

Myths and Facts about Vitiligo: An Epidemiological Study

SUJA ABRAHAM* AND PADMA RAGHAVAN

Department of Pharmacy Practice, Amrita School of Pharmacy, Amrita Viswavidyapeetham University, AIMS Healthscience Campus, Kochi-682 026, India

Abraham and Raghavan: Perspectives in Vitiligo

Vitiligo is a pigmentary disorder associated with many disease conditions that necessitates multiple drug regimens, which make the treatment complicated. This stigmatic disease forces the patient to approach all system of medicines as well as alternative medicines of non proven value, which further worsens the situation. At the same time the nonadherence to the treatment reflects poor prognosis, which is misunderstood for lack of response resulting in poor faith to the medications. The aim of this work was to assess the patient compliance and the factors affecting, and to monitor the adverse effects as well as drug interactions. The study was carried out in the Institute of Applied Dermatology for a period of one year. Patient compliance was assessed using Morisky Medication Adherence Scale and found that 71% of the patients were low adherent to medications. Family support, faith in doctor, higher educational status and effectiveness of the treatment were some of the reasons for medication adherence whereas forgetfulness, feasibility, occupational problem, polypharmacy, longer duration of treatment and the feeling that the disease under is control were some of the reasons listed for nonadherence. Three adverse reactions were reported with narrow band ultraviolet B and topical tacrolimus therapy and they were categorized into possible and probable according to causality assessment by Naranjo scale. Five drug interactions were reported and the causality assessment was done using drug interaction probability scale. None of the reactions were serious or life threatening. The present study revealed the hurdles in providing safe and effective treatment to the patients and also it suggest the need of doing more research on this disease since there is a general belief that vitiligo is an incurable disease.

Key words: Vitiligo, medication adherence, adverse reactions, drug interactions

Vitiligo is a cosmetically distressing condition associated with multiple disorders and needs various drug regimens, resulting complication in the treatment. Most commonly the disease begins during childhood or young adulthood with onset of 10 to 30 years but can occur at any age^[1]. Mexico and India are pointing the highest incidence of this condition^[2]. Based on the dermatological outpatient's records, the incidence of vitiligo is found to be 0.25-2.5% in India^[3]. Although this pigmentary disorder does not produce any physical impairment, it may significantly influence the psychological well being of the patients^[4]. They are subjected to isolation, whispered comments, antagonism and insult. In India, this disease is associated with many religious beliefs and the patients are out casted from the family and the society. This makes the patient and their family to go behind rituals rather than seeking a medical help. The delay in treatment further complicates the disease condition. Patients

get depressed because of the cosmetic impact of the disease, which further triggers their disease condition.

The prognosis of the disease is very slow and depends on the patient's skin condition and the triggering factors like stress level. The patients, as they are not aware of this fact, prematurely discontinue the treatment; switch on to another doctor, again leading to noncompliance. Patient compliance is an important aspect in achieving the desired clinical outcomes. The chronic nature, the need of long term treatment, lack of uniform effective therapy and unpredicted course of the disease with tendency to consume alternative medicine of non proven value might pose a greater risk of adverse drug reaction and drug interaction^[5]. The occurrence of adverse effects and drug interaction creates additional burden to the patients, which weakens their faith in the medications. There is a need to monitor adverse drug reaction (ADR) in vitiligo patients, because the current market of medications enable them to try self medication apart from the prescription drugs with a notion that they will get cured of the

***Address for correspondence**

E-mail: suja_srmc@yahoo.co.in

Current Address: Aster Medcity, Aster DM Healthcare Pvt. Ltd, Kochi-682 027, India

disease. This work was mainly done to understand the sociodemographic profile and to monitor the adverse drug reactions, side effects, drug interactions and compliance status in vitiligo patients.

MATERIALS AND METHODS

A prospective observational study was carried out in the outpatient department of Institute of Applied Dermatology, Kasargod, Kerala. The study was approved by the Institutional ethical committee of Amrita Institute of Medical Sciences, Kochi, Kerala (Approval no. Dissertation Review/Pharma/2011/04) and Institute of Applied Dermatology, Kasargod, Kerala. The study was designed for one year and data were collected for a period of 7 months. Outpatients who visited the department (both new and old patients) during the study period and satisfied the inclusion criteria were included in the study. The patients were selected according to systematic random sampling technique. During the visit the patients were interviewed and relevant details regarding their sociodemographic, medical and medication history, side effects, drug interactions and adverse drug reactions were recorded in the standard data collection form. Boey's stress rating scale was used to assess the stress levels in the patients^[6]. The scale has eleven numbers from 0 to 10 and the patient is asked to circle the numbers to indicate their level of stress. The medication adherence behavior of the patients was assessed using Morisky Medication Adherence Scale (MMAS) -8 item questionnaire and the individual scores were assigned^[7]. If the total score is more than 2, the patient is considered as low adherent, if it is 1 or 2 then medium adherent and the patient with zero score is said to be highly adherent. The patients were also interviewed about the reasons for nonadherence to the medication. Throughout the study period patients were monitored for adverse drug reaction and drug interactions and were analyzed using Naranjo adverse drug reaction probability scale^[8] and drug interaction probability scale, respectively^[9]. Naranjo scale consists of 10 structured questions with three responses (yes/no/unknown). If the total score is >9 , then the occurrence of ADR is probable, if it is between 1-4 then ADR is possible and if the score is ≤ 0 then it is doubtful. In case of drug interaction probability scale, if the total score obtained is >8 , then the interaction is highly probable, if the total score lies between 5 and 8,

then it is probable. The drug interaction is said to be possible if the score is between 2 and 4 and is doubtful if it is <2 . The collected data were compiled using Microsoft excel and were presented in tables and graphs. The data were analyzed using statistical package for the social sciences (SPSS) version 17.0. The statistical significance of the study was assessed at 95% level of significance.

RESULTS AND DISCUSSION

Out of the 100 patients, 50% were males and 50% were females. The age of the patients under this study ranges from 23.3 to 57.1 years and the mean was found to be 40.2 ± 16.8 years. The assessment of educational status revealed that majority of the study population had only the primary level of education (39%) and a few of them were illiterate (6%). Occupation-wise distribution of the patients indicated that majority of the patients were housewives (31%). The other categories involved students (13%), industrial workers (4%), coolis (5%), business persons (9%), office workers (7%) and chefs (4%). Social habits revealed that about 15% patients were addicted to alcohol, 12% were on tobacco, 10% were on smoking and the past addicts to tobacco and smoking were 2% and 4%, respectively. Majority of the patients were consuming stimulants (60%) like tea, coffee and also had the habit of consuming large amount of oily food items (59%). In the study population, about 44% patients had the habit of consuming large amount of the milk and milk products like sour yoghurt and curd. Twenty six percent of patients reported to consume large amount of citrus fruits like lemon and orange. The study population was found to be allergic to chemicals (10%), drugs (9%) and other agents such as cosmetics (3%), metals (3%), clothing material (3%) food (4%) and dust (5%). About 18% of the total population had a family history of vitiligo. First-degree relatives were affected in 12% of the study population and second-degree relatives were affected in 6% of the patients.

Stress levels were determined using Boey's 11-point stress rating scale. The patients were asked to rate the scores for their stress levels and accordingly they were categorized into extreme, moderate and not at all stressful. About 51% of the patients reported that they undergo extreme level of stress. The majority of the patients (48%) who accounted for extreme stress

belong to the age group 15-60 years. The details were provided in Table 1.

The associated diseases in the study population were endocrine disorders (16.5%), cutaneous diseases (13.2%), hypertension (12.1%) and alopecia areata (8.8%). The cutaneous disorders mainly involved were eczema (37.9%), fungal infection (15.2%), herpes zoster (7.6%), lichen planus (7.6%), acne (7.6%) and other disorders (15.2%). Different types of vitiligo were analyzed and found that vitiligo vulgaris was found to be the most common type (63%) followed by focal vitiligo (23%). This was listed in Table 2.

Duration of the disease at the time of presentation ranges from one week to 41 years. Majority of the patients (39%) reported their duration as 1-5 years, which was followed by less than 3 months (22%). Majority of the patients had the initial site of lesions on their legs (27%), hands (21%) and face (16%).

The precipitating factor for vitiligo was assessed and found that 39% patients had autoimmune disorders, 18% patients had family history of vitiligo and 43% patients experienced Koebner phenomenon. The precipitating factors for Koebner phenomenon were surgery, injury, burns, chemical and accident. The current study showed that there is statistically significant relationship between Koebner phenomenon

and history of accidents ($P < 0.01$) while the history of surgery had no significant relationship with Koebner phenomenon ($P > 0.05$).

Out of the 100 patients, 57% of them had a history of previous treatment in various systems of medicine. About 70.2% had tried for allopathic treatments and 50.9% were tried ayurvedic treatment. Table 3 provides the current treatment modalities in vitiligo patients. Most of the patients were prescribed psoralen and ultraviolet A from solar light (PUVA Sol, 43%). Among phototherapy, narrow band ultraviolet B (NBUVB) treatment was prescribed for 22% patients, at the same time psoralen and PUVA therapy was given only for 2% of the patients. Apart from this, topical tacrolimus (53%) was also given. Integrated treatment was given for 18% patients.

While analyzing the side effect profile, itching (30%) was the main side effect reported by majority of the patients. The short-term side effects reported were erythema, nausea, dizziness, irritation, tanning and headache. The other side effects observed were acne and fatigue and each of them were recorded in less than 5% of the patients. PUVA Sol contributed for higher side effects, which was followed by NBUVB and then topical tacrolimus. Details were given in Table 4.

The pattern of adherence was assessed using Morisky Medication adherence scale. The patients were classified as high, medium and low adherent according to the scores obtained. Low scores indicated higher adherence levels and the higher score indicate lower adherence level. Table 5 depicts the adherence level of patients. The reasons for medication

TABLE 1: STRESS LEVEL EXHIBITED BY PATIENTS IN DIFFERENT AGE GROUPS

Age group (in years)	Number of patients (n=100)			Total number of patients
	Extreme	Moderate	Not at all	
<15	0	3	3	6
15-30	12	2	12	26
31-45	19	3	10	32
46-60	17	2	6	25
>60	3	3	5	11
Total	51	13	36	100

TABLE 2: CLASSIFICATION BASED ON TYPES OF VITILIGO

Type of vitiligo	No of patients in different age group (years)					Total
	<15	15-30	31-45	46-60	>60	
Acrofacial	2	4	1	2	0	9
Focal	2	7	5	7	2	23
Segmental	0	1	0	0	1	2
Universal	0	0	2	0	1	3
Vulgaris	2	14	24	16	7	63
Total	6	26	32	25	11	100

TABLE 3: TREATMENT MODALITIES FOR MANAGEMENT OF VITILIGO

Treatment modality	Percentage of patients
Phototherapy	
PUVASol	43
NBUVB	22
PUVA	2
Topical therapies	
Tacrolimus	53
Corticosteroids	4
Adjunctive therapies	
Sunscreen	2
Calcium supplements	9
Vitamin supplements	4
Integrated treatment	18

PUVASol: Psoralen and ultraviolet a from solar light, NBUVB: Narrow band ultraviolet B

TABLE 4: SIDE EFFECTS EXPERIENCED BY PATIENTS UNDERGOING DIFFERENT TREATMENT MODALITIES

Side effects	PUVASol (n=26)	PUVA (n=2)	NBUVB (n=22)	Tacrolimus (n=53)	PT (n=9)	NT (n=8)	Total (n=100)
Cutaneous side effects							
Itching	16	1	7	1	2	3	30
Erythema	1	0	8	0	0	4	13
Tanning	3	0	1	0	0	4	8
Irritation	1	0	0	5	1	2	9
Redness	2	0	0	0	0	0	2
Acnelike	1	0	0	0	0	0	1
CNS side effects							
Dizziness	5	0	0	2	0	2	9
Headache	1	0	3	2	0	2	8
Excess sleep	3	0	2	0	0	0	5
Fatigue	1	0	0	0	0	0	1
Malaise	0	0	0	1	0	0	1
GI side effects							
Nausea	5	0	2	0	1	2	10
GI irritation	4	0	1	0	1	0	6

PT: PUVASol and topical tacrolimus, NT: Narrowband UVB and topical tacrolimus

TABLE 5: LEVEL OF ADHERENCE TO VITILIGO MEDICATIONS

Adherence level	Percentage of patients
High	12
Medium	17
Low	71

High-score zero, Medium-score 1,2, Low-score >2

adherence in 29 patients who showed high (12) and medium (17) level of adherence was assessed and provided in Table 6.

The patients who reported to be poor adherent (medium and low) were interviewed for reasons for medication non-adherence. The reasons were classified into patient related and treatment related reasons. Table 7 provides the information regarding patient related reasons for medication nonadherence. Treatment related reasons for medication adherence were provided in Table 8. Lack of effectiveness of the therapy and high cost of treatment were some of the reasons. During the study period 3 patients experienced adverse drug reactions, who received NBUVB and topical tacrolimus treatment and were assessed using Naranjo probability scale. The details were provided in Table 9.

Five drug interactions were observed during the study period and these were assessed using drug interaction probability scale (DIPS). Details were depicted in Table 10. None of the reaction were reported to be life threatening. The photosensitivity reactions produced by the drug interaction in PUVASol treated patients involved erythema and itching.

Vitiligo is a cosmetically disfiguring condition, which has a major impact on the patient's family and social life^[4]. In the current scenario, the physician could hardly spend a few minutes with the patients, therefore the patients lack the information regarding their disease and treatment. This makes the patients to be noncompliant to their medications. The present study revealed that vitiligo affects both genders equally. This was in accordance with previous study conducted by Arycan *et al.*^[10]. It is important to assess the occupational status as there are conditions where the patients expose themselves to triggering factors like chemical, sunlight and others. Patients who were working as chef and in industries met with burns and this led to Koebner phenomenon. The present study reported about 26 patients had the habit of consuming large amount of citrus fruits per day. There are not many details in literature regarding the dietary habits to be followed in vitiligo patients, usually sour food items like citrus fruits, milk products, pickle and others are discouraged^[11].

Stress was found to be the major triggering factor in case of patients who showed progression of their disease condition^[12]. Al-Abadie *et al.* indicated that psychosocial stress increases level of neuro endocrine hormones, which affects the immune system and alters the level of neuropeptides^[13]. In a study conducted by Parsad, it was suggested that the increase in the level of neuropeptides may be the initiating event in the pathogenesis of vitiligo^[4].

The most common type of vitiligo was found to be vitiligo vulgaris (63%), followed by focal, acrofacial,

TABLE 6: REASONS FOR ADHERENCE TO VITILIGO MEDICATIONS

Reason for medication adherence	No. of patients (n=29)	Percentage of patients
Family support	29	100
Repigmentation	24	83
Faith in doctor	19	66
Education	14	48
Fear in future	14	48
Affecting social life	14	48
Feasibility	12	41
Feeling that children will get affected	7	24

TABLE 7: PATIENT RELATED REASONS FOR MEDICATION NON ADHERENCE

Patient related reasons for medication non adherence	No. of patients (n=88)	Percentage of patients
Forgetfulness	44	50
Feasibility	40	45
Occupation problem	28	32
Illiterate	7	8
Lack of support	5	6
Polypharmacy	2	2
Other reasons*	8	9

*do not like to take medication, religious reasons

TABLE 8: TREATMENT RELATED REASONS FOR NON ADHERENCE TO VITILIGO MEDICATIONS

Treatment related reasons for medication non adherence	No. of patients (n=88)	Percentage of patients
Not effective	26	30
Long duration	17	19
Feel that disease under control	5	6
Fear of side effects	4	5
Difficulty to follow dietary regimens	18	20
High cost	9	10
Privacy	8	9
Others	15	17

TABLE 9: CAUSALITY ASSESSMENT OF ADVERSE DRUG REACTIONS REPORTED USING NARANJO SCALE

Treatment modality	Adverse reaction	Causality assessment
NBUVB	Desquamation	Probable
NBUVB	Bullous lesion	Possible
Topical tacrolimus	Blister formation	Possible

NBUVB: Narrow band ultraviolet B

universal and segmental vitiligo. Kovacs also reported that the most common type of vitiligo was vitiligo vulgaris^[14]. When the patients were interviewed, regarding the history of previous treatment about 57% of the patients had taken past medications for vitiligo. At the same time, in a study conducted by Al-Khawajah reported out of 52 patients, 23 patients sought treatment by folk (herbal)

medicine^[15]. The major treatments given in this study were topical tacrolimus (53%), PUVASol (43%) and NBUVB (22%). In the study done by Ping *et al.* the commonly used treatments were topical corticosteroids (70%), topical tacrolimus (51%) and phototherapy (24%). The side effect profile was analyzed in this study and cutaneous side effects were found in most of the patients. Among this 30% of the patients experienced itching and this was recorded highest in PUVASol patients^[16]. This was reported in a study conducted by Al-Aboosi^[11]. This could be because of the longer exposure to sunlight by the patients intentionally or unintentionally. There are misbeliefs in the patients like re pigmentation enhances if they expose to sunlight for a longer time, but this could only lead to adverse effects. Erythema was another cutaneous side effect reported by 13% of the patients and this was observed highest in patients treated with NBUVB. In another study 7% of the patients reported erythema^[16]. This was found in patients who need to travel a long distance from the treatment center to their home. The exposure to sun soon after receiving the NBUVB treatment may be the causative factor responsible for erythema. This was followed by patients treated with PUVASol and the combination of topical tacrolimus and NBUVB. In a previous study this side effect was reported to be 22% in patients treated with PUVA.

The assessment of patient compliance showed that 71% of the patients were noncompliant to their medications. The overall mean medication adherence in the study conducted by Zaghoul *et al.* was 60.6±33%^[17]. Another study conducted by Richards *et al.* found that 40% of the patients don't use their medication as directed^[18]. The reasons for adherence and nonadherence were assessed from the high and low adherent patients. It is interesting to note that there are patients tried medications only for a short period of time and prematurely discontinued the treatment. The trend of changing from one physician to another and one system of medicine to another was reflected during the interviews with the patients. It was observed that the patient lacked the knowledge regarding the disease and the treatments. In a study conducted by Richards *et al.* it was found that the three facets, which helped in optimizing patient adherence, were patient doctor relationship; optimism with the treatment prescribed and limited side effects^[18]. The major patient related reasons for nonadherence suggested by the patients in our study include forgetfulness, feasibility

TABLE 10: CAUSALITY ASSESSMENT OF DRUG INTERACTIONS REPORTED USING DRUG INTERACTION PROBABILITY SCALE

Treatment modality	Interacting drug	Reaction	Causality assessment
NBUVB	Topical tacrolimus	Hyper pigmentation	Probable
NBUVB	Cephalosporin	Desquamation, body pain, itching	Possible
PUVASol	Sparfloxacin	Photosensitivity	Probable
PUVASol	Tetracyclin	Photosensitivity	Probable
PUVASol	Citrus fruit (orange)	Photosensitivity	Possible

NBUVB: Narrow band ultraviolet B, PUVASol: Psoralen and ultraviolet a from solar light

and occupational problems. Brown *et al.* suggested forgetfulness as the main reason for nonadherence^[19]. At the same time Zaghoul *et al.* reported the major reasons for missing treatment were the consumption of alcohol, being fed up with the disease and treatment, forgetfulness and being too busy^[20]. Zaghoul *et al.* also suggested that the time needed for application of topical agents and the potential of oral therapies to produce adverse effects result in many patients belief that medical treatment is of limited value.

During the study period the adverse reactions were monitored and the causality assessment was done by using Naranjo Probability scale. About three patient reported ADR and none of them were life threatening. The main adverse reactions were bullous lesion, desquamation and blister formation caused by NBUVB and topical tacrolimus. Studies have reported the bullous pemphigoid induced by PUVA therapy and NBUVB in psoriasis^[21,22]. Drug interactions were also checked and found five interactions, mainly with PUVASol. One drug-food interaction was also observed with PUVA therapy. The photosensitivity reaction observed was due to orange and the previous study conducted by Egen reported that the commonly occurring photosensitizing plants include citrus fruits^[23].

The study has found various factors that hamper the provision of safe and effective treatment in the management of vitiligo. Patients lack adequate information about the disease and treatment, which forces them to discontinue the treatment. The occurrence of adverse effects and drug interaction creates additional burden to the patients, which weakens their faith in accessing the medication. There is a general belief that vitiligo is an incurable disease. This study suggests that the healthcare system should not neglect this disease and further studies have to be conducted in this field.

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