EFFICACY AND TOLERABILITY OF BIOINOVATIVE ADAPALENE (MICRONISED) 0.1% PLUS BENZOYL PEROXIDE (MICROENCAPSULATED) 2.5% IN ACNE MANAGEMENT

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ABSTRACT

BACKGROUND

Acne vulgaris is a universal skin disease affecting both genders. Acne affects more than 85% of the teenagers as well as some adults and persists in large number of people in their 20s and 30s age. A single-center clinic-based study from a teaching hospital in India reported prevalence of acne among boys and girls between 12-17 years of age as 50.6% and 38.13%, respectively. Combination therapy is an effective approach in the management of acne as it can simultaneously act on several pathogenic mechanisms. The current (2016) European Dermatology Forum (EDF) guidelines recommend combination therapy for all grades of acne as initial treatment.

The aim of the study is to evaluate efficacy, safety and patient satisfaction of a bioinnovative fixed-dose combination of adapalene (micronised) 0.1% plus benzoyl peroxide (microencapsulated) 2.5% gel in the treatment of acne.

MATERIALS AND METHODS

In this prospective survey, acne patients treated with adapalene (micronised) 0.1% plus benzoyl peroxide (microencapsulated) 2.5% for four weeks were enrolled. Grade of acne, investigator global assessment and patient satisfaction scores were noted at baseline, week 2 and week 4. Safety was assessed by recording adverse events and incidence of dryness, erythema or irritation. Global adverse event score was calculated by adding the number of adverse events at week 2 and 4.

RESULTS

A total of 412 patients with mean duration of acne was 6.98 (5.81) months were enrolled. Number of patients with grade 3 or 4 acne reduced from 202 (49%) at baseline to 73 (17.7%) at week 2 and 31 (7.5%) at week 4, whereas number of patients with grade 1 acne increased from 27 (6.6%) at baseline to 155 (37.6%) after 2 weeks and 277 (67.2%) at 4 weeks (p=0.001, both at 2 and 4 weeks). Number of patients with severe acne reduced from 47 (11.4%) at baseline to 17 (4.1%) after week 2 and 8 (1.9%) after 4 weeks. The improvement in investigator global assessment after treatment at 2 and 4 weeks was statistically significant (p=0.001). After 4 weeks of treatment, 374 (95.6%) patients were either satisfied or more than satisfied. Mean global adverse event score reduced from 2.35 (±2.27) at week 2 to 1.68 (±1.88) after 4 weeks with 28.5% in mean global adverse event score (p=0.001).

CONCLUSION

Technologically-enhanced formulation of adapalene (micronised) 0.1% plus benzoyl peroxide (microencapsulated) 2.5% is significantly effective and very well tolerated in patients with acne.

KEYWORDS

Acne, Tolerability, Safety.

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BACKGROUND

Acne vulgaris is a universal skin disease affecting both genders. Acne affects more than 85% of the teenagers as well as some adults[1] and persists in large number of people in their 20s and 30s age.[2] A single-center clinic-based study from a teaching hospital in India reported prevalence of acne among boys and girls between 12-17 years of age as 50.6% and 38.13%, respectively.[3] Combination therapy is an effective approach in the management of acne as it can simultaneously act on several pathogenic mechanisms. The current (2016) European Dermatology Forum (EDF) guidelines[4] recommend combination therapy for all grades of acne as initial treatment. In severe cases, the combination therapy is recommended along with systemic antibiotics. Since adapalene gel 0.1% causes significantly less irritation compared to tretinoin cream 0.025% or tretinoin microsphere gel 0.1%.[5] It is one of the preferred topical

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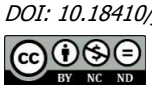

retinoids in the treatment of acne. Adapalene is the only retinoid, which shows compatibility when combined with Benzoyl Peroxide (BPO).[6] Fixed-dose combination of adapalene with BPO is first line treatment of acne vulgaris. Adapalene 0.1% plus 2.5% BPO combination is only approved by DCGI.[7] In moderate acne, combination therapy has shown significantly higher success rates with faster onset of action compared individual monotherapy and also significantly greater reductions in total, inflammatory and non-inflammatory lesion counts. Although, gel is generally well tolerated, cutaneous tolerability,[8] especially erythema, dryness and scaling remain the most common adverse events.[9] Irritation with topical therapies may result in reduced adherence and discontinuation of therapy.[10] In order to improve the tolerability and acceptance, technological advancements have been done during formulation development. Microsphere formulation of BPO results in consistent delivery and is associated with improved tolerability and very low chance of irritation.[10]

Adapalene (micronised) 0.1% benzoyl peroxide (microencapsulated) 2.5% is prepared with improvised technology. Bio-adhesive polymer in this product enables adhesion of aqueous suspension to the skin. Benzoyl peroxide present in encapsulated form ensures its stability, penetration and sustained release over time and also prevents the oxidation of adapalene. The technology helps to reduce the particle size significantly. The size of micronised adapalene is much smaller than other formulations in the market.[11] The 10% formulation retains nearly 95% of the BPO over 30 days at 42˚C, whereas the other commonly used formulation loses over 40% of the BPO under identical conditions.[11] Release of BPO is smoother and penetration is enhanced due to much smaller particle size (~0.6 micron) compared to average particle size of free BPO (~500 micron). The formulation ensures enhanced longevity on the skin and better deposition from a rinse-off. An in-vivo trial in human volunteers revealed that the technologically-advanced formulation releases benzoyl peroxide onto the skin more slowly than free BPO.[11] Understanding opinions of the patients who have used this product will be useful to understand, if these benefits are seen in real life settings.

Objective- The objective of this study was to evaluate efficacy, safety and patient satisfaction of adapalene (micronised) 0.1% plus benzoyl peroxide (microencapsulated) 2.5% gel in the treatment of acne.

MATERIALS AND METHODS

In this prospective survey, acne patients treated with adapalene (micronised) 0.1% plus benzoyl peroxide (microencapsulated) 2.5% gel were enrolled. Duration of acne and personal history regarding diet, smoking, face wash, use of cosmetics, hair oils, presence of dandruff, medication history and family history was recorded. In female patients, use of oral contraceptives or hormone replacement treatment, history of polycystic ovarian disease or menstrual disorder, if any and relevant obstetric history was recorded. Grade of acne, investigator global assessment and patient satisfaction scores were noted at baseline, week 2 and week 4. Acne grading was done into four grades. Grade 1- Comedones, occasional papules; Grade 2- Papules, comedones, few pustules; Grade 3- Predominant pustules, a few nodules and Grade 4- Mainly cysts, abscesses, widespread scarring.[12] Investigator's Global Assessment (IGA) of acne severity was performed on 5-point scale 0- 'Clear' (residual hyperpigmentation and erythema maybe present); 1- 'Almost clear' (a few scattered comedones and a few small papules); 2- 'Mild' (easily recognisable; less than half the face is involved, some comedones and some papules and pustules); 3- 'Moderate' (more than half of the face is involved; many comedones, papules and pustules. Only one nodule maybe present) and 4- 'Severe' (entire face is involved, covered with comedones, numerous papules and pustules, and few nodules and cysts).[13]

Patient Satisfaction (PS) Scoring was done on 3-point scale; "more than satisfied" "satisfied" and "not satisfied." Safety was assessed by recording dryness, erythema or irritation with the use of study medication. Severity of adverse event was classified as mild, moderate or severe. Global adverse event score was calculated by adding the number of adverse events at week 2 and 4.

Statistical Analysis- Categorical data are presented as number and percentage, whereas continuous data are presented as mean and standard deviation. Change in severity of acne grading and investigator's global assessment was assessed by Chi-square test. Change in mean global adverse event score from week 2 to week 4 was assessed by Student's t-test.

RESULTS

A total of 412 patients participated in this study. Mean duration of acne was 6.98 (±5.81) months with range between 1 to 36 months. A total of 204 (49.5%) patients had history of high carbohydrate/sugar consumption in diet, whereas 195 (47.3%) patients reported presence of dandruff. History of smoking was present in 61 (14.8%) patients, family history of acne and PCOD/any other menstrual disorder was present in 40 (9.7%) and 49 (11.9%) patients, respectively. Consumption of oral contraceptives or Hormone Replacement Therapy (HRT) was reported by 23 (5.6%) patients (Table 1).

Personal History	N (%)
High carbohydrate/sugar or lactose diet	204 (49.5%)
Smoking	61 (14.8%)
Presence of dandruff	195 (47.3%)
Currently on any medication	60 (14.6%)
Family history	40 (9.7%)
Any systemic complaints	11 (2.7%)
Using oral contraceptives or HRT	23 (5.6%)
Diagnosed with PCOD or any menstrual disorder	49 (11.9%)

Table 1. Personal History (n=412)

	Baseline N (%)	2 Weeks N (%)	4 Weeks N (%)
Grade 1	27 (6.6%)	155 (37.6%)	277 (67.2%)
Grade 2	183 (44.4%)	184 (44.7%)	104 (25.3%)
Grade 3	165 (40%)	56 (13.6%)	24 (5.8%)
Grade 4	37 (9%)	17 (4.1%)	7 (1.7%)

Table 2. Changes in Proportion of Cases with Severity of Acne after the Treatment (n=412)

At baseline, 202 (49%) patients had grade 3 or 4 acne. After 2 and 4 weeks of treatment, the number of patients with grade 3 or 4 acne reduced to 73 (17.7%) and 31 (7.5%), respectively (Table 2). Number of patients with grade 1 acne increased from 27 (6.6%) at baseline to 155 (37.6%) after 2 weeks and 277 (67.2%) after 4 weeks. This change in severity of acne grade was statistically significant (Table 2; p=0.001).

	Baseline N (%)	2 Weeks N (%)	4 Weeks N (%)
Clear/almost clear	28 (6.8%)	151 (36.7%)	283 (68.7%)
Mild	161 (39.1%)	183 (44.4%)	96 (23.3%)
Moderate	176 (42.7%)	61 (14.8%)	25 (6.1%)
Severe	47 (11.4%)	17 (4.1%)	8 (1.9%)

Table 3. Investigator Global Assessment After The Treatment (n=412)

Results of investigator's global assessment after treatment are shown in Table 3. At baseline, numbers of patients with clear/almost clear, acne were only 28 (6.8%) patients. Number of patients with mild, moderate and severe acne at baseline were 161 (39.1%), 176 (42.7%) and 47 (11.4%), respectively. After 2 weeks of treatment, number of patients with severe acne reduced to 17 (4.1%) and 8 (1.9%) after 4 weeks of treatment. After 4 weeks of treatment, lesions of acne were clear/almost clear in 283 (68.7%) patients (Table 3). The improvement in investigator global assessment after treatment at 2 and 4 weeks was statistically significant (p=0.001). Responses of patient satisfaction ratings are shown in Figure 1 and 2.

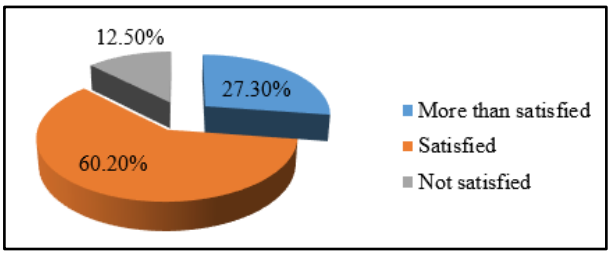

Figure 1. Patient Satisfaction After 2 Weeks of Treatment (n=392)

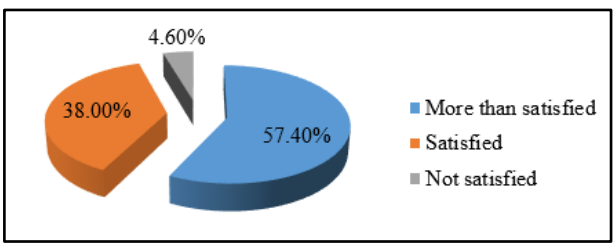

Figure 2. Patient Satisfaction After 4 Weeks of Treatment (n=392)

A total of 343 (87.5%) patients were either satisfied or more than satisfied after 2 weeks of treatment. After 4 weeks of treatment, 374 (95.6%) patients were either satisfied or more than satisfied. Only 4.6% patients were not satisfied with the response after 4 weeks (Figure 2).

Table 4 shows number and percentages of patients with dryness, erythema and irritation after 2 and 4 weeks of treatment. A total of 157 (38.1%) and 203 (49.2%) patients did not have dryness after 2 and 4 weeks, respectively. Number of patients without erythema at 2 weeks and 4 weeks were 214 (51.9%) and 235 (57%), respectively. Numbers of patients without irritation at 2 and 4 weeks were 210 (51%) and 242 (58.7%), respectively.

	Dryness		Erythema		Irritation	
	2 Weeks N (%)	4 Weeks N (%)	2 Weeks N (%)	4 Weeks N (%)	2 Weeks N (%)	4 Weeks N (%)
None	157 (38.1%)	203 (49.2%)	214 (51.9%)	235 (57.1%)	210 (51%)	242 (58.7%)
Mild	145 (35.2%)	156 (37.9%)	120 (29.2%)	147 (35.7%)	105 (25.5%)	124 (30.1%)
Moderate	100 (24.3%)	46 (11.2%)	70 (17%)	29 (7%)	85 (20.6%)	44 (10.7%)
Severe	10 (2.4%)	7 (1.7%)	8 (1.9%)	1 (0.2%)	12 (2.9%)	2 (0.5%)

Table 4. Proportion of Cases with Dryness After the Treatment (n=412)

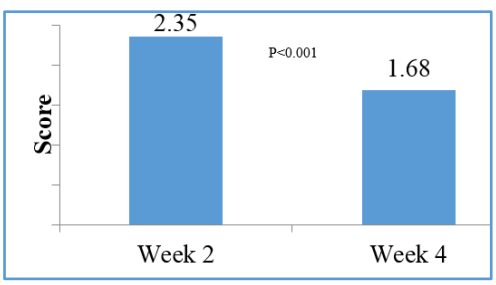

Figure 3. Changes in Mean Global Adverse Event Score Among Study Cases (n=412)

Mean global adverse event score at week 2 was 2.35 (±2.27), which reduced to 1.68 (±1.88) after 4 weeks. This change (28.5%) in mean global adverse event score was statistically significant (Figure 3; p=0.001).

DISCUSSION

Acne is a common dermatological disorder seen in clinical practice. Several factors including diet, smoking, genetics and ethnicity have role in the development of acne.[2] In our study, almost half of the participants reported consumption

of high carbohydrate diet. Considering this association, patients are advised to reduce high carbohydrate diet. Family history is a risk factor for early and more severe form of acne.[2] In our study, close to 10% patients had positive family history and had severe acne in 11.4% according to Investigator's Global Assessment. It would be worthwhile to see, if all the severe cases had positive family history. Role of smoking in acne is controversial.[2] In our study, 14.8% patients reported history of smoking.

Topical retinoid is the first line therapy for mild comedonal form of acne, while for papular/pustular form of mild acne, its combination with topical antimicrobial agent is recommended as first choice of therapy. In moderate-to-severe acne, topical retinoid plus BPO plays an important role.[14]

Combination therapy of topical adapalene/BPO or with antibiotics is preferred in mild-to-moderate acne.

Several guidelines recommend use of topical retinoid plus BPO in the management of acne.[4,15-17] The combination is recommended as initial therapy in the management of mild and moderate acne,[4,16,17] whereas in severe cases, it is recommended along with oral antibiotics.[4,16] Being directly toxic to the P. acne, BPO offers advantages over antibiotics in the treatment of acne vulgaris. It is not associated with development of P. acne resistance[18] and also has an ability to reduce resistant P. acne strains.[19] Alteration of microenvironment by BPO can decrease attachment of P. acne to the follicular lining, which helps to reduce biofilm formation.[20]

Efficacy of adapalene plus BPO in the treatment of acne vulgaris is very well known.[13,14,21,22] Combination of adapalene- BPO has been shown to work better in patients with more number of lesions at the start of therapy.[23] A recently published study showed topical long-term treatment (6 months) with combination of adapalene 0.1% plus benzoyl peroxide 2.5% reduces risk of atrophic scars and results in improvement of the global severity of scarring.[24]

Even in the mild acne, topical retinoid plus BPO is one of the recommended initial therapies by Indian guideline on acne management.[25] In line with the published evidence, we also observed similar results. Compared to baseline, number of patients with moderate and severe acne reduced significantly over time in our study. Investigator's global assessment was also consistent. According to the investigator global assessment, the response after treatment was statistically significant. Efficacy is not the major concern with adapalene plus BPO combination.

Local irritancy is a common adverse event with topical retinoids and combination of adapalene plus BPO. Erythema, dryness, peeling/scaling and burning are the most common local adverse events with these formulations.[9,26] Irritation caused by adapalene gel 0.1% is lesser as compared to other topical retinoids, i.e. tretinoin cream 0.025% or tretinoin microsphere gel 0.1%.[5] Topical adverse events in the form of dryness, erythema and irritation may reduce acceptance and compliance in some patients. Consistent efforts are done to reduce the incidence and severity of these adverse events. One of the measures is to improvise the product formulation. Technology used in the manufacturing of gel provides advantages of reduced particle size, adhesion of aqueous suspension to the skin, stability, penetration and sustained release over time.[11] These advantages might improve the tolerability of the formulation. In order to understand, the profile of local adverse events with technology-enhanced formulation (micronization and microencapsulation), we recorded severity of these adverse events at 2 and 4 weeks and found no dryness, erythema and irritation in 49.2%, 57.1% and 58.7% patients after 4 weeks of treatment. Overall, dryness, erythema and irritation were absent or mild in nature among 87.1%, 92.8% and 88.8% patients, respectively. There was significant reduction in mean global adverse event from week 2 to week 4. These observations confirm good safety profile of the formulation.

Open label, non-comparative study design and subjective evaluation are the limitations of our study. Considering these limitations, we suggest to carefully extrapolate our findings.

CONCLUSION

Technologically-advanced formulation of adapalene BPO confirms efficacy in patients with acne. Importantly, adverse events are minimised with the improvised formulation. Considering balanced efficacy and tolerability, it may be considered as preferred first line agent for acne treatment.

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