and fostering an environment conducive to the formation of melanocytes. This second-line treatment usually involves applying psoralen topically or ingesting it and then exposing it to UVA. Psoralens are taken orally for 1-3 hours before UVA exposure. Other physical management techniques in use include combined Fraxel Erbium and UVA1 lasers and laser therapy excimer laser (EL).

Drug used in vitiligo condition

Table no. 4: Drug used in vitiligo condition.

Class of drugs	Main Drugs	Treatment goals of drugs	Mechanism of action
JAK Inhibitors	Ruxolitinib(JAK1/2)	Supress the immune system	1] Cytokinine signalling (IFN, IL-15) Disruption
	Tofacitinib(JAK1/3)		
	ATI-50002(JAK1/3)		
	PF-06651600(JAK3)		
	PF-06700841(JAK1/TYK2)		
Multiple kinase inhibitor	Cerdulatinib (JAK1/3, SYK)	Supress the immune system	1] Cytokine signalling (IFN-γ) Disruption
Anti-IL-15biologics	Anti-IL-15mAb Anti-CD122mAb	1] Supress the immune system 2] Elimination of TRM cells	1] IL-15signaling blocking
PlasmidHSP70i gene therapy	HSP70iQ435A	Block endogenous innate immune activation	1] Mutant HSP70 counteracts innate immune active action by endogenous HSP70i
Wnt agonist Mc1 Ragonist	SKL2001 Afamelanotide	Regeneration of melanocytes	1] Melanocyte Stimulation 2] stem cell proliferation and migration

Advances in vitiligo treatments

Therapeutic options available for stabilizing and repigmenting vitiligo have been modestly expanded in recent years, although only depigmentation therapy using monobenzone is approved by the FDA. Depigmentation therapy is reserved for the treatment of remaining normal skin in those with extensive vitiligo affecting the majority of one's body. Traditional therapies for repigmentation, including topical agents and phototherapy, remain mainstays of current treatment. Topical treatments include corticosteroids, calcineurin inhibitors, and vitamin D analogues.[46–49] Phototherapy treatments include narrowband UVB (NB-UVB) or psoralen and UVA (PUVA). NB-UVB, which consists of 311–313 nm, can be given to the whole body using lamps or as a focused, targeted treatment using a 308 nm xenon-chloride monochromatic excimer light emitted through a laser or incoherent lamp. More recently, studies have evaluated other types of phototherapy such as broad band UVB (280–320 nm), psoralen combined with NB-UVB, UVA-1, and PUVA sol.[53–56] Newer studies of traditional treatments have compared the use of these treatments as monotherapies as well as evaluated the efficacy of combining treatments for a multi modal approach.[57–60] Several studies have found that phototherapy combined with topical creams yield faster and greater repigmentation than each treatment modality as a monotherapy.[57,59,60] While the combination approach has led to successful repigmentation for many patients, there remain many individuals who have unsatisfactory results and for whom alternative treatment options are needed. Advances in vitiligo therapy have sought to investigate these alternative treatments, which include topical, oral, and procedural treatments that seek to target different pathways involved in the pathogenesis of vitiligo.

CONCLUSION

Vitiligo is a multifactorial autoimmune pigmentary disorder with a complex interplay of genetic, environmental, oxidative, and immune-mediated mechanisms. Although considerable progress has been made in understanding its pathogenesis—particularly the roles of oxidative stress, heat shock proteins, and T-cell–mediated melanocyte destruction—the precise molecular triggers and pathways remain incompletely defined. Current therapeutic approaches, including topical corticosteroids, vitamin D analogues, phototherapy, and emerging immunomodulators such as JAK inhibitors, offer partial and often temporary repigmentation.

Recent advances in molecular biology and immunodermatology have opened promising avenues for targeted therapies aimed at restoring immune tolerance,

enhancing melanocyte regeneration, and modulating inflammatory signaling. The advent of biologics, gene-based treatments, and combination phototherapies represents a new era of hope for patients with vitiligo. However, interindividual variability in response and the relapsing nature of the disease highlight the need for personalized, multimodal treatment strategies.

Future research must focus on elucidating the precise immunogenetic networks driving melanocyte loss, identifying reliable biomarkers for disease activity, and conducting large-scale, randomized clinical trials to validate emerging therapies. With continued scientific exploration and patient-centered innovation, the ultimate goal of durable, complete repigmentation in vitiligo may soon move from possibility to reality.

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