ABOUT THE AUTHOR

Ajith Cy, MD

Dr. Ajith Cy is a dermatologist and clinical researcher practising in Waterloo, Ontario. He completed his fellowship in pediatric dermatology at The Hospital for Sick Children in Toronto and his dermatology residency at the University of Toronto. His practice focus is medical dermatology.

AN UPDATE ON EXISTING & EMERGING TREATMENTS FOR VITILIGO

Vitiligo is characterized by chronic depigmented patches due to selective loss of melanocytes. The estimated prevalence of vitiligo is about 0.5 to 2% worldwide and, in addition to its significant cosmetic effect, it may cause major psychological distress.[1,2]

Based on clinical distribution, vitiligo is divided into segmental vitiligo (SV) and non-segmental vitiligo (NSV). NSV is further sub-categorized based on the distribution of lesions into five distinct categories: vulgaris, generalized, acral, acrofacial and mucosal vitiligo.[3]

The pathogenesis of vitiligo involves a complex interplay of autoimmune factors, intrinsic melanocyte defects, neural and oxidative stress. Immunologically, a type I immune response is believed to be responsible for the development of vitiligo.[3, 4, 5]

In the last few years, there have been great strides made in understanding the pathogenesis of vitiligo at both the molecular and genetic level. In light of these developments, the future for vitiligo treatment looks promising as several new topical and systemic agents are in various phases of development. These future treatments may even prevent disease recurrence, once an unthinkable aim for vitiligo, as mechanistic models have elucidated targets by which memory T-cells can be altered in animal models.[3,6, 7]

Current treatment options

Current treatment modalities being used are primarily off-label, with the 3 main goals of treatment as follows:

1. Attaining stability of disease process and thereby limit spread of disease by using topical and /or systemic immunosuppressants / immunomodulators

2. Inducing re-pigmentation by stimulating melanogenesis (phototherapy, afamelanotide, and surgical treatments)

3. Reducing intrinsic stress on melanocytes by the use of oral anti-oxidants

Most treatment agents provide varying levels of impact in one or more of the above targets and current treatment modalities can broadly be classified into medical (topical & systemic agents), phototherapy, laser, and surgical methods. [3, 6, 8]

Topical medications

Topical corticosteroids

Corticosteroids are the most commonly used topical medications for vitiligo worldwide. Corticosteroids act by blocking cytotoxic T-lymphocyte activation. Among the various topical corticosteroids used, the literature has shown that mometasone has similar efficacy to clobetasol propionate but with the advantage of fewer side effects and a better safety profile in both the pediatric and adult population.[8-10]

Topical Calcineurin Inhibitors (TCI)

TCIs, such as tacrolimus, play an important role in the treatment of vitiligo by exerting an immunomodulatory effect through the blockade IL-2 and IFN- α, thereby inhibiting cytotoxic T-cells. Tacrolimus also helps in promoting melanogenesis by reducing systemic antioxidant stress. Tacrolimus 0.1% ointment has shown superior results to pimecrolimus 1% cream. TCIs are effective and safe, may be used long term and work best in the management of vitiligo when used in combination with other modalities of treatment.[3, 11, 12]

Latanoprost

When originally used as a treatment for glaucoma, topical prostaglandin analogues caused hyperpigmentation as a side effect which prompted studies in vitiligo. Their mechanism of action involves the induction of tyrosinase and an upregulation of melanocyte proliferation. Latanoprost has shown statistically superior results to placebo on both facial and non-facial skin but is likely more effective on the face and is safe for periocular vitiligo.[13, 14]

Phototherapy

Phototherapy is a first-line treatment modality for those with extensive vitiligo. Narrowband UVB (NBUVB) has mostly replaced PUVA as the primary phototherapy modality. Its mechanism of action is to induce tyrosinase enzyme and it has shown superior efficacy than PUVA in achieving disease stability and repigmentation.[6, 10, 15]

Lasers

A FDA-approved laser used for treating vitiligo is the monochromatic excimer light (MEL) 308nm laser with peer-reviewed results suggesting that the face responds better than other regions. Compared to NBUVB, the MEL laser may deliver superior clinical outcomes, but this treatment modality is more expensive and challenging to use for those with extensive vitiligo.[16,17] Another laser that has been tested for vitiligo is the Helium-neon laser (632.8nm). In use for head and neck segmental vitiligo, the HE-Ne laser has shown greater than 50% repigmentation in 60% of patients.[3]

Systemic treatments

Systemic Corticosteroids

For patients who have failed topicals and NBUVB, systemic immunosuppressants may be the next option to consider. The primary aim of systemic immunosuppressants is to attain disease stability (i.e. no newer / progressing lesions), and also to help with repigmentation. With this in mind, the most commonly used agents are systemic corticosteroids. Longer acting systemic corticosteroids used at a lower dose are commonly referred to as oral mini pulse (OMP) treatment, which involves giving either oral dexamethasone 2.5 mg or oral betamethasone 2.5 mg or 5 mg on 2 consecutive days in a week for up to 6 months. Several studies have shown the arresting of disease activity with OMP treatment in up to 90% of patients with recurrence upon discontinuation of the OMP regimen being noted in about 13% of patients. Compared to regular-dosed prednisone, much of the peer-reviewed literature suggests that OMP is better tolerated for arresting progressive unstable vitiligo with minimal adverse events. Adverse events reported were similar to those seen with corticosteroids including weight gain, acneiform eruptions, and lethargy.[18, 19]

Cyclosporine
As IL-2 is a major cytokine for recruitment of T-Cells, cyclosporine can be a therapeutic choice in the treatment of vitiligo for achieving stability in progressive and unstable disease. Taneja et al showed a significant improvement in the vitiligo area severity index (VASI) score with the use of cyclosporine at 3 mg/kg/day for 3 months.[20]

Methotrexate
In some patients with extensive disease that tends to follow a progressive unstable course over many years, immunosuppressants may be needed long term. In these patients, methotrexate is an option. A comparative study of low-dose methotrexate (10 mg weekly) demonstrated that it was well tolerated by patients and resulted in comparable outcomes to OMP with betamethasone.[3, 21]

Surgical methods
Surgical treatments in vitiligo involve reintroducing melanocytes harvested from pigmented skin of the same person. One of the most important aspects of utilizing surgical methods for the treatment of vitiligo is appropriate patient selection, with the specific aim of ensuring that the disease is stable for at least 1 year (i.e. no new or progressive lesions in the past 1-year period). In unstable / progressive disease, surgery may cause Koebnerization and induce new lesions. Two categories of surgical treatments are tissue grafting and cellular grafting with cellular grafting providing significantly better patient outcomes but requiring more expertise, and laboratory support.[22, 23]

Depigmenting treatment
In patients with extensive vitiligo not responding to treatment, the option of depigmenting remaining normal skin may give better cosmetic outcomes. Monobenzyl ether of hydroquinone (MBEH) 20% is a FDA-approved depigmenting agent for vitiligo. MBEH's mechanism of action involves the induction of lysosomal degradation and oxidative stress of melanocytes leading to immune destruction of the remaining melanocytes. The possible adverse events associated with the use of MBEH are rare but can include conjunctival melanosis and irritant contact dermatitis.[24]

Emerging treatment options in Vitiligo
Newer options currently in development include targeted immunotherapeutic agents such as JAK / STAT inhibitors, and newer phototherapy and laser options which will be reviewed below.

JAK Inhibitors
Janus kinases (JAKs) are a family of 4 proteins: JAK1, JAK2, JAK3, and TYK2. These proteins cause immunomodulation by activation of intracytoplasmic transcription factors called signal transducer and activator of transcription (STAT). Once activated, they dimerize and move to the nucleus where they modulate gene expression. Laboratory work in mice with vitiligo have helped illuminate the crucial role of the JAK/STAT pathway in the pathogenesis of vitiligo.[30] JAK inhibitors (JAKI) are broadly classified into first and second generation agents. First generation JAK inhibitors block more than 1 or all of the janus kinase family of proteins and have been the agents used with greatest frequency for vitiligo to date.[7, 25, 26]

Tofacitinib
Tofacitinib is a JAK 1/3 inhibitor. Both systemic and topical tofacitinib have been used in vitiligo. In various case series', the use of oral tofacitinib at doses of 5 mg po OD or BID for 3 to 6 months has demonstrated significant improvement in repigmentation.[26,27,28] Topical tofacitinib citrate 2% given for facial vitiligo achieved a mean improvement of 70% based on the difference in mean facial VASI at baseline and at follow-up (mean follow-up of 112 days).[29]

Ruxolitinib
Topical ruxolitinib 1.5% cream has shown great response in vitiligo, especially for facial vitiligo. In an open-label trial, a mean improvement of 92% was observed in facial lesions calculated as improvement in overall VASI for enrolled patients (n = 8) at week 52 from baseline. The results of a multicenter phase 2 study of topical Ruxolitinib cream in vitiligo has been recently published and shows significant improvement in vitiligo as measured by approximately 50% of patients on ruxolitinib cream achieving F-VASI50 (50% improvement in facial VASI) compared to only 3% of those on placebo.[30] A Phase 3 clinical trial is actively ongoing and results are expected in 2021. Transient acneiform eruption, worsening of acne, and mild erythema were the most commonly reported side effects.[30]

It is worth noting that there are better repigmentation rates in patients who received both JAK inhibitors and NBUVB at sites of chronic UV exposure such as the face and extensor forearms. Therefore, significant repigmentation in vitiligo using JAK inhibitors may also require photostimulation of melanocytes. Clinical trials examining this are ongoing with JAK inhibitors and NBUVB.

Alpha-melanocyte-stimulating hormone (α-MSH) analogue afamelanotide is a synthetic analogue of alpha-melanocyte-stimulating hormone (α-MSH) which induces melanogenesis. A clinical trial involving the use of afamelanotide with NBUVB vs NBUVB alone has shown that afamelanotide with NBUVB had superior repigmentation rates.[31]

Basic Fibroblast Growth Factor (b-FGF)

In vitro studies have shown that b-FGF is capable of stimulating melanogenesis and a recent phase IV double-blind randomized controlled trial has shown b-FGF with NBUVB to be superior to NBUVB alone with a very good tolerability profile.[32]

Bioskin evolution micro phototherapy

Bioskin evolution is a targeted 311-nm narrowband micro phototherapy device that is suitable for lesions involving <10% body surface area (BSA). The advantages of this device are that it can be used in patients with limited disease including sensitive areas such as eyelid skin and it is more convenient than having to expose the whole body to NBUVB treatment.[33]

311nm Titanium: Sapphire laser (TSL)

A 311nm TSL for vitiligo along with topical tacrolimus 0.1% ointment has shown significant benefit to complete repigmentation in 79% of patients. Results from TSL were similar to 308nm excimer laser (EL), but with better safety profile.[34]

UVA-1 lasers

The Laser Alba 355®, a UVA-1 laser with 355nm spectrum, has shown successful repigmentation in up to 75% of patients.[35] Utilization of a UVA-1 laser works well due to its deeper penetration and immunomodulatory properties.[35]

Oral Antioxidants

Oral antioxidants are now part of first line management of vitiligo in some countries, as they may help to decrease the oxidant stress on melanocytes. Oral gingko biloba, polypodium leucotomus, vitamin E, vitamin C, and alpha lipoic acid have all been shown to promote repigmentation.[36-38]

Future treatment prospects

Programmed cell death-1 ligand (PDL-1) is currently being studied for psoriasis and inflammatory bowel disease and might be beneficial for vitiligo as well, as it helps to maintain immune balance.

IL-15 causes oxidative stress mediated destruction of melanocytes; therefore inhibiting IL-15 may be explored as a future potential mechanism of action in the treatment of vitiligo. Inducing mi-RNA via a miR-155 agonist has also shown to improve melanocyte regeneration.[39] Hence mi-RNA induction may be a future treatment option for vitiligo.[3, 40-42]

Conclusion

The treatment of vitiligo cannot be addressed as one size fits all, but must be individualized to address patient expectations, impact of disease, and compliance. The effective treatment of vitiligo may require a multimodal approach including minimizing oxidative stress with anti-oxidants, implementing topical or systemic immunomodulatory agents, and initiating treatment modalities to regenerate melanocyte function by phototherapy and surgical methods. Future treatments, especially those involving the JAK-STAT pathway, hold promising potential.

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