

## Research Article



## A Pharmacovigilance Study of Topical Acne Monotherapy with 0.1% Adapalene, and a Molecular Analytical Review of Adapalene in Evidence-based Dermatopharmacological Treatment

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### ABSTRACT

Acne vulgaris causes cosmetic impairment. User-friendly anti-acne monotherapy with adapalene has activity against the acne pathophysiology, with very minimal adverse effects. Retinoids, like adapalene, are comedolytic and anti-inflammatory. This study was conducted as a pharmacovigilance study of topical acne monotherapy with 0.1% adapalene, and a molecular analytical review of adapalene in evidence-based dermatopharmacological treatment. A prospective, open-labelled study was done, on 75 patients, with mild to moderate acne. Patients applied 0.1% adapalene topical monotherapy, once daily in the evening, over affected areas on the face, and left overnight. Efficacy was measured by percentage reduction in non-inflammatory, inflammatory and total lesion counts on 0, 15, 30, 60 and 90 days; and severity of lesions was assessed by Investigator's Global Evaluation Scale and the occurrence of adverse effects like erythema, dryness, scaling, burning and pruritus, were assessed by the Local Irritation Scale, among the patients receiving the monotherapy. An analytical review of the molecular pharmacology of adapalene in evidence-based dermatopharmacological treatment was thoroughly performed. The patients showed highly significant reduction in total lesion counts from baseline. No serious adverse effects were observed; and the observations were statistically non-significant. The molecular analytical review described significantly effective evidence-based dermatopharmacological response mechanisms of adapalene therapeutics. Topical 0.1% adapalene monotherapy was effective and safe, with significant evidence-based molecular dermatopharmacological efficacy.

**Keywords:** Retinoids, Adapalene, Local Irritation Scale, Dermatopharmacology, Pharmacovigilance, Molecular Pharmacology, Evidence-Based Medicine.

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### INTRODUCTION

**A**cne vulgaris is a self-limited, chronic inflammatory disease of pilosebaceous unit.<sup>1,2</sup> It is a common skin disease characterized by non-inflammatory follicular papules or comedones and by inflammatory papules, pustules and nodules, in its more severe forms. The pathogenesis of acne vulgaris is multifactorial. Four main key factors are responsible for the development of acne lesion and these are follicular epidermal hyperproliferation with subsequent plugging of the follicle, excess sebum production, the presence and activity of *Propionibacterium acnes* and inflammation.<sup>3</sup>

Acne vulgaris causes cosmetic impairment.<sup>4</sup> User-friendly anti-acne monotherapy with adapalene has activity against the acne pathophysiology, with very minimal adverse effects.<sup>5</sup>

Retinoids, like adapalene, are comedolytic and anti-inflammatory.<sup>6,7</sup>

To supplement the available research studies, this study was conducted to assess the safety of topical monotherapy of adapalene in mild to moderate acne vulgaris, with a molecular review of adapalene in evidence-based dermatopharmacological treatment.

### Objective

The aim of this study was a pharmacovigilance study of topical acne monotherapy with 0.1% adapalene, and a molecular analytical review of adapalene in evidence-based dermatopharmacological treatment.

### MATERIALS AND METHODS

This study was prospective, and open-labelled, expanding over three months, along with the compilation of the study literature, performed between September 2013 to



November 2013, January 2016, and July 2021 to August 2021. 75 patients from multi-centre tertiary care centres, having mild to moderate acne, were chosen for the study.

The clearance and the approval from the Institutional Ethical Committee were obtained, before conducting the study. The patients were selected based on the inclusion and the exclusion criteria given below, and the patients fulfilling those criteria, were included in the study.

The inclusion criteria were as follows:

- a. Patients aged 12-25 years of either sex
- b. Patients with mild to moderate acne (Grade – I & II) on face above the jaw line (according to Investigator's Global Evaluation scale)
- c. Women of child bearing potential are required to have a negative urine pregnancy test result and to agree to use an effective form of contraception for the duration of study (12 weeks).
- d. Patients who have given consent and are willing to go for a follow up.

The exclusion criteria were as follows:

- a. Patients with severe acne vulgaris (Grade – III & IV).
- b. Patients with acne lesions predominantly involving trunk (truncal acne).
- c. Other variants of acne: chloracne, oil acne, tropical acne, mechanical acne, severe variants like acne conglobata and acne fulminans.
- d. Drug induced acne.
- e. If at follow up disease progresses and necessitates systemic therapy.
- f. Patients not willing to give informed consent and follow up.
- g. Pregnancy and lactating mother.
- h. Patients with known hypersensitivity to any of the components of the drug.
- g. Female patients using hormonal contraceptives.
- h. Patients who are already on topical therapy for acne or any other topical therapy, during the previous four weeks.
- i. Immunocompromised and patients on medication for any chronic medical illness.

An informed consent was obtained from each individual. A detailed history was obtained with the proforma, giving special attention to the predisposition to acne. At first visit, the patients were interviewed for their demographic profile, present and past history, personal history, medication history etc. Systemic examination was performed. Then, the dermatological evaluations were made. Each patient was examined with the baseline non-inflammatory, inflammatory and total lesions counting and documented in their respective case record forms. Each

patient was also assessed for the baseline Acne Severity Grading as per the Investigator's Global Evaluation Scale.<sup>8</sup>

75 patients, suffering from mild to moderate acne on face, were advised to apply adapalene monotherapy. The patients received topical 0.1% adapalene monotherapy, as anti-acne treatment.

Before the application of the topical anti-acne agent, the patients were advised to wash the face with clean water and dry it well. The patients were prescribed to apply 1 fingertip unit (approximately 0.5 gram) of adapalene, at night, over the forehead, cheeks, chin and nose, with a thin film evenly spread over the entire face. Special precaution was taken to avoid the periorbital, para nasal and perioral areas.

According to the prescription, the patients, falling in either group, applied 0.1% adapalene, which was left overnight.

The efficacy of the drugs was evaluated at 2, 4, 8 and at 12 weeks follow-up, by the non-inflammatory, inflammatory and total lesions counting. At the baseline, the total number of lesions on the face was taken as 100%. Any reduction in the number of acne lesions, at follow up, was compared with the baseline and was expressed as the percentage of improvement and graded. Thus, the efficacy assessment was done by mean reduction in non-inflammatory lesions, inflammatory lesions and total lesions count, after 12 weeks of therapy. Efficacy was assessed with the help of Investigator Global Evaluation Scale of acne.

The skin tolerability of the medications and the consequent side effects were observed during the course of therapy by the assessment of dryness, erythema, burning, peeling and irritation and were graded at 2, 4, 8 and 12 weeks follow-up, by the Local Irritation Scale.<sup>9</sup>

The efficacy and tolerability were assessed. Efficacy was assessed by comparing the mean reduction in non-inflammatory lesions, inflammatory lesions and total lesions count, after 12 weeks of therapy. As per the EGSS for acne, only those patients who were in clear or almost clear category after 12 weeks of therapy on EGSS were regarded as improved patients (treatment success). Then the percentage of patients showing improvement were calculated for the patients.

The statistical analyses were made by unpaired 't' test, Chi-Square test, one way ANOVA test and two sample Z – test.

An analytical review of the molecular pharmacology of adapalene in evidence-based dermatopharmacological treatment was thoroughly performed, from a wide range of study literature, spanning various types of researches, reviews, qualitative analyses, case presentations, case reports, case series, systematic reviews, meta-analyses, medical records, and medical databases.

## RESULTS

In this study, 75 patients, treated with 0.1% adapalene monotherapy, were observed to be safe. The patients



showed highly significant reduction in total lesion counts from baseline. Table 1 depicts that no serious adverse effects were observed with 0.1% adapalene monotherapy; and the observations were statistically non-significant.

**Table 1:** The occurrence of adverse effects with 0.1% adapalene monotherapy

Adverse effects	Number of patient occurrence	Z value	p value
Dryness	0	-	non-significant
Erythema	0	-	non-significant
Burning	0	-	non-significant
Peeling	0	-	non-significant
Irritation	0	-	non-significant

The analytical review of the molecular pharmacology of adapalene in evidence-based dermatopharmacological treatment, showed that adapalene is comedolytic and anti-inflammatory. Along with the expected effects of retinoids on non-inflammatory lesions, adapalene also has a significant anti-inflammatory effect that enhances the therapeutic action of antibiotics on inflammatory lesions. Adapalene and antibiotics have both complementary and discreet mechanism of action, which lead to an additive and synergistic clinical effect, not only for reducing comedones, but also in reducing inflammatory acne lesions. Although adapalene is similar to all-trans-retinoic acid in its efficacy for acne, it is more stable chemically, less photo-labile, and more lipophilic, which enables it to penetrate follicles quickly. Adapalene has selective affinity for retinoid receptors, including retinoic acid receptor  $\beta$  and retinoic acid receptor  $\alpha$ , and it also acts indirectly on cellular function through anti-AP-1 mechanism. It does not bind to cytosolic receptor protein, and therefore no affinity for cellular (cytosolic) retinol binding protein, but induces CRBPII messenger ribonucleic acid when applied under occlusion for 4 days to the human skin. Fluorescence microscopic studies have shown that adapalene microcrystals penetrate follicular openings to the level of sebaceous gland within 5 minutes of application. The selective uptake by follicles is thought to be due to its lipophilicity and might contribute to adapalene's success in the treatment of acne. As adapalene also has anti-inflammatory action and only a trace of drug is absorbed systemically, it is preferred.<sup>10, 11, 12</sup>

## DISCUSSION

This study was designed to investigate 0.1% adapalene monotherapy. Adapalene provided a significant efficacy in the treatment of mild to moderate acne vulgaris, with adequate safety. Results showed that applying a 0.1% adapalene gel produced a clinically significant treatment efficacy for acne vulgaris. After 12 weeks of therapy, there were significant reduction in inflammatory, non-inflammatory and total lesion counts among patients treated with adapalene monotherapy.

Adapalene as a monotherapy was well-tolerated. There were no serious adverse effects observed among the patients. The significant anti-inflammatory property of adapalene may contribute to the good tolerability.

This molecular analytical review described significantly effective evidence-based dermatopharmacological response mechanisms of adapalene therapeutics.

The research and review outcomes in this study have extensive as well as intensive implications for the management of acne vulgaris. The significant reduction in acne lesions obtained by applying adapalene indicated that this monotherapy can be used as a routine therapy for obtaining a better clinical response.

The more rapid action of the combination of adapalene with the antibiotics, is likely to lead to greater patient compliance, with no significant tolerability burden. In addition, the enhanced speed and efficacy of the combination might reduce the duration of antibiotic therapy and as the antibiotic resistance is a common phenomenon that occurs in patients of acne treatment, due to the quick action of this combination, it would help to reduce the potential for developing bacterial resistance.<sup>12</sup>

## CONCLUSION

The topical 0.1% adapalene monotherapy was effective and was well tolerated among the mild to moderate acne vulgaris patients. The molecular analytical review described significantly effective evidence-based dermatopharmacological response mechanisms of adapalene therapeutics.

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