Safety and efficacy of adapalene gel 0.1% in acne vulgaris: Results of a post-marketing surveillance study

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ABSTRACT

Introduction: Adapalene is a novel retinoid indicated for the topical treatment of acne vulgaris. The drug was introduced in India in 2001. **Aims:** A post-marketing surveillance study was conducted to assess the safety and efficacy of adapalene gel 0.1% when used as monotherapy or in combination with other anti-acne agents in Indian patients of acne vulgaris. **Material and Methods:** A 12-week, multicentre, open-label, non-comparative study involving 571 patients from 21 centers across India was conducted between January and September of 2002. Concomitant prescription of other anti-acne drugs was permitted, if needed. **Results:** Of the 571 patients, 441 completed the treatment as per protocol. At the end of therapy, 96.3% of patients showed an improvement in their acne from baseline, with greater than 75% improvement seen in two-thirds of patients. Adverse events were reported in 24% of the patients, none of which were serious. The tolerability of therapy was rated as excellent/good in 81% of patients by physicians and in 78% by the patients. **Conclusion:** Adapalene gel 0.1% is a safe and effective topical agent in the treatment of mild to moderate acne vulgaris in Indian patients. It may be safely combined with other topical and oral anti-acne agents.

Key Words: Acne vulgaris, Treatment, Adapalene, Safety and efficacy, Indian skin

INTRODUCTION

Adapalene is a naphthoic acid derivative with retinoid receptor agonist properties, which was developed as a topical treatment for acne.[1] In 2001, adapalene was introduced in India as a 0.1% gel (Adaferin; Galderma India Pvt. Ltd., India).

In vitro assays have shown that adapalene modulates keratinization and possesses anti-inflammatory activity.[1] The drug selectively interacts with only the β and γ subtypes of the nuclear retinoic acid receptors (RARs).[2] This is in contrast to the first generation retinoid, tretinoin, which binds to all RARs and also to cytosolic retinoic acid binding protein (CRABP). Selective binding of adapalene to RARs is believed to contribute to its lesser capacity to cause irritation and greater patient acceptability. Unlike tretinoin, adapalene is very stable, even in the presence of a strong oxidizer (e. g. benzoyl peroxide) and light.[3] Adapalene has been demonstrated to penetrate the sebaceous follicle within five minutes of its application on the skin.[4] Adaferin® gel is a customized formulation containing evenly dispersed micro crystals of adapalene in the range of 3-10 mm, which have been shown to selectively penetrate the follicular ducts.[4]

Clinical experience has shown that local skin irritation reduces patient compliance with topical anti-acne therapy.[5] Several multicentre, parallel, randomized and controlled clinical trials have shown that adapalene gel 0.1% is significantly less irritating than both tretinoin gel 0.025% and tretinoin cream 0.05%.[6-8] Another important feature of adapalene is the ability to use it in combination with other topical agents without any significant additive irritant effect.[9] This is beneficial in

most patients because the multifactorial nature of acne often requires combining more than one drug to achieve optimal results.[10]

As the skin type of Indians varies from Europeans and Americans, it is important to demonstrate the tolerability and efficacy of adapalene gel 0.1% in Indian patients suffering from acne vulgaris. Therefore the aim of this 12-week, phase IV, post-marketing surveillance (PMS) study was to evaluate the safety and efficacy of adapalene gel 0.1% when used as monotherapy or in combination with other anti-acne agents for the treatment of acne vulgaris in Indian patients.

MATERIAL AND METHODS

This 12-week, multicentre, open-label, non-comparative study of adapalene gel 0.1% enrolled 571 patients from 21 centers across India between January and September 2002. Patients were excluded from the study if they had severe (grade IV) acne, known hypersensitivity to any of the ingredients of adapalene gel 0.1%, or if they were pregnant or lactating women. Written informed consent was obtained from all patients prior to study enrollment. The patients were instructed to apply 1 fingertip unit (approximately 0.5 grams) of adapalene gel 0.1% over the entire face once daily at bedtime for a period of 12 weeks. Concomitant prescription of other anti-acne drugs was permitted based on the clinical judgment of the investigator. Adapalene gel and other topical anti-acne agents could be applied to the chest and/or to the back in the case of acne involvement of those areas.

Assessment of efficacy and safety was conducted at the end of weeks 1, 4, 8 and 12. The physician's evaluation of the overall response to therapy was recorded according to the following scale:

- Cleared = 100% improvement
- Marked improvement = >75% improvement
- Moderate improvement = 50 - 75% improvement
- Slight improvement = 25% - 50% improvement
- Unchanged = no detectable improvement from pretreatment evaluation
- Worsened = flaring up of the clinical lesions

Any adverse event reported by the patient or observed by the investigator, regardless of its relationship to the study drug, was noted in the case record form. No formal hypothesis testing was done for this study. The data has been presented descriptively and summary statistics with frequency distribution are provided.

RESULTS

A total of 571 patients were enrolled in the post-marketing surveillance study on an intent-to-treat basis, of which 441 completed treatment as per protocol (12 week period). Treatment was discontinued early in 130 patients for various reasons (lost to follow-up, patient's request and non-compliance). The sex ratio was 1:1 and the mean age was 21 years. Mild acne (Grade I) was seen in 21%, moderate acne (Grade II) in 60% and moderately severe acne (Grade III) in 19%. Of the 571 patients, 193 patients received one or more concomitant anti-acne medications, which included topical antimicrobials (clindamycin, erythromycin and benzoyl peroxide), oral antibiotics (tetracycline, doxycycline, minocycline, azithromycin, roxithromycin and cephalexin), oral contraceptives, dapsone and spironolactone.

Efficacy

The percentage of patients showing an improvement in their disease increased at each evaluation time-point (Table 1). Of the 441 patients who completed 12 weeks of therapy, 96.3% showed a global improvement in their acne (clear of acne or significant, moderate or slight improvement) from baseline. Eighteen percent showed a complete clearing of lesions and another 44% showed a significant improvement (> 75%). Lesions remained unchanged or worsened in only 13 patients (3%) and 3 patients (0.7%) respectively.

Tolerability

Tolerability to the prescribed therapy at the end of 12 weeks was rated as either excellent or good by 78% of the patients, and as 81% as per the physician's global evaluation (Table 2).

Table 1: Evaluation of efficacy

	Week 1		Week 4		Week 8		Week 12	
	No.	%	No.	%	No.	%	No.	%
Cured	0	0.00	0	0	7	1.53	80	18.14
Significant improvement (>75 %)	5	0.98	42	8.62	175	38.13	194	43.99
Moderate improvement (50-75 %)	52	10.22	203	41.68	178	38.78	114	25.85
Slight improvement (25-50 %)	234	45.97	185	37.99	73	15.90	37	8.39
Unchanged	174	34.18	29	5.95	23	5.01	13	2.95
Worsened	44	8.64	28	5.75	3	0.65	3	0.68
Total	**509**	**100**	**487**	**100**	**459**	**100**	**441**	**100**

Table 2: Physicians and patients global evaluation of tolerability of therapy at week 12

	Patient		Investigator	
	No.	%	No.	%
Excellent	156	33.55	184	39.83
Good	204	43.87	188	40.69
Fair	79	16.99	70	15.15
Poor	26	5.59	20	4.33

Adverse Events

Out of the 571 subjects, 137 patients reported a total of 232 adverse events. The most common ones were burning (23%), dryness (16%), itching (12%), irritation (5%) and erythema (5%). Post-inflammatory hyperpigmentation was observed in only 2 patients (0.86%). The overall incidence of adverse events was 24%. Of the 137 patients, 56 had received concomitant anti-acne therapy. All the adverse events were mild to moderate in severity and were reversible on discontinuation of therapy. In the majority of patients, adverse events did not interfere with completion of treatment.

DISCUSSION

Topical retinoids are an integral component of any combination therapy for acne vulgaris because they promote comedonal drainage, (which facilitates the penetration of other topical agents) clear current inflammatory and non-inflammatory acne lesions, and prevent new acne lesions from forming.[11] Post-marketing surveillance studies are conducted with the aim of gathering data on the efficacy and more importantly on the safety of a drug when used in the population at large. When compared to Phase III studies, PMS studies have certain advantages, viz. a) there is greater flexibility in the enrollment of the study subjects, b) concomitant medication use is not restricted, and c) capture of data is from usage of the drug in actual clinical practice.

This study demonstrated that at the end of 12 weeks, 18% of the subjects were cleared of their acne, while 44% had significant improvement and 25.85% had moderate improvement in their disease. Only 3% of the patients demonstrated no change in their clinical condition and less than 1% had worsening of their disease. These data conform to the results obtained in other randomized controlled trials.[6-8] The high efficacy and tolerability of adapalene, as well as its compatibility with other concurrent acne medications,[9] makes topical adapalene a key component in the treatment of both comedonal and inflammatory acne.[10]

Poor patient compliance is one of the main reasons for treatment failures in acne. The high incidence of "retinoid dermatitis" associated with the use of tretinoin has been shown to adversely affect patient compliance.[5] Several comparative studies have shown adapalene to have a superior cutaneous safety profile as compared to different formulations (gel, cream and micro sphere gel) of tretinoin[7,8,12,13] as well as isotretinoin gel.[14] Even in this study the tolerability of adapalene gel as monotherapy or in combination with other anti-acne agents was found to be well accepted by both patients and physicians. In only 4% of the patients did the investigators rate the tolerability of therapy as poor. Likewise only 6% of the patients opined that they tolerated prescribed therapy poorly.

The overall incidence of adverse events reported in this study was 24% (inclusive of adverse events reported with concomitant medications), which conforms to the 10-40% incidence of adverse events as mentioned in the product labeling of adapalene gel. Although the potential of post-inflammatory hyperpigmentation is

higher in Asian skin types as compared to Europeans and Americans, and many topical anti-acne agents are known to enhance such hyperpigmentation, it is very significant to note that only 2 patients (0.86%) reported an increase in lesional skin pigmentation after the use of adapalene in this study.

This study has clearly demonstrated the efficacy and tolerability of adapalene gel in the Indian skin type. The results conform to the results obtained in trials conducted in Chinese[15,16] and African[17,18] patients. In conclusion it can be said that adapalene gel 0.1% (Adaferin®) is an effective and safe modality of treatment alone or in combination in Indian patients suffering from mild to moderately severe (Grades I, II and III) acne vulgaris.

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