CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1477760

Available online at: http://www.iajps.com Review Article

MANAGEMENT AND TREATMENT OF VITILIGO; A REVIEW OF RECENT LITERATURE

Alshafie , Ali Yahya A [1], Bakri,Sultan Mousa A [2], Dalal Ibrahim O Alesa [3], Reham Othman Mohammed Alzahrani [4], Noor Ali Alqallaf [5] , Sabei, Ali Ibrahim H [6] , Ali Mohammed Alshaikh [7], Reem H. Alenazi [8], Ali Jaber Ahmad Asiry [9], Abdulelah saleh alhabib [10]

[1] NGH- Jeddah
[2]PMNH-jazan
[3]Dermatology Resident at Al-Noor Specialist Hospital
[4] Taif University
[5] Medical University of Warsaw
[6]General Physician at Salhaba and New Sabya Primary Health Care Centre in Jazan
[7] Family Resident, Abha
[8]King Abdulaziz University
[9]King Khalid University
[10] King Saud University

Abstract:

Introduction: *Vitiligo is a relatively common autoimmune pathology that causes disfigurement and leads to negative impact of the self-esteem and quality of life. Generally, vitiligo is known to be a result of several factors including genetic and environmental factors.*

Aim of work: *In this review, we aim to discuss recent advances in the treatment modalities of vitiligo.*

Methods: *We did a systematic search for vitiligo using PubMed and Google Scholar search engines. The terms used in the search were: vitiligo, pathophysiology, mechanisms, management, treatment, recent modalities.*

Conclusions: *Treatment vitiligo consists of three main phases: stop the spread of the disease, recover damaged areas, and prevent relapses. Several treatment modalities have been used to achieve these three phases. However, no current protocol achieves all three phases completely. Systemic corticosteroids and methotrexate have been successfully used in stopping the spread of the disease. Phototherapy, topical steroids, and intralesional steroids have all been use to induce repigmentation in damaged lesions. However, no treatment until now has provided satisfactory declines in relapse rates. Several new treatments are being tested and developed for vitiligo like topical prostaglandins therapy.*

Keywords: *vitiligo, skin disorders, dermatological therapy*

Corresponding author:

Alshafie,

NGH- Jeddah

QR code

Please cite this article in press Alshafie et al., ***Management and Treatment of Vitiligo; A Review of Recent Literature.,*** *Indo Am. J. P. Sci, 2018; 05(11).*

INTRODUCTION:

Vitiligo is a relatively common autoimmune pathology that causes disfigurement and leads to negative impact of the self-esteem and quality of life of the patient[1]. The current used treatment for vitiligo includes several non-specific immunosuppressive drugs that are used off-label and lead only to mild benefits. Therefore, it is essential to develop better more efficient drugs and treatments that could improve the outcomes. However, to be able to develop more efficient treatments, the first step is to better understand the pathophysiology and etiologies of the disease[2]. Generally, vitiligo is known to be a result of several factors including genetic and environmental factors. These all work together and lead to an immune response against the skin melanocytes. Vitiligo is caused by a dynamic interplay between genetic and environmental risks that initiates an autoimmune attack on melanocytes in the skin [2].

When providing treatment for a patient with vitiligo, there are three goals: stop the progression of the disease, allow the repigmentation of already affected areas, and prevent recurrence of the disease. Unfortunately, no treatments are currently available to completely achieve all these goals, and current therapies only provide partial relief of symptoms. In addition, some therapies can affect vitiligo lesions present in certain areas in the body (like the face) but be ineffective in other areas (like the feet) [3].

Recent efforts have led to significant improvements in our knowledge and understanding of vitiligo and aided the development of new possible therapies. It has been established that the interferon gamma/Janus kinase/CSCL10 pathway is primarily involved in the pathophysiology of developing skin depigmentation[3]. This discovery has led to the hypothesis that if we target this pathway, we may be able to cause significant improvement in the patients' clinical picture by decreasing rates of depigmentation [4]. However, it is still not clear if this mechanism would be able to repigment already damaged areas.

Other researchers have suggested the involvement of the Wnt signaling pathway in the process of vitiligo by prohibiting stem cells from differentiation into melanocytes. This mechanism has been observed in areas like the hands and feet which are known to synthesize wnt inhibitors. Until now, the most efficient modality that has been successful in stimulating melanocytes differentiation is the use of ultraviolet radiation, which is also thought to involve Wnt pathways [5]. Therefore, there has recent approaches to produce topical therapies that would cause repigmentation. In this review, we aim to discuss recent advances in the treatment modalities of vitiligo.

METHODOLOGY:

We did a systematic search for vitiligo using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). Our search also looked for pathophysiology, and treatment of prostatitis. All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: vitiligo, pathophysiology, mechanisms, management, treatment, recent modalities.

Vitiligo pathogenesis:

Several mechanisms have been reported to be involved in the pathogenesis of vitiligo. Researchers have noticed that vitiligo risk is generally higher among relatives, which led to the thought that genetic predisposition can play a role in the pathophysiology of the disease. For example, the risk of developing vitiligo in a patient with a sibling with vitiligo can be 6%, while the risk of vitiligo in the general population is less than 1%[6]. Moreover, the risk of vitiligo significantly increases with the presence of another autoimmune disease like diabetes mellitus type 1, autoimmune thyroiditis, Addison's disease, and pernicious anemia. This also led to the conclusion that vitiligo could involve autoimmune mechanisms[7].Several other studies have suggested the involvement of oxidative stress mechanisms in the development of vitiligo [8].

Environmental factors are also believed to be involved in the pathophysiology and development of vitiligo. This, however, is still not completely understood. Several researchers have suggested that certain environmental exposures can work in combination with genetic predisposition to start the disease. In fact, a previous study has reported the incidence of vitiligo in several co-workers simultaneously following their exposure to monobenzone. Since then, studies have been conducted to establish the exact role of environmental exposures in the development of vitiligo[9].

Vitiligo treatment:

Our current understanding of the pathophysiology of vitiligo helps us find better and more efficient treatment modalities. These modalities can act by decreasing the stress on melanocytes, regulating the response of the immune system, and stimulating the

regeneration of melanocytes. We will discuss current and emerging treatments in the following sections of this review article.

Systemic Steroids:
The use of high-dose systemic corticosteroids in a pulsed manner has been known to quickly stop vitiligo spreading and increase the rate of lesions repigmentation[10]. In addition, clinical studies on different regimens of systemic corticosteroids therapy have found rates of remission, and repigmentation to be up to 85% and 70% of patients, respectively. However, a significant limitation in steroids use is the development of adverse events like lethargy, and increased wait in about 10% of patients. In addition, it is relatively common to relapse following the stopping of treatment, especially in younger patients, who have a relapse rate that can reach 47%[11]. However, until this day, no randomized clinical trials have been performed to compare the use of corticosteroids against placebo. These, along with the high rates of side effects, make corticosteroids unfavorable and controversial.

Intralesional corticosteroids:
The use of corticosteroids as intralesional treatment was first introduced to clinical practice more than thirty years ago. However, it was limited by pain, and the risk of skin atrophy, which occurred in about 35% of patients. However, in a more recent trial that authors reported the treatment of all included patients using triamcinolone acetonide intralesional injections for duration of 4 months, with only one patient developing cutaneous atrophy, and two patients reporting irregularities in the menstrual cycle [12]. Another systematic review and meta-analysis was published and concluded that both tropical steroids and intralesional steroids have similar effects. Therefore, they recommended the use of topical steroids due to their better safety profile [13]. Generally, both modalities were found to cause better repigmentation rates than systemic corticosteroids [13].

When aiming at repigmentation of a small localized vitiligo lesion, topical corticosteroids therapy remains to be one the best treatment modalities. Their efficacy and superiority than many other older modalities have been established in several trials and meta-analyses[14]. Following the administration of localized corticosteroids, repigmentation starts to occur after few months from the lesions' margins. However, cutaneous atrophy, acne, telangiectasia, striae, rosacea, ecchymoses, remain to be significant limitations of the use of localized topical steroids[14]. A reduction in the dose or potency of corticosteroids may decrease the rates of adverse events. This, however, will result in significant decline in the efficacy of treatment.

Another limitation of topical, localized corticosteroids is the inability to use this treatment in cases where there are multiple large lesions, as this can potentially lead to the development of hypothalamic-pituitary-adrenal axis suppression. Therefore, it is not recommended to use topical steroids on large areas, and on important areas like the face. It is also recommended to include intervals with no treatment in the treatment plan. These treatment-free intervals can potentially reverse cutaneous atrophy or prevent it from the first place [15].

Methotrexate:
The use of methotrexate in treatment of vitiligo was initially discovered incidentally when a rheumatoid arthritis patient received methotrexate, and her vitiligo improved [16]. Since then, several studies have been conducted to evaluate the efficacy of methotrexate in vitiligo and compare it with the use of corticosteroids. A recent clinical trial has concluded that methotrexate can have an efficacy in treating vitiligo and stopping its progression that can be comparable with the effects of corticosteroids [17].

Minocycline:
The hypothesis behind the use of minocycline in the treatment of vitiligo was to use its anti-inflammatory and immunomodulatory effects of it to improve the disease. A recent randomized trial showed a high efficacy of minocycline in stopping the progression of vitiligo. However, this efficacy remained similar to systemic corticosteroids therapy with no significant differences between the two modalities [18].

On the other hand, another study has compared the use of minocycline against the use of ultraviolet light in active vitiligo and concluded that ultraviolet treatment was associated with significantly higher efficacy in stopping the disease than minocycline. Moreover, rates of repigmentation were also significantly higher in the ultraviolet group when compared to the minocycline group [19].

However, both studies are limited by the absence of a placebo control group to be able to compare interventions with the normal progression of the disease, making it necessary to evaluate minocycline in more clinical studies [18,19].

Topical Calcineurin Inhibitors:
Several trials have assessed the use of pimecrolimus and tacrolimus, which are both calcineurin inhibitors, in the treatment of generalized and localized vitiligo. A recent study has compared the use of tacrolimus versus clobetasol propionate in young vitiligo patients and concluded that tacrolimus can be beneficial in causing repigmentation. However, rates and extent of pigmentation were similar in both topical tacrolimus and clobetasol [20].

Generally, both tacrolimus and clobetasol can be efficiently used to induce repigmentation and were proven to cause improvements when compared with placebo. They have also been proven to cause repigmentation in the face in higher rates than lesions in other regions of the body. When used twice a day, tacrolimus led to even improved results. Pimecrolimus was also found to have similar outcomes when compared to tacrolimus [21].

Calcineurin inhibitors demonstrated best outcomes in areas that is exposed to the sun. In a previous trial, researchers assessed the efficacy of topical tacrolimus, topical pimecrolimus, and ultraviolet light in the induction of repigmentation. They concluded that the three modalities for treatment were associated with similar outcomes regarding repigmentation. However, they found that combining one of the topical treatments with ultraviolet light led to the best outcomes [22].

Other Topical Medical Treatments:
The use of topical vitamin D alone or in combination with ultraviolet light has been proposed for the treatment of vitiligo and the induction of repigmentation. A previous trial ha concluded that the use of calcipotriol monotherapy led to no significant benefits in vitiligo [23].

Results regarding the use of vitamin D are generally conflicting with no conclusive recommendation. The rationale behind the use of vitamin D along with other antioxidants may be scientifically strong. However, clinical data seem not to find significant benefits. This could be explained by the inability to efficiently deliver antioxidants to the skin. Therefore, further research regarding this issue is still needed before conclusions and recommendations are made.

Preventing Vitiligo Relapses:
Following the successful sopping of the disease, and efficient repigmentation of lesions, it remains a challenging issue to prevent the disease from relapsing and causing new lesions. Reports estimate that over 40% of patients will relapse even after successful repigmentation treatment [24].
Current data from previous clinical trails on vitiligo and its treatment modalities indicate that topical steroids can lead to a decrease in the rates of relapse following treatment, along with Calcineurin inhibitors. However, it is still not clear how long these preventive measurements could continue for following achievement of repigmentation. Moreover, the sufficient dose in this preventive phase is also not exactly clear. Therefore, further studies and trials are still needed to address these issues.

Potential Emerging Medical Treatments:
Apart from the previously-mentioned treatment, several potential treatment modalities and possible therapies have been developing lately in attempts to improve vitiligo treatment protocols, and lead to better outcomes. in the next section of this article, we will discuss briefly these emerging modalities:

Topical Prostaglandins:
Prostaglandins are hypothesized to act by stimulating melanocytes and melanogenesis proliferation. Previous trials have inspected the use of prostaglandins topically in the treatment of vitiligo lesions, and found promising results as prostaglandins achieved good efficacy with a relatively safe profile [25].

However, it is still early to reach any conclusions regarding the use of prostaglandins in vitiligo, and more studies are currently needed to establish and recommendation in this issue.

Afamelanotide:
Afamelanotide is drug that acts by stimulating the a melanocortin-1 receptor. A previous trial was conducted to assess its effects on patients with vitiligo and found promising results that supports its use. They found that combining afamelanotide with ultraviolet light treatment led to significant improvement in outcomes when compared to ultraviolet light alone. However, adverse events of afamelanotide included nausea and fatigue, and led to incompliance of some patients. They also found that afamelanotide was more efficient in patients with darker skin [26].

However, current data are not sufficient to make any recommendations of afamelanotide use. This is mainly due to the limited number of studies on it, and the absence of studies that assess its efficacy alone versus placebo. Future studies, with improved design to prevent bias, are needed in this field.

Janus Kinase Inhibitors:

Recently, several studies have suggested the involvement of the IFN-g/JAK/CXCL10 pathway in the pathophysiology of vitiligo[3]. This assumption has led to several hypotheses regarding the treatment of vitiligo. Currently, data on using JAK inhibitors are still insufficient with only two case reports published in literature.

One study has reported the use of a tofacitinib, which is a JAK inhibitor in the treatment of vitiligo. This study reported the case of a patient with rheumatoid arthritis who was treated by tofacitinib for her arthritis, and her vitiligo incidentally improved. Moreover, following five months of treatment, she was able to achieve complete repigmentation. The other case reported a man with alopecia areata who was receiving ruxolitinib for his alopecia treatment, and showed improvements in vitiligo after about five months of treatment. However, this patient completely relapsed following the discontinuation of treatment [4].

More studies are needed to study this category of drugs before drawing any conclusions. Currently no clinical trial has been conducted to assess the efficacy of these drugs in vitiligo, but current hypotheses are encouraging and support their use in vitiligo.

CONCLUSIONS:

Vitiligo is a relatively common autoimmune disease that is more prevalent among relatives. It is considered to be the result of several genetic and environmental factors. However, it is exact pathophysiological mechanisms are still not well understood, making it relatively hard to provide definitive specific treatment. Treatment vitiligo consists of three main phases: stop the spread of the disease, recover damaged areas, and prevent relapses. Several treatment modalities have been used to achieve these three phases. However, no current protocol achieves all three phases completely. Systemic corticosteroids and methotrexate have been successfully used in stopping the spread of the disease. Phototherapy, topical steroids, and intralesional steroids have all been use to induce repigmentation in damaged lesions. However, no treatment until now has provided satisfactory declines in relapse rates. Several new treatments are being tested and developed for vitiligo like topical prostaglandins therapy.

REFERENCES:

1. Ezzedine K, Eleftheriadou V, Whitton M, van Geel N. Vitiligo. Lancet. 2015; 386(9988):74–84.
2. Rashighi M, Harris JE. Interfering with the IFN-gamma/CXCL10 pathway to develop new targeted treatments for vitiligo. Ann Transl Med. 2015; 3(21):343.
3. Rashighi M, Agarwal P, Richmond JM, et al. CXCL10 is critical for the progression and maintenance of depigmentation in a mouse model of vitiligo. Sci Transl Med. 2014; 6:223
4. Harris JE, Rashighi M, Nguyen N, et al. Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA). J Am Acad Dermatol. 2016;74:370–1.
5. Fukunaga-Kalabis M, Hristova DM, Wang JX, et al. UV-Induced Wnt7a in the Human Skin Microenvironment Specifies the Fate of Neural Crest-Like Cells via Suppression of Notch. J Invest Dermatol. 2015; 135:1521–32.
6. Taieb A, Picardo M. Clinical practice. Vitiligo. N Engl J Med. 2009; 360(2):160–169.
7. Gill L, Zarbo A, Isedeh P, Jacobsen G, Lim HW, Hamzavi I. Comorbid autoimmune diseases in patients with vitiligo: A cross-sectional study. J Am Acad Dermatol. 2016; 74(2):295–302.
8. Shen C, Gao J, Sheng Y, Dou J, Zhou F, Zheng X, et al. Genetic Susceptibility to Vitiligo: GWAS Approaches for Identifying Vitiligo Susceptibility Genes and Loci. Front Genet. 2016; 7:3.
9. Wu S, Li WQ, Cho E, Harris JE, Speizer F, Qureshi AA. Use of permanent hair dyes and risk of vitiligo in women. Pigment Cell Melanoma Res. 2015; 28(6):744–746.
10. Seiter S, Ugurel S, Tilgen W, et al. Use of high-dose methylprednisolone pulse therapy in patients with progressive and stable vitiligo. Int J Dermatol. 2000;39:624–7.
11. Kanwar AJ, Mahajan R, Parsad D. Low-dose oral mini-pulse dexamethasone therapy in progressive unstable vitiligo. J Cutan Med Surg. 2013;17:259–68.
12. Wang E, Koo J, Levy E. Intralesional corticosteroid injections for vitiligo: a new therapeutic option. J Am Acad Dermatol. 2014;71:391–3.
13. Njoo MD, Spuls PI, Bos JD, et al. Nonsurgical repigmentation therapies in vitiligo. Meta-analysis of the literature. Arch Dermatol. 1998;134:1532–40.
14. Whitton M, Pinart M, Batchelor JM, et al. Evidence- Based Management of vitiligo: summary of a Cochrane systematic review. Br J Dermatol. 2015; 174(5):962–9.
15. Sassi F, Cazzaniga S, Tessari G, et al. Randomized controlled trial comparing the effectiveness of 308-nm excimer laser alone or in

combination with topical hydrocortisone 17-butyrate cream in the treatment of vitiligo of the face and neck. Br J Dermatol. 2008;159:1186–91.
16. Sandra A, Pai S, Shenoi SD. Unstable vitiligo responding to methotrexate. Indian J Dermatol Venereol Leprol. 1998;64:309.
17. Alghamdi K, Khurrum. Methotrexate for the treatment of generalized vitiligo. Saudi Pharm J. 2013; 21:423–4.
18. Singh A, Kanwar AJ, Parsad D, et al. Randomized controlled study to evaluate the effectiveness of dexamethasone oral minipulse therapy versus oral minocycline in patients with active vitiligo vulgaris. Indian J Dermatol Venereol Leprol. 2014;80:29–35.
19. Siadat AH, Zeinali N, Iraji F, et al. Narrow-Band Ultraviolet B versus Oral Minocycline in Treatment of Unstable Vitiligo: A Prospective Comparative Trial. Dermatol Res Pract 2014. 2014:240856.
20. Ho N, Pope E, Weinstein M, et al. A double-blind, randomized, placebo-controlled trial of topical tacrolimus 0.1% vs. clobetasol propionate 0.05% in childhood vitiligo. Br J Dermatol. 2011;165:626–32.
21. Coskun B, Saral Y, Turgut D. Topical 0.05% clobetasol propionate versus 1% pimecrolimus ointment in vitiligo. Eur J Dermatol. 2005;15:88–91.
22. Stinco G, Piccirillo F, Forcione M, et al. An open randomized study to compare narrow band UVB, topical pimecrolimus and topical tacrolimus in the treatment of vitiligo. Eur J Dermatol. 2009;19:588–93.
23. Chiaverini C, Passeron T, Ortonne JP. Treatment of vitiligo by topical calcipotriol. J Eur Acad Dermatol Venereol. 2002;16:137–8.
24. Nicolaidou E, Antoniou C, Stratigos AJ, et al. Efficacy, predictors of response, and long-term followup in patients with vitiligo treated with narrowband UVB phototherapy. J Am Acad Dermatol. 2007;56: 274–8.
25. Kapoor R, Phiske MM, Jerajani HR. Evaluation of safety and efficacy of topical prostaglandin E2 in treatment of vitiligo. Br J Dermatol. 2009;160: 861–3.
26. Lim HW, Grimes PE, Agbai O, et al. Afamelanotide and Narrowband UV-B Phototherapy for the Treatment of Vitiligo: A Randomized Multicenter Trial. JAMA Dermatol. 2014;151(1):42–50.