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Advances in vitiligo: pathophysiology, psychosocial impact and emerging therapy

Introduction

Vitiligo is a chronic autoimmune skin disorder that affects approximately 0.5–2% of the world's population.[1] It is characterized by the loss of pigment-producing melanocytes, resulting in depigmented patches on the skin. Vitiligo occurs equally in all genders and across the skin colour spectrum. Although vitiligo can start at any age, 50% of affected individuals experience the onset of the condition before the age of 20.[2] Recent developments in vitiligo research have advanced the understanding of its pathophysiology, epidemiology, and psychosocial impact on patients. While traditional treatment options have been of limited benefit, several emerging therapies are in development and may soon be available to Canadian patients with vitiligo.

Vitiligo is primarily classified into two morphologic types, which are non-segmental vitiligo and segmental vitiligo. Non-segmental vitiligo is the most common presentation. Segmental vitiligo presents with depigmented patches occurring in a Blaschkovian distribution pattern. These depigmented patches may be single or multiple. Segmental vitiligo is seen in only 5% of adults with vitiligo, however, up to 20% of children are affected. Segmental vitiligo is not associated with thyroid disease or other autoimmune comorbidities.[1]

Vitiligo pathophysiology

Recent advances in the understanding of vitiligo's pathophysiology have highlighted its autoimmune nature, which involves complex interactions between genetic, environmental, and immunological factors.

Immunological dysregulation:[3]

One of the central pillars of vitiligo pathophysiology is the immune system's role in melanocyte destruction. Changes in both innate and adaptive immunity play a role in the pathophysiology of vitiligo.

Innate immunity:

- The innate immune system appears to be the bridge between oxidative stress **Figure 1** and adaptive immunity in vitiligo.
- Activated CD56+ / granzyme B+ natural killer (NK) cells and interferon (IFN)-γ-producing cells have

been identified in the blood and non-lesional skin of patients with vitiligo.

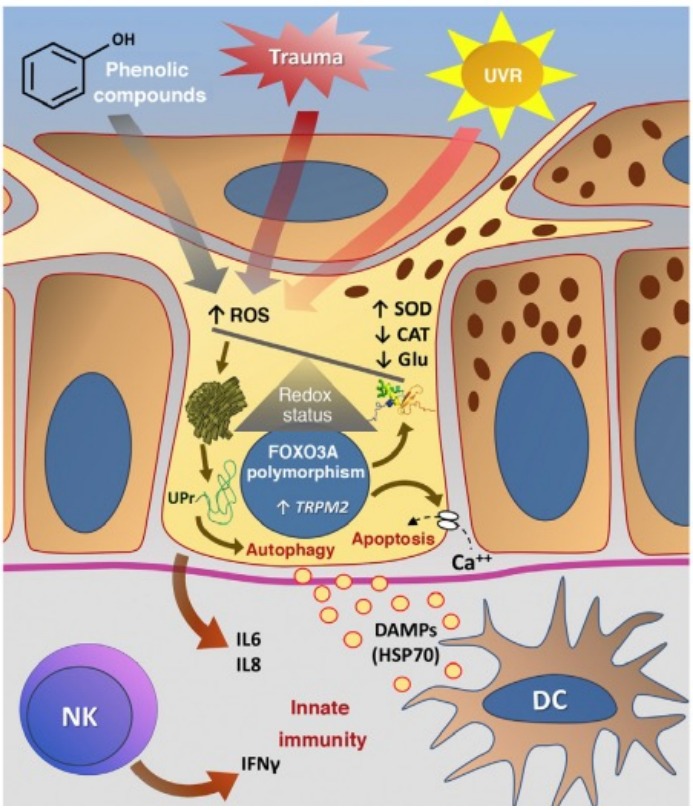

Figure 1: Representation of oxidative stress and activation of innate immunity in vitiligo. CAT, catalase; DAMPs, (damage-associated molecular patterns); DC, dendritic cells; FOXO3A, forkhead transcription factor 3A; Glu, glutathione; Il, interleukin; NK, natural killer cells; ROS, reactive oxygen species; SOD, superoxide dismutase enzyme; TRPM2, transient receptor potential cation channel subfamily M member 2; UPr, unfolded proteins; UVR, ultraviolet radiation.[3]

Adaptive Immunity:

- There is an increase in proinflammatory cytokines in both the serum and skin of patients with vitiligo, including interleukin (IL)-1α, IL-1β, IL-6, IL-8, IL-12, IL-15, and tumour necrosis factor (TNF)-α.
- Activated NK-cell driven expression of IFN-γ is a central event in a host of adaptive immune system responses in vitiligo.
- CD8+ cytotoxic T lymphocytes (CTLs) are major players in melanocyte destruction in vitiligo. These CTLs recognize melanocyte antigens and induce apoptosis, leading to the loss of melanocytes.
- The role of anti-melanocyte antibodies is still being elucidated. These antibodies do occur, but their titers do not correlate with disease activity.
- Elevated levels of IFN-γ have been observed in vitiligo lesions, contributing to melanocyte damage. IFN-γ promotes the expression of major histocompatibility complex class I molecules on melanocytes, making them more susceptible to CTL-mediated cytotoxicity.
- Dysregulation of regulatory T cells (T_{regs}) has been implicated in vitiligo pathogenesis. Reduced T_{reg} function allows for uncontrolled activation of autoreactive T cells against melanocytes.

Genetic factors:

Genetic susceptibility plays a crucial role in the development of vitiligo. Recent advances in genomics have identified several susceptibility genes associated with the disease.

- Human leukocyte antigen (HLA) genes: Variants in HLA genes have been strongly linked to vitiligo susceptibility. Specific HLA alleles, such as *HLA-A02 and HLA-DRB107* (among several others), are associated with an increased risk of developing vitiligo.
- Non-HLA genes: Genome-wide association studies have identified non-HLA genes, including *NACHT leucine-rich-repeat protein 1 (NLRP1), Lymphoid protein tyrosine phosphatase non-receptor type 22 (PTPN22), and Tyrosinase (TYR)*, as potential genetic risk factors for vitiligo. These genes are involved in immune regulation and melanocyte function.

Oxidative stress and melanocyte damage:[3,5]

Oxidative stress-induced damage to melanocytes is a critical pathophysiological mechanism in vitiligo. It may well contribute to many of the pathophysiologic mechanisms implicated in vitiligo. Ultraviolet light, exposure to phenolic compounds, or mechanical trauma may increase production of reactive oxygen species (ROS) within melanocytes, causing oxidative stress, which can trigger apoptosis and melanocyte destruction.

- ROS: Recent studies have elucidated the role of ROS and its impact on melanocyte destruction as a trigger for aberrant mitochondrial function, and as a trigger for a host of innate immune system responses.
- Antioxidant deficiency: Vitiligo-affected skin also has reduced levels of antioxidants, such as catalase and superoxide dismutase.
- Antioxidant supplementation: (eg, superoxide dismutase and polypodium leucotomos) may have a protective role against melanocyte damage.

Mitochondria and melanocyte interactions:[4]

- As noted above, oxidative stress can impact both mitochondrial function and mitochondria-associated gene expression.
- Disruption of mitophagy, a biochemical process that protects cells by removing damaged mitochondria, has been implicated as one pathogenetic factor in vitiligo.

- Mitochondrial-melanosome crosstalk might be perturbed by the alteration of several key genes in vitiligo.

Neuroimmunology:[4]

Emerging evidence suggests a link between the nervous system and vitiligo pathophysiology.

- Neurotransmitters and neuropeptides: The presence of neurotransmitters and neuropeptides, such as substance P and calcitonin gene-related peptide, in vitiligo-affected skin has been demonstrated. These neurochemicals modulate immune responses and melanocyte function.
- Neural-melanocyte interactions: Neural-melanocyte interactions, including the release of neurotransmitters by nerve endings near melanocytes, play a role in melanocyte dysfunction and autoimmune responses.

Psychosocial impact of vitiligo

Vitiligo's visible nature can have a profound psychosocial impact on affected individuals, leading to diminished quality of life, depression, anxiety, and social isolation. These patients experience a high level of stress and psychiatric disorders in addition to physical involvement. Depression, anxiety, suicidal ideation and behaviour, embarrassment, social isolation, discomfort, cognitive impairment, and physical limitation were reported in vitiligo patients.[6]

While vitiligo can occur across the skin colour spectrum, it disproportionately affects people with more richly pigmented skin. This is partly owing to depigmentation being more strikingly visible in patients with constitutively more melanized skin. However, societal biases and limited understanding of the nature of vitiligo unfortunately still play a role. Patients with vitiligo who identify as female tend to experience more of a significant impact on psychosocial functioning than those who identify as men. These effects are magnified based on the extent of disease as well as by the involvement of more visible areas (ie, facial and hand involvement).[7]

Patients with vitiligo are hospitalized for mental health concerns at a higher rate than patients without vitiligo, and their hospitalizations last longer and cost more.[8]

Approximately 17% of patients begin antidepressants or anxiolytics in the year following a vitiligo diagnosis due to self injurious behaviour as a result of their diagnosis. Rates of anxiety and depression may be as high as 60%, and suicidal ideation may occur in up to 25% of patients.[9]

Intriguingly, there is some evidence of a bidirectional relationship between vitiligo and mental health diagnoses, specifically major depression.[10]

Vitiligo therapy

Traditional therapeutic approaches:

There is widespread support for a shared decision-making model in vitiligo to determine desired versus expected outcomes.[11] Stabilization of disease, repigmentation or, less frequently, depigmentation therapy may all be appropriate therapeutic targets. Further, the therapeutic target may evolve through the course of the disease and after considering the patient's response to treatment. In addition, therapeutic outcome targets will also evolve as new therapeutic options emerge.

Steroid oral minipulse therapy (OMP):[12,13] For active and progressive vitiligo, OMP steroid therapy is considered the standard of care. The suggested dosing is betamethasone (5 mg), dexamethasone (2.5–5 mg) or prednisone (15–30 mg, depending on body weight) twice weekly, on 2 consecutive days per week, for up to 3 months.[9]

Methotrexate (MTX): MTX is a treatment alternative for disease stabilization, but its efficacy is less clear.

Topical corticosteroids and calcineurin inhibitors: Topical corticosteroids and calcineurin inhibitors continue to be standard treatments for localized vitiligo. These agents are often used as adjunctive therapies with systemic agents or phototherapy.

Narrowband ultraviolet B (UVB) phototherapy: Stabilizing disease (for example, treatment with OMP steroids) is often not enough to induce repigmentation. Combination (or sequential) narrowband UVB phototherapy effectively promotes repigmentation in vitiligo lesions. While narrowband UVB phototherapy is considered the first-line standard of care for repigmentation in some published guidelines,[14] access and convenience may limit its utility to some extent.

Excimer laser: Excimer laser therapy is a treatment option that delivers targeted UVB light to depigmented areas, offering improved results for segmental vitiligo.

Polypodium leucotomos and SOD: Polypodium leucotomos, an orally administered photoprotective antioxidant, has been used as adjuvant therapy for vitiligo patients also being treated with phototherapy. Repigmentation rates are higher with combination therapy that includes polypodium leucotomos and psoralen and UVA (PUVA) or narrow band UVB (NB-UVB) compared with either photochemotherapy or NB-UVB phototherapy alone.[15]

Emerging vitiligo therapies:

As the understanding of the pathogenesis of vitiligo continues to be elucidated, more directed therapies are being developed. For example, Janus kinase (JAK) inhibitors may represent a potential breakthrough in vitiligo treatment, with recent clinical trials demonstrating their effectiveness in repigmentation.

Topical ruxolitinib: Approved for the treatment of vitiligo in the EU and in the US, topical ruxolitinib cream offers excellent repigmentation rates. However, patient and physician expectations need to be aligned, since achieving meaningful repigmentation may take as long as 24 months. In a recent poster presentation, patients who showed no significant repigmentation at 24 weeks who had continued therapy with ruxolitinib, achieved high repigmentation rates by weeks 52 and 104.[16]

Povorcitinib: Povorcitinib is a selective oral JAK1 inhibitor. The results of a phase 2b, placebo-controlled dose-ranging study that included 171 patients showed significant rates of repigmentation (measured as Total Vitiligo Area Scoring Index and Facial Vitiligo Area Scoring Index) at week 24, and continued to improve up to week 52. Significantly, this response was maintained at a high rate during a 24-week withdrawal period. Safety assessments were consistent with the selective JAK inhibitor class of medications.[17]

Upadacitinib: Upadacitinib is an oral selective anti-JAK1 inhibitor (already approved in Canada for atopic dermatitis, inflammatory bowel disease, and inflammatory arthritides), shows promise for vitiligo in its Phase 2 trials.[18]

Ritlecitinib: Ritlecitinib is a selective oral JAK3/TEC inhibitor that is expected to receive approval for alopecia areata in Canada and is also being assessed for vitiligo. Ritlecitinib also showed statistically significant and clinically meaningful repigmentation versus placebo at week 24, and "accelerated improvement was observed after week 28 during the extension period."[19]

Baricitinib: Baricitinib, in combination with NB-UVB, has also shown benefit in a recent double-blinded phase 2 proof of concept trial.[20]

Other agents in development: As our understanding of the immunologic basis of vitiligo improves, many more agents are likely to be assessed for their potential to control vitiligo outcomes. Along with JAK inhibitors, on the horizon are many other novel therapeutic options in development, including Wnt-signalling agonists, cytokine targeting agents, Treg inducers, and anti-IL-15 agents, among others.[21]

Surgical options for vitiligo, such as punch grafting, can be of benefit. In addition, more recent developments in autologous melanocyte transplantation techniques, such as non-cultured epidermal suspension and follicular unit extraction, may be procedural alternatives in the future.

Conclusion

Recent advancements in vitiligo research have expanded our understanding of the disease's pathophysiology, epidemiology, and psychosocial impact. These insights have paved the way for innovative therapeutic approaches that offer new, more targeted approaches to management of vitiligo. While new treatment options will reduce vitiligo's overall impact, efforts to reduce stigma and improve the psychosocial well-being of affected individuals remain crucial aspects of comprehensive vitiligo management, particularly among Black, Indigenous, Hispanic, and Asian patients in addition to other patients of colour.

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