HIGH SCHOOL EDITION
Journal of Student Research
Volume 11 Issue 1 (2022)

Treatments for Vitiligo

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ABSTRACT

Vitiligo is a skin condition that leads to skin depigmentation in irregular patterns with potentially severe esthetic and psychological effects on the affected individual. While its etiology is not well understood, it seems to be a multifactorial condition that may be caused by hereditary factors and autoimmune processes among others. By reviewing various publications found through different databases like PubMed and Google Scholar, this paper summarizes the different therapeutic options available for vitiligo. This includes JAK inhibitors, both topical and oral, and other types of topical drugs, such as vitamin D, calcineurin inhibitors, and steroids. There are also various phototherapy techniques, which all utilize ultraviolet (UV) light. Phototherapy devices are able to deliver the wavelengths that are most beneficial for the stimulation of re-pigmentation through special filtering. These different treatments give hope to millions of individuals afflicted by this condition worldwide. The following paper overviews and compares the different JAK inhibitors, other topical drugs, and phototherapy options available to treat vitiligo.

Introduction

Affecting 0.5-2% of the population, vitiligo is a common skin condition that causes depigmentation in irregular patterns. Affecting both males and females equally, vitiligo can start at any age and spread to all parts of the body. Researchers have many different theories and speculations on the possible cause of vitiligo, including hereditary reasons, autoimmune diseases, or a multifactorial cause. Although the etiology remains unclear, a large amount of research has been done on the biological background of vitiligo. Depigmentation begins when the number of melanocytes in a patch of skin starts to decrease as pigment cells in the skin are lost. The reason for the loss of pigment cells is due to being destroyed by autoimmunity. The destruction of melanocytes progressively causes the development of white spots or depigmented areas. Due to its effect on cosmetic appearance, vitiligo can often feel psychologically burdensome as it progresses throughout a patient's entire life (Bergqvist & Ezzedine, 2020).

Researchers have made notable strides in understanding the pathology of vitiligo, which has allowed for the development of various new treatments. These treatments include JAK inhibitors (both topical and oral), other topical drugs, and phototherapy. After confirming that vitiligo is present on the skin through use of natural light and wood lamps (hand-held lamps that send waves of ultraviolet light to illuminate areas of the skin), the best treatment can be tailored based on the level of severity and the needs of each patient. The duration of the disease, rate of growth of the depigmentation areas, and skin phototype are all imperative elements in the selection of treatments (Ezzedine & Silverberg, 2016).

While there are currently no FDA-approved drugs that reverse vitiligo, there are many that have been proven to significantly improve lesions of depigmentation (Agarwal, 2015). This review will compare and overview updates on the various current treatments available.

Results

JAK Inhibitors

Although there is no approved or labeled treatment for vitiligo, Janus Kinase (JAK) inhibitors have proven to be of immense benefit to people suffering from the disease, and have advanced the world of dermatology (Ezzedine & Silverberg, 2016).

JAK proteins are part of a family of tyrosine kinases that promote important signaling pathways (Damasky & King, 2017). For example, the JAK-STAT pathway connects the "intracellular signals of more than 60 cytokines, growth factors, and hormones" (Relke & Gooderham, 2019). Once an extracellular ligand, such as a cytokine, binds to the membrane receptor, the JAK protein phosphorylates the receptor, which attracts the STAT (signaling transducers and activators of transcription) protein. A phosphorylated STAT (pSTAT) then travels to the nucleus to activate transcription and gene expression (Samaka, 2019).

In regard to vitiligo, the action of interferon gamma (IFN**γ**) signaling plays a major role in vitiligo's pathogenesis. IFN**γ** activates the JAK-STAT pathway and leads to the transcription of CXCL9 and CXCL10. Both genes are enlisted by CD8 T-cells to attack melanocytes in the skin. CD8 T-cells are vital immune cells that work as a defense against bacteria, viruses, or cancer cells in the body by killing any infected cells. Because vitiligo is involved with the JAK-STAT pathway and IFN**γ**, the disease is susceptible to treatment using JAK inhibitors. In other words, the JAK inhibitors interfere with the IFN**γ** signaling, blocking the activity of vitiligo and allowing for repigmentation (Samaka, 2019).

There are two types of JAK inhibitors: topical and oral. In conjunction with supplementary treatments, primarily phototherapy, these inhibitors can help begin the repigmentation process in many areas of the body. The most well-known JAK inhibitors include tofacitinib and ruxolitinib. Both of these inhibitors can be used "systemically as oral drugs or locally in topical formulations" (Solimani & Meier, 2019).

Approved by the US Food and Drug Administration, tofacitinib is a JAK 1/3 inhibitor (Damsky & King, 2017). Tofacitinib has shown major success in treating patients with Alopecia Areata, a disorder that results in areas of hair loss. Due to the common pathogenesis of alopecia areata and vitiligo, it does not come as a surprise that tofacitinib is also effective in treating vitiligo (Rork, 2016). Topical 1.5% ruxolitinib cream, a JAK1 and JAK2 inhibitor, has also proven to be effective. Especially for patients with facial vitiligo, JAK inhibitors have generally been successful in repigmentation (Rothstein, 2017).

Other Topical Drugs

Other types of topical drugs used for vitiligo include topical vitamin D, topical calcineurin inhibitors (TCIs), and topical corticosteroids (TCS). Selecting which drug is best for each patient depends on identifying where the lesions of depigmentation occur. For example, "The European Dermatology Forum consensus group has recently published guidelines favoring the use of topical calcineurin inhibitors (TCIs) as a first-line option for face and neck on a bidaily basis, as these have fewer side effects in these particular areas" (Ezzedine & Silverberg, 2016).

TCIs, which include tacrolimus and pimecrolimus, reduce the activity of T-cells as well as the production of proinflammatory cytokines. On the other hand, TCS can be used daily for any remaining areas of the body and may be used on and off for the duration of many months. This is done to ensure that the patient does not suffer from any potential side effects of the cream. TCIs are also used when results following the application of TCS are not successful (Ezzedine & Silverberg, 2016).

Table 1. Topical Drugs for Vitiligo

	Areas of Use	Most Common Side Effects
Topical Calcineurin Inhibitors (TCI)	Sensitive areas (face and neck) (Ezzedine & Silverberg, 2016)	Burning sensation post application (Ezzedine & Silverberg, 2016)
Topical Corticosteroids (TCS)	Remaining areas of the body (Ezzedine & Silverberg, 2016)	Stretch marks, thinning of the skin, acne (Ezzedine & Silverberg, 2016)

Phototherapy

Another very promising treatment for vitiligo is phototherapy. There is a large variety of phototherapy types that have been very beneficial in the treatment of different dermatological diseases. Phototherapy is primarily used "[for] extensive disease[s] and in disease that is spreading rapidly" (Ezzedine & Silverberg, 2016). It utilizes the exact same type of light that can be found in sunlight, ultraviolet (UV) light. UV light is able to deliver the wavelengths that are most beneficial for the stimulation of repigmentation through special filtering. For vitiligo, psoralen–UV-A (PUVA) and narrowband UV-B (NBUVB) light therapy are most often used (Bae, 2017).

In 1948, PUVA phototherapy was introduced as a treatment for vitiligo (Bae, 2017). This treatment is quite unique and distinct from others. Following radiation of psoralen-sensitized skin, PUVA has a delayed erythemal reaction (Ibbotson, 2018). Due to psoralen's origin being a chemical found in specific plants that cause the skin to become sensitive to ultraviolet radiation (UVA) for a short period of time, the skin becomes sensitized and has a late appearance of redness. While it has been shown to be effective, it also has many limitations. Some of these include "phototoxic effects, nausea, and the potential risk for skin cancer" (Bae, 2017). Another constraint is that PUVA phototherapy cannot be used to treat children or pregnant women because of the presence of psoralen, due to its toxicity and the possibility of causing birth defects (Bae, 2017).

Gradually replacing PUVA is NBUVB phototherapy, which was first reported in 1997 (Bae, 2017). This type of treatment involves the continuous, controlled delivery of UV light, specifically the narrowband region of the UVB spectrum (Ibbotson, 2018). When deciding on which phototherapy to use to treat vitiligo, NBUVB is most often the first choice for physicians. This is due to it being cost-effective and notably safe and effective for patients. Compared to PUVA, NBUVB has fewer side effects, does not require a photosensitizer, and utilizes a smaller dose of UVB light (Bae, 2017). The therapeutic effects are also clear when comparing the two phototherapy options: "NB-UVB has been shown to be superior to PUVA with respect to rates of repigmentation, particularly for unstable extensive vitiligo, and in achieving more cosmetically acceptable even repigmentation" (Ibbotson, 2018).

Dermatologists consider treating patients with phototherapy, or NBUVB, when they do not observe successful repigmentation after using topical agents (Ibbotson, 2018). The disadvantages of narrowband UV-B phototherapy, however, are mild burning, itching, and erythema. Nevertheless these drawbacks have been shown to be easily tolerated and not long lasting (Bae, 2017).

Table 2. Types of phototherapies

Phototherapy	Year Established	Recommended for	Side effects	Use of psoralen
NBUVB	1997 (Bae, 2017)	Everyone (Bae, 2017)	Mild burning, itching, and erythema, and induction of photosensitivity diseases (Bae, 2017)	No (Bae, 2017)
PUVA	1947 (Bae, 2017)	Everyone except children and pregnant women (Bae, 2017)	Nausea, phototoxic reactions, and longer-term risk of skin carcinogenesis (Bae, 2017)	Yes (Bae, 2017)

Methods

PubMed and Google Scholar were the main databases used to search for peer-reviewed, published literature. The following combination of keywords were used: vitiligo, treatments, JAK inhibitors, oral, topical, phototherapy, NBUVB phototherapy, PUVA phototherapy, and cures. All publications chosen focused on specific treatments for vitiligo and their reducement of depigmentation areas. The papers' publication years ranged from 2002 to 2020. Any information on pathogenesis and classification of vitiligo was excluded. Early ideas for this review focused on the different speculations for the origins of vitiligo; however, available literature is currently limited. Therefore, the focus was switched to treatments for vitiligo.

Conclusion

Vitiligo, the cause of patchy depigmentation areas, is a common disease that destroys melanocytes in the skin. In addition to being hard to treat and having unpredictable progression, it can also be extremely disfiguring for some when it affects the face as well as other visible areas of the body. Although the source of vitiligo continues to remain unknown, dismissing the countless speculations, there are a few treatments that have proven to be extremely successful in the improvement of the condition. Some of the most common include JAK inhibitors, topical drugs, and phototherapy. Through targeting the JAK-STAT pathways, it was found that JAK inhibitors, tofacitinib and ruxolitinib, have shown great success in reducing the size of vitiligo macules. Furthermore, it is recommended to combine the use of JAK inhibitors with phototherapy for maximum effectiveness. The two types of phototherapies include NBUVB, which is most physicians' first choice, and PUVA. Topical therapies, such as topical calcineurin inhibitors (TCIs) and topical corticosteroids (TCS), are also suggested for use, but are limited to less than 20% of body surface area.

There seemed to be a lack of research pertaining to treatments of vitiligo, as there was not as much information as anticipated. A literature review combining information about JAK inhibitors and phototherapy is a very necessary addition to the medical world, especially for those looking for the more successful treatments or for those simply wanting to be updated on the current ones. This paper compares JAK inhibitors, topical therapies, and phototherapy through tables and in-depth information. Limitations of this paper include a lack of research on the newer surgical treatment options. Additionally, there were not many articles going in depth, soley about these two treatments.

In an effort to combat the scarcity of research done in managing vitiligo, there should be more investigative work done on the cause of vitiligo to better understand the disease and find new treatments to reverse it.

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