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Original article

Effectiveness of vitiligo therapy in prospective observational study of 250 cases with review of consensus and individualized care perspective

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Abstract

Patients and methods Outcomes of six month therapy in 250 patients bearing varying disease profiles and treatment regimens delivered either in conformity or divergence from consensus guidelines were compared. Influence of trait variables of patients and disease on the outcomes was also examined.

Results Consensus approach yielded superior rates of repigmentation and improved quality of life. The latter effect significantly influenced the former. Therapy adhering guidelines did not yield optimal benefit in patients of younger age, with disease of shorter standing and involving resistant sites. Steroids best benefited the localized disease as topical monotherapy. Combination of steroid with photochemotherapy adhering guidelines benefited less in moderate disease extent. Steroid overtreatment in extensive disease compromised the prospects of repigmentation.

Conclusions Localized short duration disease may better be first treated with steroid-alternative immunosuppressants. Wider spread more than 3% body surface may also respond to their combination with steroids, prior applying photochemotherapy. Additive therapies are prudent with steroid/photochemotherapy than injudicious steroid overuse in progressive extensive disease. Strategies to counter steroid unresponsiveness and adverse effects, psychiatric address to stress, nutrient and environmental interventions deserve emphasis.

Key words
Vitiligo, pharmacotherapy, therapeutic guidelines, observational study.

Introduction

Contemporary drug therapies in vitiligo aim at correcting deficit of melanocyte numbers and pigment production.[1-3] Origin and continuance of vulnerability of pigment cell system remains ill-understood.[4,5] Pathogenesis of vitiligo may be a systemic disorder,[6] or specific autoimmune or metabolic-toxic damage of melanocyte.[7] A reconciliatory view,[8] considers a non immune genetic defect of melanocyte and/or other epidermal cell structure and metabolism that increases susceptibility of melanocytes to ordinary internal and external perturbations.[9,10] Some stressors cause abnormalities of membrane lipids and disturb homing of protein elements serving as enzymes and receptors. Altered expression and release of proteins may provoke autoimmunity. Melanocytes disorder depends on magnitude and duration of stress and autoimmunity. Poor understanding of pathology has led to therapy with poor predictability of

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success. Glucocorticosteroids constitute preferred therapeutic option, while more intensive photochemotherapy is generally combined. Alternative immunosuppressive like calcineurin inhibitors and vitamin D3 analogues, are not frequently used. The metabolic-toxic theory guides use of remedies to combat oxidative stress and low antioxidant profiles in vitiligo. L-phenylalanine supplement is proposed due to disorder of this essential amino acid metabolism in vitiligo.[2,11] Psychological distress is recognized to be duly addressed for success of vitiligo treatment.

The therapy decision in vitiligo is largely clinical in absence of valid markers for disease activity. Grading of disease has been attempted by histopathologic studies.[12] Vast differences in prevalence rates of vitiligo are observed in Indian population with 0.5% in east[13] to 4% in the west.[14] This limits valid consensus approach to treatment. Studies on effectiveness of therapeutic decisions which are different due to constraints of local or regional resources and patients traits are necessary to generate essential evidence for making guideline proposals. Regional contributions are more likely to foster affiliation, wider acceptance and utilization for better medical care.[15] Present study in 250 vitiligo patients from mid-north India examines repigmentation achieved following therapeutic decisions conforming to or different from consensus of guidelines, also in context of treatment independent variables. Guideline perspective in the regional context is contemplated and promise and claims of missed therapeutic options are deliberated upon.

Patients and methods

At the dermatology outpatients of S.S. Hospital Banaras Hindu University; patients reporting fresh or already on treatment for vitiligo, without significant other complaints or treatment, of all ages and either sex were explained purpose of the study. With free consent and assurance of concealing identity they were included in this observational study. Detailed history was elicited. Clinical examination findings, and treatment prescribed were recorded after due scrutiny of percent affliction of body surface area, lesion distribution, onset and duration of disease and patient age. The prescribed treatment was assessed for conformity or difference with consensus guidelines and groups for comparison were made for each common set of prescriptions. Popular national and international literature was referred in the context.[16-20] Body surface area (BSA) percentage was determined as reported elsewhere.[21,22] Dermatology life quality index (DLQI)[23] were determined in personal interview with help of standard questionnaire.

Therapeutic prescriptions came under following three sets as shown in **Table 1**.

The repigmentation outcomes were assessed following six month uninterrupted treatment by various adopted regimens. Data of 250 such patients completing the process were taken to analysis. Instances of default were 31 cases excluded from study.

Patients attaining repigmentation is 25% of the lesion area (i.e. reduction of initial estimated body surface area involved in vitiligo by 25%) or more were considered good responders and others poor responders. Their proportions with each treatment regimens were compared in groups receiving therapy in conformity with or digression from consensus approach. Statistical significance of differences was analyzed with Fisher's exact test. For easy perception, proportions are presented as percentage values.

Table 1 Three groups of patients according to regimen used.

Regimen	*N*	*Drug used (alone or in combination)*	*Consensus or Guidelines*
Regimen 1	60	Topical fluticasone propionate 0.05%.	Adequate for under 3% BSA affliction
Regimen 2	99	Topical fluticasone propionate 0.05% clobetasol propionate 0.05% in combination with oral methoxsalen (0.6 mg./kg. E.O.D.) with sunlight exposure.	For lesions exceeding 3% and up to <10% BSA but not aggressively progressive
Regimen 3	91	Oral methoxsalen (0.6 mg./kg. E.O.D.) with sun light exposure + topical clobetasol propionate 0.05% with or without topical mometasone furoate 0.01% + oral prednisolone (0.5 mg./kg. as pulse therapy) + antacids and antioxidant 1 Capsule Per Day (containing lycopene 3 mg.).	Progressive lesions afflicting more than 3% BSA or any lesion exceeding 10% BSA

Improvement in quality of life was assessed as gains above or below the overall median improvement in DLQI score. Influence of other treatment-independent variables like segmental/non-segmental distributions, location of predominant involvement, lesion numbers, disease duration, age and sex on the outcome was also examined. Differences were analyzed for significance by Moods median statistic, on good and poor outcome rates in patients treated in conformity versus in digression of consensus guidance.

Results

Of the total 250 vitiligo cases, majority (72%) did not admit family history of vitiligo. Peak prevalence (30.8%) was seen in 11-20 year age and majority of (70.4%) cases were between 11-40 year age range. Only 8.4% cases reported for treatment in less than 1 year of noticing depigmentation, a third of cases within 3 year, while half of cases sought help after 5 or more years.

Involvement was bilateral in 73.2% cases and 67.2% cases bore more than 5 separate lesions. Only 5 cases (2%) matched dermatomal distribution of segmental disease. One third cases involved conventionally resistant sites. Going by the extent of involvement of body surface area, therapeutic decisions in one third of patients did not apparently conform to conventional guidelines (**Table 2**) specifically 6.8%, 13.6% and 12.8% patients included under regimen 1, 2 and 3 respectively.

Disease extent at time of presentation in regard to certain independent characteristics in the patients is summarized in **Table 3**. Patients above median age 27 years frequently bore extensive disease. Duration of the disease longer than median 5 year period however did not lend to significant differences in disease extent. Presenting extents of the disease did not differ in two sexes. Extensive disease was found significantly more frequently in conventionally therapy responsive locations, with bilateral spread and with multiple (more than 5) lesions (**Table 3**).

Therapy administered as per guideline yielded consistently greater rates of good (25% or more) repigmentation as well as improvement in DLQI. However higher repigmentation outcomes occurred with regimen 1 and 3 and DLQI improvements with regimen 1 and 2 at statistically significant magnitudes (**Table 4**).

Instances of good repigmentation were presented discriminately for patients with body surface area involvement lesser or greater than the

Table 2 Demographic and clinical data of study population.

Characteristics	*N (%)*
Sex	
Male	112 (44.8)
Female	138 (55.2)
Family history of vitiligo	
Yes	70 (28)
No	180 (72)
Age (years)	
1-10	11 (4.4)
11-20	77 (30.8)
21-30	49 (19.6)
31-40	50 (20)
41-50	32 (12.8)
51-60	17 (6.8)
>60	14 (5.6)
Duration of disease (years)	
<1	21 (8.4)
1-3	63 (25.2)
>3-5	45 (18)
>5-10	51 (20.4)
Lesion profile	
Unilateral	67 (26.2)
Bilateral	183 (73.2)
<5	82 (32.8)
≥5	168 (67.2)
<3% body area involved	109 (43.6)
>3% body area involved	141 (56.4)
Involving resistant location	85 (34)
Not involving resistant location	165 (66)
DLQI	
<5	83 (33.2)
5-10	98 (39.2)
>10	69 (27.6)
Treatment	
As per guidelines	167 (66.8)
Not as per guidelines	83 (33.2)

DLQI: Dermatology life quality index

median value. Instances of good repigmentation were also discriminately assessed in patients with lesser or greater deteriorations than median value of DLQI. Treatment as per guidelines consistently gave superior chances of repigmentation. Benefits were more evident in cases with lesser body surface involvement and in cases with greater deterioration in DLQI (**Table 5**).

Influence if any, of independent variables on repigmentation response following therapy were examined. Therapy as per guidelines always resulted in superior rates of good repigmentation irrespective of differences of sex, age, disease duration, location, spread and multiplicity of lesions. Patients under median age 27 years, those with disease duration under the median 5 year, bearing lesions on resistant locations had less significant benefits compare to those respectively with age above median 27 years, disease duration above 5 years and affliction of therapeutically non resistant areas of body (**Table 6**).

The association of repigmentation response to degree of improvements in DLQI following therapy was also summarily examined in **Table 7**. In cases treated by regimen 1 adhering therapeutic guidelines, greater improvement in quality of life and repigmentation rates appeared to be parallel. However, consequences of digression of therapeutic guidelines on the two kinds of outcomes (repigmentation and improvement in DLQI) did not go parallel. In patients treated by regimen 2 adhering guidelines had particularly increased repigmentation rates in presence of greater improvements in DLQI. However, greater improvement in quality of life was associated with significantly greater rates of repigmentation even in cases treated digressing the guidelines. As such treatment adhering guidelines increased rates of good repigmentation irrespective of degree of improvement in DLQI in the cases.

Patients receiving regimen 3 therapy adhering guidelines had significantly enhanced repigmentation rate amid less than median improvement in DLQI but not in those with greater improvements in DLQI. Greater improvement in DLQI accompanied higher rates

Table 3 Association of some variables with baseline disease extent.

Variables	*n*	*% of cases above median 3.25% body surface area*	*P value*
Age (in years)			<0.0290
Up to 27 years	126	41.27	
>27 years	124	54.03	
Sex			
Male	113	46.02	Nonsignificant
Female	137	48.91	
Disease Duration (in years)			
Up to 5 year	129	45.74	Nonsignificant
>5 year	121	49.59	
Location			
Non resistant	165	52.73	<0.0164
Resistant	85	37.65	
Spread			
Unilateral	67	5.97	<0.0001
Bilateral	183	62.84	
Lesion numerosity			
Up to 5	82	10.98	<0.0001
>5	168	65.48	

Table 4 Percentage of cases achieving above median repigmentation (MEDIAN 26%) and improvement in DLQI (MEDIAN 50%) in various groups following treatment.

	Repigmentation			*DLQI*		
Treatment groups	*Treated as per guideline*	*Not treated as per guideline*	*P value*	*Treated as per guideline*	*Not treated as per guideline*	*P value*
Regimen 1	46.5	17.6	<0.03	51.1	17.6	<0.01
BSA Mean (SD)	0.73(0.64)	4.84(2.14)				
Regimen 2	53.8	38.2	NS	52.3	32.3	<0.04
BSA Mean (SD)	6.48(4.73)	0.95(0.84)				
Regimen 3	57.6	34.3	<0.02	52.5	34.3	NS
BSA Mean (SD)	11.27(8.52)	1.30(0.96)				

DLQI: Dermatology life quality index, NS: Non significant, BSA: Body surface area.

Table 5 Percentage of cases from milder and more severe disease strata and baseline DLQI score showing repigmentation of 25% or more lesion area

Disease Strata by baseline parameter	*n*	*Percentage of cases with above median improvement (Repigmentation 25% or more)*		*P value*
		Treated as per Guidelines	*Not treated as per Guidelines*	
BSA involvement				
Up to 3.25%	132	75.86	39.73	<0.0001
>3.25%	118	65.25 (<0.0001)	30 (NS)	<0.0124
Baseline DLQI				
Up to 9	148	61.04	40.85	<0.0108
>9	102	83.15 (<0.0019)	25 (NS)	<0.0001

BSA: Body surface area, DLQI: Dermatology life quality index, NS: Non significant.

Table 6 Percentage of cases achieving repigmentation 25% or more of lesion area under stratifications of independent variables.

Disease variables by presence or by medians		*Treated as per guideline*	*Not treated as per guideline*	*P value*
Age (in years)	Up to 27 years	70.5	46.3	<0.0076
	>27 years	74.3	30.9	<0.0001
Sex	Male	67.6	34.1	<0.0006
	Female	76	42.8	<0.0002
Disease duration (in years)	Up to 5 year	72.7	53.1	<0.0340
	>5 year	72	29.4	<0.0001
Location	Non resistant	80.1	51.2	<0.0064
	Resistant	48.7	27.2	<0.0340
Spread	Unilateral	66.67	27.5	<0.0016
	Bilateral	73.50	48.8	<0.0026
Lesion numerosity	Up to 5	62.8	34.0	<0.0088
	>5	75	44.4	<0.0007

Table 6 Percentage of achievers of 25% or more repigmentation concurrent with DLQI improvement above or below median 50% when treated by different regimen as per or against guideline.

			Percentage of cases achieving 25% or more Repigmentation		
Treatment regimen	*DLQI Improvement*	*n*	*Treated as per guideline*	*Not treated as per guideline*	*P value*
Regimen 1	Up to 50%	35	42.86	21.43	NS
	>50%	25	90.91 (<0.0009)	66.67 (NS)	NS
Regimen 2	Up to 50%	54	51.61	26.09	NS
	>50%	45	94.12 (<0.0001)	72.73 (<0.0134)	NS
Regimen 3	Up to 50%	49	67.86	14.29	<0.0002
	>50%	42	80.65 (NS)	90.91 (<0.0001)	NS

DLQI: Dermatology life quality index, NS: Non significant

of repigmentation irrespective of adherence to therapeutic guidelines (**Table 7**).

Discussion

Comparative effectiveness research assumes that complexity and severity of disease condition increases applicability of study findings. Quantification of disease extent and repigmentation with changes in quality of life served as means to examine individualized effectiveness of treatment approaches. Longer study suits judgment of effectiveness. Short three month observation period may suffice to suggest failure of a treatment and need for change. Current focus is on repigmentation outcome. Separate report will incorporate side/adverse effects issues and pharmacoeconomic perspective. Morphologic patterns and age related predisposition to disease were accounted for by including all ages. Mixed vitiligo[24] is recognized and as such therapies employed remain nondiscriminant for all phenotypes.[25]

Study in these north Indian patients revealed high prevalence of family history of vitiligo, earlier age at onset, diffuse spread of disease at diagnosis and frequent delay of more than five years in seeking treatment. This is in contrast to disease pattern studied in southern part of India[26], in which one fourth of cases had segmental pattern, in contrast to negligible 2% in present study. Quality of life deteriorated with increased disease extent suggesting mostly aggressive disease in our north Indian sample. This is calling for attentive therapeutic address. Consensus approach to treatment decision is largely guided by disease extent. That was digressed by under and overtreatment in near third of patients. Adequate samples for comparison of treatment outcomes, thus became available.

Apparently, vitiligo spread faster during early years of onset and latter slows down. The disease extent therefore did not correlate to disease duration. Majority of cases above median age 27 were still under 40 year age. Hence a more aggressive disease in late third and fourth decade of life is suggested. Significantly more extensive disease was observed in cases aged above median. Sex did not affect the disease extent. Increased disease activity in third and fourth decade may not have hormonal basis. Multiple foci and bilateral spread characterize predominant nonsegmental form in the study sample.

Melanocyte apoptosis is key histologic feature of vitiligo that is subject to varying degrees of inhibition by currently used ultraviolet radiation and drugs, specially corticosteroids.[27,28] Nonsegmental vitiligo exhibits familial tendency, association with other autoimmune disorders with evident autoimmune pathology in perilesional skin.[29] Generalized deficit of antioxidant glutathione reserve, increasing pigment cell vulnerability to oxidative stress is demonstrated in vitiligo.[30] Therapy attempts to halt disease progression and induce repigmentation. It is guided essentially by therapeutic response and certain systemic etiologies, duration of disease, location of lesions and yet ill-defined factors may affect repigmentation response to therapy.[19]

Principal digressions of consensus approach involve topical glucocorticosteroid monotherapy despite lesions exceeding 3% body surface. On the other hand, in more extensive disease glucocorticosteroids may be used in excess. Results of the study reveal higher rate of 25% or more repigmentation when such digressions were avoided. Very significant benefit of steroid monotherapy in restricted disease, indicates possibilities that nonsteroidal monotherapies like vitamin D3 analogues or calcineurin inhibitors ought be preferentially tried as monotherapies. The latter posses interesting immunomodulatory and melanocyte stimulating potentials with lesser local biochemical effects compared to steroids.[31-33]

In more extensive disease, steroid combination with photochemotherapy adhering guidelines gave less prominent benefits in cases treated with regimen 2. Steroid overtreatment digressing guidelines significantly reduced repigmentation rates in patients receiving regimen 3. Such observations indicate limitations of efficacy and possibility of steroid unresponsiveness, respectively. Above stated alternative immunomodulators with melanocyte stimulating effects therefore deserve due exploration as combination regimens with photochemotherapy. Steroid unresponsiveness is partly attributed to dermal biochemical effects. The latter can hamper physiologic integration of melanocytes with epidermal cells.[34] Steroid overtreatment can hinder DNA methylation reactions necessary for

gene expression[35] and may elevate proinflammatory homocysteine profile.[36] Both have potentially detrimental effects, given the vulnerable melanocytes in the sufferers. Mitigation of such adverse steroid effects reportedly attempted by conjoint lipid application may improve topical steroid therapy in vitiligo.[37] Instead of steroid overtreatment, resort to adjunct remedial measures holds greater appeal. Phenylalanine metabolism is disturbed in vitiligo and its supplementation was reported to boost repigmentation in cases with onset of disease before 21 year age with nonsegmental spread up to 25% of body surface.[38,39] Antioxidant supplements raising dermal catalase activity and reducing production of reactive oxygen species were found to boost repigmentation outcome of photochemotherapy.[40] Photochemotherapy upregulates variety of melanogenic factors. The latter include even inflammatory mediators and free radicals, which if exceed critical levels, will be counterproductive in vitiligo.[41] Direct topical pseudocatalase application has also proven successful.[42] Raised homocysteine profiles are considered to worsen the disease.[43,44] Correction of vitamin B 12-folate deficit with due supplementation is shown to improve repigmentation, supporting perhaps the pathogenic role of homocysteine in vitiligo. Phenolic prooxidant chemicals abounding in pesticides, paints, rubber articles and many items of vegetarian diets pose increased risk in Indian context. Interventions to curb exposure to such toxicants may be beneficial to mitigate free radical stress in vitiligo patients.[45] Adequate understanding and emphasis on using such additive measures as discussed above is desired in consensus guidelines. Since patients with early disease of short duration, younger age group and affliction on resistant body locations respond less to conventional therapeutic approach, the referred considerations may particularly be relevant for such categories.

Drug therapy of vitiligo adhering consensus approach had added merit of yielding greater improvement in quality of life. The high rates of repigmentation did not reflect similar bearing on improvement in quality of life, especially in more extensive disease treated by regimen 3. In contrast, as shown in **Table 7**, higher improvement in quality of life consistently associated with higher rates of repigmentation. The observation both suggests need for due psychiatric care, as well as, a causal role of stress in the disease in studied cases. This is in agreement with findings of larger studies.[46,47] Psychiatric address therefore needs appropriate emphasis as integral to vitiligo therapy for patients in the region.

Molecular mechanisms governing the multiple pathways involved in vitiliginous depigmentation may hint through wider observations in diverse clinical settings, guiding appropriate use of numerous existing and innovative therapeutic options. Simultaneous physiological focus on factors governing melanocyte growth, maturation and survival bears all relevance to improvise the concept of treatment guidelines, globally at large.

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