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Role of Tazarotene in Treatment of Vitiligo

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Abstract

Background: Vitiligo is a depigmenting disorder in which genetic factors, oxidative stress, autoimmune response, inflammatory mediators and detachment of melanocytes, all are mechanisms that contribute to the development of the disease. Oxidative stress plays an important role in the development of vitiligo. It is usually the triggering factor of vitiligo, as melanocytes of vitiligo patients are more susceptible to oxidative stress. Tazarotene a topical retinoidwhich have been used in several indications as psoriasis, acne vulgaris, photoaging and T cell lymphoma. Topical retinoids have the following effects i. renewing the epidermis, ii. Acting as UV filters, iii. Preventing formation of oxidative stress, iv. control bacterial flora., v. modulating melanocyte functions.

Aim of Study: Asses the efficacy of tazarotene in treatment of vitiligo.

Patients and Methods: Thirty patients with vitiligo vulgaris and acral vitiligo were included in this study. 0.1% tazarotene gel was given to all patients to be applied daily on affected area, once daily at night for 12 weeks. Evaluation was done using Vitiligo Extent Score for a Target Area (VESTA).

Results: VESTA score showed improvement after 12 weeks of treatment. The median of VESTA measured before treatment is 0% then after 6 weeks 20% then 40% after 12 weeks, with *p*-value <0.001, Patients with acral lesions showed less improvement than others with statistical significance *p*-value <0.001.

Conclusion: Tazarotene is effective in treating vitiligo, but less effective in acral vitiligo.

Key Words: *Tazarotene – Vitiligo.*

Introduction

VITILIGO is a depigmenting skin disorder characterized by disappearance of melanocytes. It is a multifactorial disease in which multiple mechanisms are involved. Genetic factors, oxidative stress, autoimmune response, inflammatory mediators and detachment of melanocytes, all are mechanisms that contribute to the development of the disease **[1].**

Oxidative stress has a major role in the development of vitiligo. It is usually the triggering factor of vitiligo, as melanocytes of vitiligo patients are more prone to damageby oxidative stress. An imbalance between pro-oxidants and antioxidants in the skin and blood occurs when melanocytes releases reactive oxygen species (ROS) in response to stress. ROS causes protein fragmentation and oxidation, DNA damage and lipid peroxidation which decrease cell functions.

Oxidative stress also decreases adherence of melanocytes at the edge of the lesion. Keratinocytes and melanocytes release chemokine ligands which recruits T cells in response to oxidative stress **[2].** Innate immunity is considered the link between the oxidative stress and the adaptive immunity. Patients with vitiligo have shown increased natural killer cells (NK) and type I innate lymphoid cells (ILCI) in the blood and non-lesional skin. Destroyed melanocytes release damage associate molecular pattern (DAMPS) are released from destroyed melanocytes activating dendritic cells which in turn primes T cells. Many cytokines are involved in the pathogenesis of vitiligo including IFN gamma and IFN gamma induced chemokines which recruits CD8 T cells **[3].**

Keratinocytes are responsible for the production of many of these cytokines. Keratinocytes in lesional skin showed increased expression of TNF alpha and IL6 and decreased expression of stem cell factor (SCF) in which they contribute in decreased melanogenesis **[3].**

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IL6 have been shown to be released by keratinocytes in vitiligo patients which in turn decreases E cadherins promoting detachment between keratinocytes and melanocytes **[4].**

Tazarotene is the one of the topical retinoids which are vitamin A derivatives which have been used in several indications as psoriasis, acne vulgaris, photoaging and T cell lymphoma. Topical retinoids have the following effects i. renewing the epidermis, ii. Acting as UV filters, iii. Preventing formation of oxidative stress, iv. control bacterial flora., v. modulating melanocyte functions **[5].**

Tazarotene is a retinoid which metabolizes to tazaroteinic acid and binds to RAR-β and RAR-γ, which then modulates retinoid responsive genes that is involved in inflammation, cell proliferation and differentiation causing downregulation keratinocytes and hyperproliferative keratins **[6,7,8].**

Many studies have been done to evaluate the antiaging effects of tazarotene. All concluded that it improved a lot of the signs of antiaging as roughness, fine wrinkles, irregular depigmentation and lentigines but the main side effect was irritation and burning sensation which increased with higher concentrations especially 0.1% tazarotene **[9,10].**

Tazarotene has anti-inflammatory and antiproliferative effect by antagonizing nuclear factor IL6 (NF-IL6) **[11]** which have been documented to be increased in vitiligo patients **[4].**

Patients and Methods

Research was conducted in accordance with the provisions of the relevant Egyptian laws and with Helsinki Declaration and an informed written consent was taken from all participants. The study was approved by Institutional Review Board (IRB # 11309).

Thirty patients were included in this study, male and female, age ranged from 18-60. Pregnant patients were excluded. Patient suffered from vitiligo vulgaris and acral vitiligo. Patients did not receive any form of treatment (topical, systemic or phototherapy) in the last 3 months. 0.1% tazarotene gel was given to all patients to be applied daily on affected area, once daily at night for 12 weeks. Images were taken before treatment. Patients were assessed every 4 weeks, using Vitiligo Extent Score for a Target Area (VESTA), in which images of both marginal and perifollicular regimentation percentage is calculated in a target area.

Statistical analysis:

Analysis of data was done by IBM computer using SPSS (statistical program for social science version 23) as follows:

- Description of quantitative variables as Mean, SD, Median and IQR according to Shapiro test of normality.
- Description of qualitative variables as number and percentage.
- Mann Whitney test was used to compare quantitative variables between two groups in non-parametric data (SD >30% mean).
- Wilcoxon Signed Rank test used to compare pre and post variables in non-parametric data
- Spearman correlation test used test for linear relations between variables.
  - *p*-value >0.05 insignificant
  - $p<0.05$ significant **[12].**

This study was conducted from May 2024 till June 2024. The patients were collected from national research center outpatient clinic.

Results

Patients included in this study, their mean age is 36, 12 males representing 46.2% and 14 females representing 53.8%. Ten patients suffered from vitiligo of abdomen and back while 16 suffered from acral vitiligo. Four patients dropped the study due to skin irritation. The duration of their disease ranges from 1-5 years with mean 2 years duration. Their median vitiligo area scoring index (VASI) score is 5. The median of VESTA measured before treatment is 0% then after 6 weeks 20% then 40% after 12 weeks, with *p*-value <0.001, showing statistical significance between the start of the treatment and after 12 weeks duration. There was statistical significance between VESTA score and gender, showing significant improvement in females than males. Patients with acral lesions showed less improvement than others with statistical significance. The treatment was well tolerated by most patients, except from mild itching, erythema and irritation that was treated by moisturizers for 5 days.

Table (1): Sociodemographic characteristics of the participants.

	Mean ± SD	Range
Age (ys)	36±12.93	18-56
Sex:	N	%
Male	12	46.20
Female	14	53.80

	N	%
Family history:		
Negative	13	50.00
Positive	13	50.00
Other Diseases:		
Negative	19	73.10
Positive	7	26.90
Area to be treated:		
Abdomen, back	10	38.50
Acral	16	61.50
Configuration of improvement:		
No	4	15.40
Darkening + decrease size	22	84.60
Side effects:		
No	10	38.50
Itching	8	30.80
Erythema	4	15.40
Burn	3	11.50
Irritation	1	3.80

	Median (IQR)	Range
Duration (years)	2 (1-3)	1-5
VASI	5 (4-8)	2-9
VESTA of the treated lesions before	0 (0-0)	0-0
VESTA of the treated lesions after 6 weeks (%)	20 (0-50)	0-90
VESTA of the treated lesions after 12 weeks (%)	40 (10-90)	0-99

Table (2): VESTA score before and after treatment at 6 and 12 weeks.

	VESTA	
	Median (IQR)	Range
Baseline (before ttt)	0 (0-0)	0-0
After 6 weeks (%)	*20 (0-50)	0-90
After 12 weeks (%)	*#40 (10-90)	0-99
p-value	<0.001	

Friedman's test of significance.
p-value significant if ≤0.05.
* After 6 weeks is significant from baseline.
# After 12 weeks is significant from 6 weeks.

Table (3): VESTA score before & after treatment at 6 and 12 weeks.

	VESTA	
	Median (IQR)	Range
After 6 weeks (%)	20 (0-50)	0-90
After 12 weeks (%)	40 (10-90)	0-99
p-value	<0.001	

Wilcoxon test of significance. *p*-value significant if ≤0.05.

Table (4): Relation between VESTA score and gender, VASI , 6 and 12 weeks of treatment.

	VESTA of the treated lesions after 6 weeks (%)		VESTA of the treated lesions after 12 weeks (%)	
	r	*p*-value	*r*	*p*-value
Age (years)	-0.306	0.129	-0.366	0.066
Duration (years)	0.213	0.296	0.235	0.248
VASI	-.437*	0.026	-.559**	0.003
VESTA of the treated lesions after 6 weeks (%)			.909**	<0.001
VESTA of the treated lesions after 12 weeks (%)	.909**	<0.001		

Spearman's rho.

Table (5): Relation between VESTA score and gender and area treated at 12 weeks.

	VESTA of the treated lesions after 12 ws (%)		*p*-value
	Median (IQR-)	Range	
Gender:			
Male	25 (5-40)	0-99	0.031
Female	55 (40-90)	0-99	
Area to be treated:			
Abdomen, back	90 (50-95)	40-99	<0.001
Acral	20 (5-40)	0-90	

Mann Whitney U test of significance. *p*-value significant if ≤0.05.

Table (6): Relation between VESTA score and gender and area treated at 6 weeks.

	VESTA of the treated lesions after 6 ws (%)		*p*-value
	Median (IQR)	Range	
Gender:			
Male	10 (0-25)	0-50	0.031
Female	40 (10-50)	0-90	
Area to be treated:			
Abdomen, back	50 (40-50)	10-90	<0.001
Acral	10 (0-20)	0-50	

Mann Whitney U test of significance. *p*-value significant if ≤0.05.

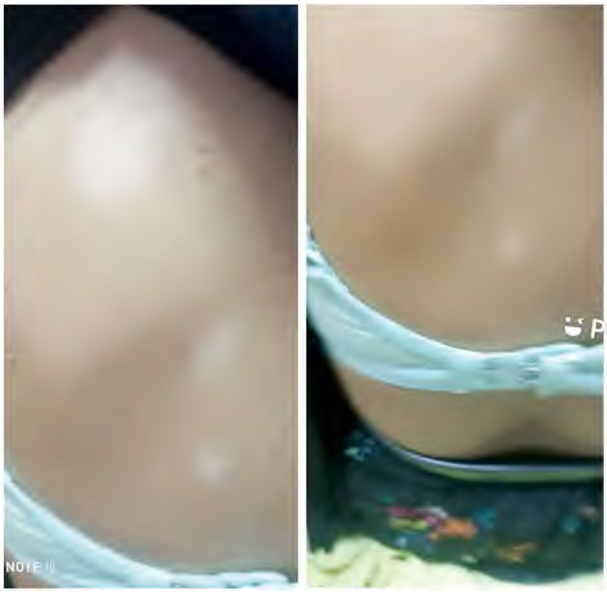

Fig. (1): Female patient, 31 Years Old, Left image shows patient prior to treatment, right image shows patient 12 weeks post treatment.

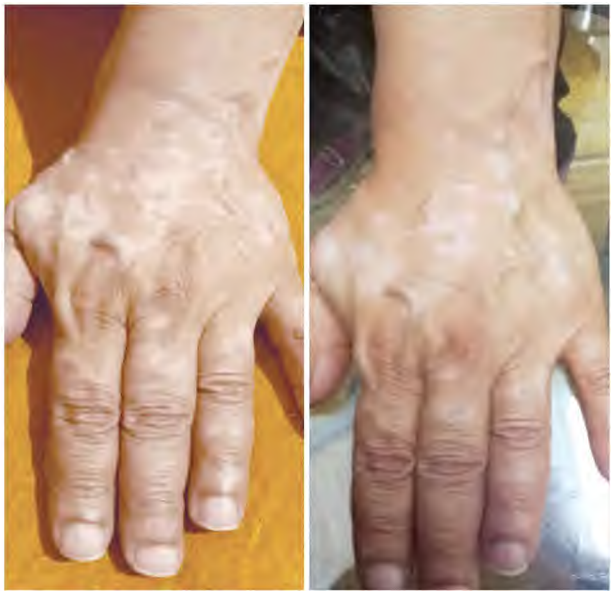

Fig. (2): Female patient, 47 Years Old, left image shows patient prior to treatment, Right image shows 12 weeks post treatment.

Before After

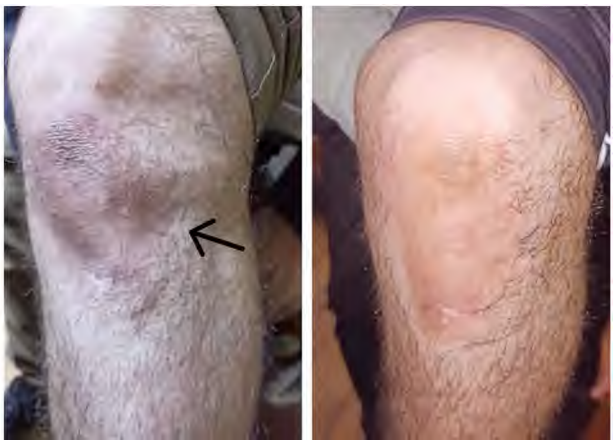

Fig. (3): Male Patient, 42 Years Old, Left Image shows patient prior to treatment, Right image shows patient 12 weeks post treatment.

Discussion

Our study showed that tazarotene can improve vitiligo patches, this was documented by VESTA score which showed re-pigmentation difference between the beginning of the treatment and after 12 weeks.

Tazarotene is a vitamin A derivative that has been used long time ago in the treatment of psoriasis, acne and skin aging. Vitamin A plays an important role on the development and regulation of immune cells and its deficiency can impair immune responses and aggravate existing inflammatory states in skin **[13].** The only topical retinoid that is indicated in psoriasis is tazarotene, it converts to tazarotenic acid which then binds to the retinoic acid receptors **[7].** This results in the regulation and expression of retinoid-responsive genes, that is involved in cell proliferation and inflammation **[14].**

Tazarotene has an anti-inflammatory property. Studies done that compare between topical tazarotene and topical fluocinonide in patients with psoriasis, showed more efficacy to steroids than tazarotene, although tazarotene showed more improvement in plaque elevation but not in erythema. However, the combination of both was superior to steroids alone. Tazarotene has a synergestic effect with steroids in treatment of psoriasis **[15,16].**

One of the main causes of vitiligo is oxidative stresses, demonstrated by increase prooxidants as superoxide dismutase, malondialdehyde and xanthine oxidase and decrease in antioxidants as catalase and superoxide dismutase in skin and blood **[1].**

Retinoids acts as antioxidants invitro, this was proved by studies done on hairless mice in which topical vitamin k3 when used in hairless mice it induced peroxidation of epidermal lipids, this effect was completely blocked by pretreatment with topical retinaldehyde 0.05%. Also, people with low serum retinol have increased risk of developing cancer **[5].**

Tazarotene gel (0.1%) was studied by Sefton et al., (2000), to improve aging on healthy women, with significant reduction in fine wrinkles and pigmentary mottling **[17].** Also, many studies was done comparing tazarotene to tretinoin in the treatment of antiaging, showing an upper hand to tazarotene over tretinoin **[9,18,19].**

Based on the following informations, we though that tazarotene can play a role in treatment of vitiligo being an antioxidant and anti-inflammatory.

Conclusion:

Tazarotene may improve in vitiligo patches with less effect in acral lesions. It may be used as an only treatment or combined with other modalities.

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دور التازاروتين فى علاج البهاق

البهاق هو مرض يمتاز بفقد الصبغة بالجلد. تلعب عده عوامل فى ظهور المرض، مثل المناعه، الإجهاد التأكسدى، والوسائط الالتهابية وانفصال الخلايا الصباغية، كلها آليات تساهم فى تطور المرض. يلعب الإجهاد التأكسدى دورًا مهمًا فى تطور البهاق. وعادة ما يكون العامل المسبب للبهاق، حيث أن الخلايا الصباغية لدى مرضى البهاق تكون أكثر عرضة للإجهاد التأكسدى. التازاروتين هو ريتينويد موضعى تم استخدامه فى عدة امراض جلديه مثل الصدفية وحب الشباب وعلاج اثار تقدم العمر بالجلد وسرطان الغدد الليمفاوية. الرتينوئيد الموضعى له التأثيرات التالية: تجديد البشرة، منع تشكيل الإجهاد التأكسديو تعديل وظائف الخلايا الصباغية. فى هذه ه الدراسه سوف يتم تقييم تأثير التازاروتين فى علاج البهاق.

ضم البحث ثلاثين مريضاً يعانون من البهاق الشائع والبهاق الطرفى. تم إعطاء ٠.١٪ جل تازاروتين لجميع المرضى ليتم وضعه يومياً على المنطقة المصابة، مرة واحدة يومياً ليلاً لمدة ١٢ أسبوع. تم إجراء التقييم باستخدام درجة مدى البهاق للمنطقة المستهدفة (VESTA). أظهرت النتائج تحسنا بعد ١٢ أسبوعا من العلاج. متوسط قياس VESTA قبل العلاج هو ٠٪ ثم بعد ٦ أسابيع ٢٠٪ ثم ٤٠٪ بعد ١٢ أسبوع، بقيمة $p<0.001$، أظهر المرضى الذين يعانون من بهاق الأطراف تحسنًا أقل من غيرهم، مما يدل علي انالتازاروتين فعال فى علاج البهاق، لكنه أقل فعالية فى البهاق الطرفى.