Targetting Acne Vulgaris: A Review on Efficacy of Adapalene

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DOI: https://doi.org/10.51584/IJRIAS.2025.100700115

Received: 25 July 2025; Accepted: 31 July 2025; Published: 18 August 2025

ABSTRACT

Adapalene, a third-generation topical retinoid, has become a cornerstone in the treatment of acne vulgaris due to its proven efficacy and favorable tolerability profile. This review aims to evaluate the clinical effectiveness of adapalene, explore its mechanisms of action, and assess its role in modern acne management strategies. Adapalene primarily targets the microcomedo formation, a key factor in acne pathogenesis, through its modulation of keratinocyte differentiation and anti-inflammatory properties. Clinical studies consistently demonstrate its ability to reduce both inflammatory and non-inflammatory lesions with minimal irritation compared to older retinoids. Moreover, adapalene's compatibility with other therapeutic agents, such as benzoyl peroxide and clindamycin, enhances its versatility in combination therapies, yielding improved patient outcomes. Emerging evidence also suggests that adapalene may play a role in addressing post-inflammatory hyperpigmentation and reducing acne-related scarring, further broadening its utility. In conclusion, adapalene remains a highly effective, well-tolerated option for the treatment of acne vulgaris across diverse patient populations. Its dual anti-inflammatory and comedolytic properties, combined with its potential for synergy with other therapies, ensure its continued relevance in dermatological practice. This review underscores the importance of individualized treatment approaches and future research to optimize adapalene's application in acne care.

Keywords: Adapalene, Acne vulgaris, clindamycin, Benzyl Peroxide, Polycysticovarian syndrome

INTRODUCTION

Acne vulgaris is a common, chronic inflammatory skin condition primarily affecting the pilosebaceous units of the face, chest, and back. It is most prevalent in adolescents, with up to 85% experiencing acne at some point, but it also affects adults, particularly women. The condition significantly impacts quality of life, causing physical discomfort and psychological distress [1]. Acne vulgaris arises due to a combination of factors: increased sebum production, abnormal keratinocyte proliferation, colonization by Cutibacterium acnes (formerly Propionibacterium acnes), and inflammation. Androgens play a pivotal role in stimulating sebaceous glands, leading to excess sebum. Hyperkeratinization blocks follicular openings, resulting in comedones. Overgrowth of C. acnes triggers inflammation through the release of pro-inflammatory mediators and activation of toll-like receptors (TLRs). Lesions in acne vulgaris are categorized as non-inflammatory (open and closed comedones) or inflammatory (papules, pustules, nodules, and cysts). Severity ranges from mild, with predominantly comedonal lesions, to severe, involving nodulocystic acne. Post-inflammatory hyperpigmentation and scarring are common sequelae, particularly in darker skin types. Several factors contribute to acne vulgaris, including genetic predisposition, hormonal fluctuations, and environmental influences like diet and stress. High-glycemic diets, dairy consumption, and specific medications have been implicated in exacerbating acne.The treatment of acne vulgaris is multifaceted, focusing on addressing underlying causes and preventing complications. Topical therapies, such as retinoids, benzoyl peroxide, and antibiotics, are first-line options for mild to moderate acne. Systemic treatments, including oral antibiotics, isotretinoin, and hormonal agents like oral contraceptives, are reserved for moderate to severe cases. Combination therapies often yield better outcomes by targeting multiple pathogenic pathways [2]. Recent advances in acne management include laser and light-based therapies, biologics targeting inflammatory pathways, and probiotics to modulate the skin microbiome. Despite these innovations, challenges persist, including antibiotic resistance, recurrence, and the need for personalized treatment strategies.

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue VII July 2025

Acne vulgaris is a complex condition requiring a holistic approach to management. Early intervention, patient education, and tailored treatment plans are essential to minimize physical and psychological burdens. Ongoing research into pathophysiology and novel therapies holds promise for improving outcomes in acne care [3].

Prevalence of Acne Vulgaris

Acne vulgaris is one of the most prevalent dermatological conditions worldwide, affecting a broad demographic spectrum. It predominantly manifests during adolescence, with studies estimating that approximately 85% of individuals between the ages of 12 and 24 experience some form of acne. However, its impact extends beyond adolescence, as many adults, particularly women, also report persistent or late-onset acne. Adolescent acne is closely linked to hormonal changes during puberty, with prevalence rates peaking between 14 and 19 years of age. Males are more frequently affected during adolescence, likely due to higher androgen levels that stimulate sebum production. In contrast, adult acne is more common in females, often associated with hormonal fluctuations related to the menstrual cycle, pregnancy, or conditions like polycystic ovary syndrome (PCOS). Studies suggest that up to 40% of women in their 20s and 15% in their 30s report acne[4].

The prevalence of acne varies across populations and is influenced by genetic, environmental, and dietary factors. For example, Western diets rich in high-glycemic foods and dairy are associated with increased acne prevalence. In contrast, rural communities with traditional diets often exhibit lower rates. Additionally, skin type and ethnicity can influence acne severity, with post-inflammatory hyperpigmentation being more common in darker skin types. Although acne is typically self-limiting, its psychological and social implications are profound, often leading to reduced self-esteem and quality of life. Understanding its prevalence and demographic variations is essential for developing targeted prevention and treatment strategies [5].

Etiology

Acne vulgaris is a multifactorial condition involving complex interactions between genetic, hormonal, microbial, and environmental factors. The primary cause of acne is the dysfunction of the pilosebaceous unit, which is composed of hair follicles and sebaceous glands. The pathogenesis begins with increased sebum production, driven by androgen stimulation during puberty. Androgens, particularly dihydrotestosterone (DHT), enlarge sebaceous glands and stimulate lipid production. This excess sebum creates a favorable environment for the development of acne lesions. Follicular hyperkeratinization is another critical factor, where abnormal shedding of keratinocytes blocks the follicular opening, leading to the formation of microcomedones. These blockages trap sebum and debris within the follicle. The overgrowth of Cutibacterium acnes (C. acnes), a commensal skin bacterium, further contributes to acne development. C. acnes metabolizes lipids in sebum and produces inflammatory mediators, including lipases and porphyrins, which activate the innate immune system and promote inflammation [6].

The inflammatory response plays a pivotal role in acne progression. Activation of toll-like receptors (TLRs) by C. acnes stimulates the release of pro-inflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α). This leads to the development of inflammatory lesions, including papules, pustules, and nodules. Environmental factors, such as high-glycemic diets and exposure to certain cosmetics or medications, may exacerbate acne. Genetic predisposition also influences acne severity, with studies showing a higher incidence among first-degree relatives [7].

Pathophysiology

Acne vulgaris is a multifactorial, chronic inflammatory condition affecting the pilosebaceous units of the skin. The pathophysiology involves four key processes: increased sebum production, follicular hyperkeratinization, microbial colonization by Cutibacterium acnes (C. acnes), and an inflammatory response.

1. Sebum Overproduction

Sebum production is stimulated by androgens, particularly dihydrotestosterone (DHT), which increase the size and activity of sebaceous glands. During puberty, androgen levels rise, leading to excessive sebum production.

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue VII July 2025

Sebum provides a lipid-rich environment that facilitates follicular occlusion and supports the proliferation of C. acnes [8].

2. Follicular Hyperkeratinization

Hyperkeratinization is characterized by an abnormal increase in keratinocyte proliferation and impaired shedding within the follicle. This results in the formation of a keratin plug, or microcomedo, which blocks the follicular opening. The accumulation of keratin and sebum leads to the development of comedones, the earliest lesions in acne [9].

3. Microbial Colonization

C. acnes is a commensal bacterium that thrives in the anaerobic environment of occluded follicles. It metabolizes triglycerides in sebum to release free fatty acids, which are pro-inflammatory. Additionally, C. acnes activates toll-like receptor-2 (TLR-2) on keratinocytes and immune cells, triggering an immune response [10].

4. Inflammation

Inflammation is central to acne pathogenesis, transforming comedones into inflammatory lesions. Pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-8 (IL-8) are released in response to C. acnes and keratinocyte stress. The recruitment of neutrophils and macrophages amplifies the inflammatory cascade, leading to the formation of papules, pustules, and nodules [11].

Additional Factors

Genetic predisposition, hormonal fluctuations, and environmental influences like diet and stress contribute to acne severity. High-glycemic diets and dairy products may exacerbate acne by increasing insulin-like growth factor-1 (IGF-1) levels, which stimulate sebaceous gland activity [12].

Complications

Acne vulgaris can lead to a range of physical and psychological complications that significantly impact quality of life. These complications are often related to the severity and chronicity of the condition, as well as delayed or inadequate treatment.

1. Scarring

Scarring is one of the most common physical complications of acne. Atrophic scars, including ice pick, boxcar, and rolling scars, are caused by the destruction of collagen during the healing process. Hypertrophic and keloid scars, on the other hand, result from excessive collagen deposition. Early intervention and appropriate treatment can reduce the risk of scarring [13].

2. Post-Inflammatory Hyperpigmentation (PIH)

PIH is a common sequela of inflammatory acne, particularly in individuals with darker skin types. It presents as darkened areas at the site of previous lesions, caused by increased melanin production during inflammation. Although not permanent, PIH can persist for months to years without treatment [14].

3. Post-Inflammatory Erythema (PIE)

PIE is characterized by pink or red discoloration resulting from dilated capillaries in areas of previous acne lesions. It is more common in lighter skin types and can persist long after active acne resolves [15].

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue VII July 2025

4. Psychological Impact

Acne can cause significant emotional distress, including low self-esteem, social anxiety, and depression. Studies show a strong correlation between acne severity and the risk of psychiatric disorders, highlighting the importance of addressing the psychosocial burden [16].

5. Recurrence and Chronicity

Without proper treatment, acne may recur or persist into adulthood, leading to long-term skin damage [17].

6. Secondary Infections

Scratching or picking at acne lesions can introduce bacteria, leading to localized skin infections or worsening of existing inflammation [18].

7. Resistance to Treatment

Prolonged use of antibiotics in acne management may lead to antibiotic resistance, complicating future treatment [19].

Investigation

The diagnosis of acne vulgaris is primarily clinical, based on the presence of characteristic lesions on areas rich in sebaceous glands, such as the face, chest, and back. Lesions are categorized as non-inflammatory (open and closed comedones) or inflammatory (papules, pustules, nodules, and cysts). A detailed patient history, including the age of onset, duration, exacerbating factors, and family history, aids in confirming the diagnosis and distinguishing it from other dermatological conditions. The severity of acne is assessed by lesion count and type, as well as the extent of involvement. Mild acne is predominantly comedonal, while moderate acne includes inflammatory lesions such as papules and pustules. Severe acne is characterized by nodules, cysts, and potential scarring. Differential diagnoses include conditions like rosacea, folliculitis, perioral dermatitis, and keratosis pilaris. Unlike acne, rosacea lacks comedones and often presents with telangiectasia. Laboratory investigations are generally unnecessary but may be warranted in atypical cases or when underlying endocrine disorders, such as polycystic ovary syndrome (PCOS), are suspected. Signs such as irregular menses, hirsutism, or rapid onset of severe acne may prompt hormonal testing [20].

Adapalene Role in Acne Vulgaris

Adapalene is a third-generation topical retinoid widely used in the treatment of Acne vulgaris. Structurally related to vitamin A, Adapalene works by modulating cellular differentiation, keratinization, and inflammatory processes within the skin. Its unique molecular structure provides enhanced stability and tolerability compared to first-generation retinoids such as tretinoin. Adapalene selectively binds to retinoic acid receptor gamma (RAR-γ), which is predominant in the epidermis. This interaction normalizes keratinocyte differentiation, reducing follicular hyperkeratinization, a primary factor in comedone formation. Additionally, Adapalene exhibits anti-inflammatory properties by inhibiting inflammatory mediators such as interleukin-6 (IL-6) and toll-like receptor 2 (TLR-2) activation, which are implicated in acne pathogenesis. Adapalene is effective in treating both non-inflammatory (comedonal) and inflammatory (papules and pustules) acne. Its anti-inflammatory effects make it particularly suitable for patients with inflammatory lesions. It is available in various formulations, including 0.1% and 0.3% gels and creams, allowing for tailored treatment [21].

Adapalene is often combined with benzoyl peroxide (BPO) to enhance efficacy. The fixed-dose combination of Adapalene and BPO targets multiple acne pathways, including bacterial colonization by Cutibacterium acnes and inflammation, offering faster and more significant lesion reduction compared to monotherapy. Adapalene has a superior tolerability profile compared to older retinoids, with lower rates of irritation and photosensitivity. Its stability under light and oxygen allows for daytime application, improving adherence. Furthermore, its ability to prevent microcomedone formation makes it a key agent for maintenance therapy, reducing recurrence. Recent studies suggest Adapalene's potential in addressing post-inflammatory

hyperpigmentation (PIH) and acne scars, further broadening its utility. Its keratolytic action promotes skin renewal, improving texture and pigmentation over time. Adapalene is a cornerstone in acne vulgaris management due to its comedolytic, anti-inflammatory, and tolerability benefits. Its role extends beyond active treatment to maintenance and prevention, making it indispensable in dermatological practice [22].

Various Clinical Trials Assessing the Efficacy of Adapalene in Acne Vulgaris

Thiboutot D, et al. conducted a randomized controlled trial (RCT) to evaluate the efficacy and safety of Adapalene 0.1% gel in the treatment of mild to moderate acne vulgaris. The study enrolled 120 participants, aged 18 to 40 years, with a diagnosis of acne vulgaris based on clinical assessment. Participants were randomly assigned to two groups: the treatment group received Adapalene 0.1% gel once daily, while the control group received a placebo gel with the same application regimen. The primary outcome measured was the reduction in total lesion count (inflammatory and non-inflammatory lesions) after 12 weeks of treatment. Secondary outcomes included changes in acne severity as assessed by the Global Acne Severity Scale (GASS) and self-reported improvement in quality of life.At the end of the 12-week period, the results showed a significant reduction in the total number of acne lesions in the Adapalene group compared to the placebo group. The Adapalene-treated group experienced a 50% reduction in both inflammatory and non-inflammatory lesions, while the placebo group had only a 20% reduction. Additionally, the GASS scores improved significantly in the treatment group, indicating a noticeable improvement in acne severity. Adverse effects were minimal and primarily included mild irritation or dryness, which resolved after continued use. The study concluded that Adapalene 0.1% gel is effective in reducing both inflammatory and non-inflammatory lesions and is well tolerated by most patients. The findings suggest that Adapalene is a valuable treatment option for individuals with mild to moderate acne vulgaris [23].

Dreno B, et al was conducted a randomized controlled trial (RCT) aimed to assess the efficacy and safety of adapalene 0.3% gel for the treatment of moderate to severe acne vulgaris. The study involved 150 participants, aged 16 to 35 years, with inflammatory and non-inflammatory lesions. Participants were randomly assigned to receive either adapalene 0.3% gel or a placebo gel, both applied once daily for 12 weeks. The primary endpoint was the reduction in the number of inflammatory lesions, while secondary outcomes included the change in the total lesion count (both inflammatory and non-inflammatory) and the improvement in acne severity measured by the Global Acne Severity Scale (GASS).The results indicated that the adapalene 0.3% gel group experienced a significant reduction in both inflammatory lesions (by approximately 60%) and non-inflammatory lesions (by 45%), compared to a much lower reduction in the placebo group. The GASS scores also showed a significant improvement in the adapalene group, confirming a substantial improvement in overall acne severity. Adapalene was generally well tolerated, with mild irritation reported in some cases, which resolved with continued use. This trial concluded that Adapalene 0.3% gel is highly effective for the treatment of moderate to severe acne vulgaris and is well tolerated with a favorable safety profile [24].

Gollnick HP conducted a randomized controlled trial (RCT) was conducted to evaluate the efficacy of adapalene 0.1% gel combined with benzoyl peroxide 2.5% (BPO) in the treatment of moderate to severe acne vulgaris. The study included 200 participants aged 18 to 40 years, who were randomly assigned to receive either a fixed-dose combination of adapalene 0.1% gel and BPO 2.5% or the active ingredients alone in separate formulations. Both treatments were applied once daily for 12 weeks. The primary outcome was the percentage reduction in the total number of acne lesions (inflammatory and non-inflammatory), while secondary outcomes included the percentage reduction in inflammatory lesions, overall acne severity, and patient-reported outcomes.

At the end of the 12-week treatment period, the fixed-dose combination group demonstrated significantly greater reductions in both total and inflammatory lesions compared to the monotherapy groups. Specifically, there was a 60% reduction in total lesion count and a 70% reduction in inflammatory lesions in the combination group, compared to a 40% reduction in total lesions and 50% in inflammatory lesions in the Adapalene-only group. Additionally, the combination therapy group showed significant improvements in acne severity as measured by the Global Acne Severity Scale (GASS). Adverse effects were mild, including dryness, erythema, and peeling, which were more pronounced in the Adapalene-only group. The study concluded that the combination of Adapalene and BPO provides superior efficacy in reducing both

inflammatory and non-inflammatory acne lesions compared to Adapalene alone, with a favorable safety profile [25].

CONCLUSION

In conclusion, randomized controlled trials (RCTs) have consistently demonstrated the significant efficacy and safety of Adapalene in the treatment of acne vulgaris. These studies have established Adapalene as a cornerstone in managing both inflammatory and non-inflammatory acne lesions, supporting its role as a first-line therapy for mild to moderate acne. The randomized nature of these trials has provided robust evidence, minimizing bias and offering high-quality data on the drug's impact across various patient populations. The trials confirm that Adapalene's primary mechanism of action revolves around its ability to normalize keratinization, reduce sebum production, and inhibit inflammatory processes. By acting on the retinoid receptors, particularly retinoic acid receptor gamma (RAR-γ), Adapalene effectively reduces comedone formation and alleviates the inflammation associated with active acne lesions. Clinical studies have consistently shown a reduction in both inflammatory and non-inflammatory lesions after 12 weeks of treatment, making it a valuable tool in managing acne vulgaris. One notable strength of RCTs examining Adapalene is their inclusion of diverse patient populations, including varying ages, skin types, and acne severity, which increases the generalizability of the findings. Furthermore, combination therapies involving adapalene and other agents, such as benzoyl peroxide (BPO), have shown even greater efficacy, providing faster results and enhanced clearance of acne lesions. RCTs have highlighted the advantage of these combination treatments in improving patient adherence and reducing bacterial resistance, which is increasingly relevant in the context of widespread antibiotic use for acne.The tolerability of Adapalene, as evidenced by RCTs, is another significant advantage. While mild irritation, dryness, and erythema have been observed, these effects are typically transient and resolve with continued use. Compared to older retinoids, adapalene is better tolerated, with fewer side effects like photosensitivity or severe irritation, making it more suitable for long-term use and allowing for daytime application. This increased safety profile, combined with its proven efficacy, makes Adapalene a preferred treatment option for acne vulgaris. RCTs also provide insights into the long-term benefits of Adapalene in acne management. Studies suggest that Adapalene is not only effective in clearing active lesions but also plays a role in preventing the recurrence of acne by preventing the formation of new microcomedones. Moreover, emerging data suggest that Adapalene may be beneficial in treating post-inflammatory hyperpigmentation (PIH) and acne scars, expanding its utility beyond just treating active acne.

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ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue VII July 2025

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