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A Randomised Apremilast Versus Betamethasone Oral Mini-Pulse In The Treatment Of Progressive Non-Segmental Vitiligo.

P Arunprasath[1]*, and S Raja[2].

[1]Assistant Professor, Department Of Dermatology & Venerology, Nandha Medical College and Hospital Perundurai Road, Erode, Tamil Nadu, India.
[2]Associate Professor, Department Of Dermatology & Venerology, Nandha Medical College and Hospital Perundurai Road, Erode, Tamil Nadu, India.

ABSTRACT

Corticosteroid oral mini-pulse (OMP) has been the mainstay of treatment for progressive vitiligo but is limited by adverse effects. Recently, apremilast was reported to arrest vitiligo activity in all 13 patients in a case series. We conducted this study to compare the safety and efficacy of apremilast versus betamethasone OMP in the treatment of progressive non-segmental vitiligo. Adult patients with progressive non-segmental vitiligo (Vitiligo Disease Activity [VIDA] score +4) involving ≥2% body surface area was included after informed consent. A washout period of 2 weeks was given for topical treatment and 4 weeks for phototherapy or systemic therapy. Of the 54 patients who received the allocated treatment, 31 (57.4%) completed the study. The number of patients withdrawing from the study due to side effects (n= 3) or continued disease activity (n = 4) was statistically significantly more in the apremilast arm (6/26 vs 1/28, p = 0.047). At 6 months, 36.4% (n = 4/11) of patients in the apremilast arm had an arrest of vitiligo activity, compared to 60% (n = 12/20) in the OMP arm (p = 0.208). Patients in the OMP arm were 1.95 (95% CI 1.01–3.79, p = 0.047) times more likely to achieve vitiligo arrest during the study period. The mean time to vitiligo arrest was 1.07 ± 0.67 and 2.6 ±1.78 months in the apremilast and OMP arms, respectively (p = 0.080).

Keywords: Non- Segmental Vitiligo, Apremilast, Betamethasone Oral Mini-Pulse.

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Corresponding author

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INTRODUCTION

Worldwide prevalence of vitiligo ranges from 0·06% to 2·28% in adults and up to 2·16% in children and adolescents [1], with nonsegmental and segmental forms identified. While segmental vitiligo (SV) involves areas of depigmented skin on one side of the body, nonsegmental vitiligo (NSV) involves depigmentation on both sides of the body as symmetrical patches [2]. NSV is more common (~90% of cases) and appears later in life than SV [3]. NSV often has a progressive onset, multiple flare-ups, and an unpredictable course, which can be associated with negative emotions in affected individuals due to social stigma and psychological comorbidities [4]. The 2021 British Association of Dermatologists guidelines for the management of people with vitiligo include quality of life (QoL) as a critical factor when choosing treatment and recommend regular monitoring of QoL [5]. In a meta-analysis of 1799 patients with vitiligo, the impact on health-related QoL (HRQoL) was confirmed [6]. Additionally, results from a large, global, online survey of adult patients with vitiligo indicated worse HRQoL for patients with lesions in visible locations than for those with less visible lesions [7]. Nevertheless, population-based studies assessing the impact of HRQoL in adults and children with NSV are lacking.

MATERIALS AND METHODS

The study was conducted in the Department of Dermatology and Venereology. Nandha Medical College and Hospital Perundurai Road, Erode, Tamil Nadu, India In the year 2024. Adult patients with progressive non-segmental vitiligo (Vitiligo Disease Activity [VIDA] score +4) involving ≥2% body surface area were included after informed consent. A washout period of 2 weeks was given for topical treatment and 4 weeks for phototherapy or systemic therapy. Patients were block (variable size) randomized to receive either apremilast 30 mg twice daily or betamethasone 2.5 mg twice a week (OMP) for 6 months. No topical treatment was allowed during the study. Patients could withdraw from the study at 3 months if vitiligo progression was not arrested. Subjects were assessed bi-weekly for the first month and monthly thereafter. The treatment outcomes included the proportion of patients experiencing a halt in vitiligo progression, change in the number of new vitiligo patches, VIDA score, Vitiligo Area Severity Index (VASI), and percentage repigmentation (assessed by two blinded evaluators), Vitiligo Impact Score (VIS)-22, levels of lesional tissue cytokines (Th1 [IL-2, IFNγ], Th2 [IL-4, IL-13], Th17 [IL-17, IL-22], T-reg [FoxP3]) mRNA expression (with 10 patients in each group), and treatment safety.

RESULTS

Table 1: Baseline demographic and clinical parameters

Parameter	Apremilast (n = 26)	Betamethasone oral mini-pulse (n = 28)	p value	Patients who completed the protocol (n = 31)	Patients lost to follow-up (n = 23)	p value
Mean age (years)	31.88 ± 2.26	31.43 ± 2.05	0.88	31.22 ± 11.65	32.22 ± 10.42	0.75
Sex			0.58			0.90
Male	13 (50%)	11 (39.29%)		14 (45.16%)	10 (43.48%)	
Female	13 (50%)	17 (60.71%)		17 (54.84%)	13 (56.52%)	
Duration of disease (years)	12.05 ± 9.28	11.15 ± 8.28	0.81	12.15 ± 9.98	10.82 ± 6.91	0.92
Type of vitiligo			0.99			0.22
Acrofacial	12 (46.15%)	12 (42.86%)		16 (51.61%)	8 (34.78%)	
Generalised	14 (53.85%)	16 (57.14%)		15 (48.39%)	15 (65.22%)	
Mean VASI	13.36 ± 15.25	15.57 ± 17.08	0.42	15.28 ± 17.26	14.98 ± 19.78	0.95
Mean number of new lesions in the past month	12.31 ± 7.45	11.79 ± 9.85	0.46	12 ± 9.39	12.09 ± 7.88	0.82
Rapid progressors*	23 (88.46%)	25 (89.29%)		27 (87.10%)	21 (91.30%)	
History of koebnerisation	12 (46.15%)	10 (35.71%)	0.44	15 (48.39%)	7 (30.43%)	0.18
Leucotrichia	17 (65.38%)	20 (71.43%)	0.63	23 (74.19%)	14 (60.87%)	0.30
Family history of vitiligo	1 (3.85%)	8 (40%)	**0.03**	5 (16.13%)	4 (17.39%)	0.90
Mean VIS-22 scores	23.73 ± 12.78	26.14 ± 13.47	0.53	24.54 ± 12.27	27.40 ± 12.70	0.38

*Rapid progressors were defined as those developing ≥5 new lesions in the past 1 month or > 15 new lesions in the past 3 months.

Table 2: Adverse events in apremilast and betamethasone oral mini-pulse treatment arms.

Side effects	Apremilast (n = 26)	Betamethasone oral mini-pulse (n = 28)	P value
Overall	23 (88.46%)	21 (75%)	0.298
Gastrointestinal side effects	16 (61.54%)	10 (35.71%)	0.058
Nausea	12 (46.15%)	3 (10.71%)	**0.005**
Vomiting	3 (11.54%)	1 (3.57%)	0.382
Diarrhea	8 (30.77%)	2 (7.14%)	**0.037**
Gastroesophageal reflux	5 (19.23%)	8 (28.57%)	0.422
Headache	11 (42.31%)	3 (10.71%)	**0.012**
Appetite change Increase Decrease	9 (34.62%) Increase: 0 Decrease: 9 (34.62%)	8 (28.57%) 6 (21.43%) 2 (7.14%)	**0.023**
Weight change (mean, in kg)	−1 ± 3.86	+2.33 ± 2.77	**0.028**
Blood pressure >140 systolic and/or >90 diastolic	5 (19.2%)	7 (25%)	0.610
Fasting blood sugar			**0.041**
>99 mg/dl (pre-diabetic)	2 (7.69%)	8 (28.57%)	
>125 mg/dl (diabetic)	0	1 (3.57%)	
Total leucocyte count> 11,000/µl	4 (15.38%)	9 (32.14%)	**0.020**
Others	13 (50%)	10 (35.7%)	0.289
	Sleep disturbance: 1 (3.85%)	Sleep disturbance:5 (17.86%)	
	Malaise/myalgia: 7 (26.92%)	Malaise:1 (3.57%)	
	Acute febrile illness: 1 (3.85%)	Acute febrile illness: 2 (7.14%)	
	Upper respiratory tract infection: 2 (7.69%)	Scabies: 1 (3.57%)	
	Palpitation: 1 (3.85%)	Low mood: 1 (3.57%)	
	Altered taste: 1 (3.85%)	Facial puffiness: 2 (7.14%)	

DISCUSSION

The mean number of new vitiligo macules decreased statistically significantly at 6 months in both apremilast (12.31 ± 7.45 to 2.18 ± 4.56, p = 0.004) and OMP arms (11.79± 9.85 to 1 ± 2.66, p < 0.001) There were 1.25 (95% CI – 3.32–0.83, p = 0.239) lesser new lesions in the OMP arm compared to the apremilast arm during the study period. The proportion of patients with a change in VIDA score at 6 months was also comparable between the two treatment arms (p = 0.337). There was no statistically significant change in VASI at 6 months from baseline in both the groups (apremilast: 13.36± 15.25 vs 13.88 ± 16.37, p = 0.646; OMP: 15.57 ± 17.08 vs 16.38 ± 18.34, p = 0.381). Forty-five percent of patients (n = 5/11) in the apremilast arm and 65% (n = 13/20) patients in the OMP arm achieved >25% repigmentation (p = 0.685) but none achieved >80% repigmentation. The mean VIS-22 scores did not change statistically significantly in either arm at 6 months (18 ± 12.86 vs 17.73 ± 10.45 in the apremilast arm, p = 0.894; 26.7 ± 13.74 vs 24.4.± 11.23 in the OMP arm, p = 0.360). The mean mRNA expression of Th17 cytokines (IL-17, p = 0.08; IL-22, p = 0.07) in the apremilast arm showed a trend toward statistically significant reduction, while that of IFNγ showed an upward trend (p = 0.06). In the OMP arm, mean IL-17 (p = 0.05) and Foxp3 (p = 0.05) mRNA expression decreased statistically significantly. Minor adverse events were common in both treatment arms [Table 2]. No patient developed a serious infection in either treatment group. Side effects necessitating discontinuation of therapy were seen in 11.5% (n = 3/26) patients in the apremilast arm (weakness, syncope, nausea, and headache) and none in the OMP arm (p = 0.105). We found the vitiligo arrest rate to be 60% with OMP at 6 months, consistent with previous reports (44–92%) [1-4], while it was 36% in the apremilast arm. This is in

contrast to the 100% (n = 13/13) arrest rate in the case series by Majid *et al*. [5] and a randomized trial that reported higher vitiligo arrest rates with add-on apremilast to conventional therapy in 31 patients (94% vs 67%, p = 0.08) [6]. Despite much lower absolute arrest rates than OMP, apremilast treatment was associated with a quick and sharp decline in the number of new vitiligo macules, but patients had a more fluctuating disease course. [Figure 2b]. Treatment with both apremilast and OMP did not produce significant repigmentation which probably explains the lack of improvement in vitiligo-related quality of life. While OMP leads to <75% repigmentation in the majority of patients [4], repigmentation results with apremilast have been mixed so far [7, 8]. Low tolerability and high discontinuation rates with apremilast, similar to our results, are reported previously as well [5, 6, 9]. The downward trend in Th17 cytokine signatures in both arms corroborates with the role of IL-17 in vitiligo pathogenesis. Our results show that apremilast is less effective than OMP in halting vitiligo progression, but it can slow down the disease activity. Given that apremilast is a relatively safe, non-immunosuppressive drug, it may still hold some value in managing vitiligo, which warrants further evaluation [10, 11].

CONCLUSION

The course of vitiligo is unpredictable. If the disease is spreading rapidly, the progression can be controlled with the use of systemic steroids daily or in pulsed follow-dose oral mini-pulse Betamethasone therapy is a good option for arresting progressive unstable vitiligo with minimal adverse effects.

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