Topical treatment of acne; an update

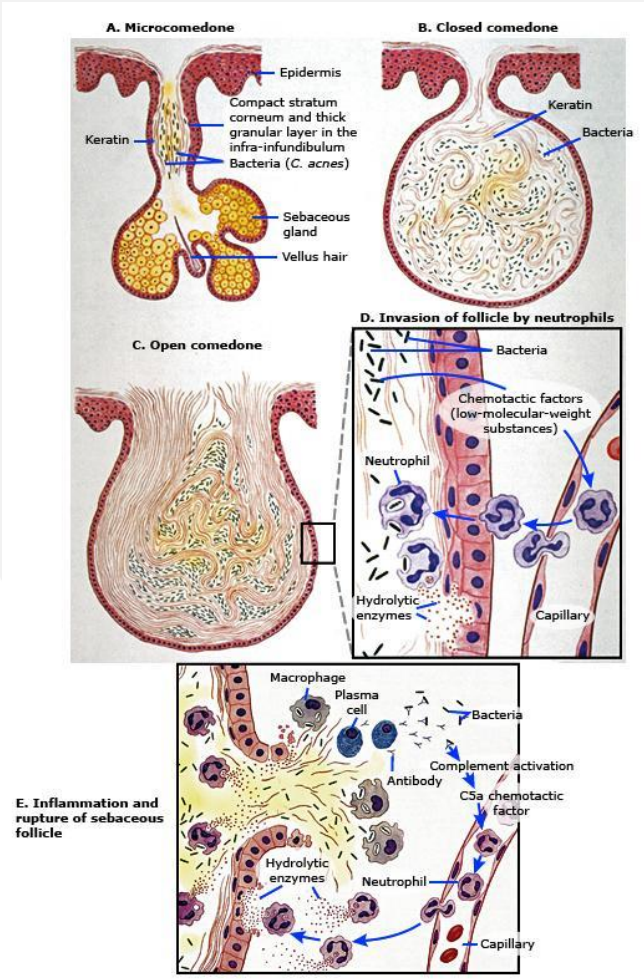
Shahin Hamzelou. MD

Assisstant Professor of Dermatology

Tehran University of Medical Sciences

TREATMENT PRINCIPLES

- Medical therapies for acne target **one or more of four key factors** that promote the development of acne lesions:
  - ✓Follicular hyperproliferation and abnormal desquamation
  - ✓Increased sebum production
  - ✓*Cutibacterium* (formerly *propionibacterium*) *acnes* proliferation
  - ✓Inflammation



Follicular hyperproliferation and abnormal desquamation

- Topical retinoids
- Oral retinoids
- Azelaic acid
- Salicylic acid
- Hormonal therapies

Increased sebum production

- Oral isotretinoin
- Hormonal therapies

C. acnes proliferation

- Benzoyl peroxide
- Topical and oral antibiotics
- Azelaic acid

Inflammation

- Oral isotretinoin
- Oral tetracyclines
- Topical retinoids
- Azelaic acid

Open Access Original Article

DOI: 10.7759/cureus.17606

Treatment of Acne Vulgaris by Topical Spironolactone Solution Compared With Clindamycin Solution

Adil Noaimi [1] , Shatha R. Al-Saadi [2]

1. Department of Dermatology and Venereology, College of Medicine, Baghdad University, Baghdad, IRQ 2. Dermatology Centre, Baghdad Teaching Hospital, Baghdad, IRQ

Corresponding author: Shatha R. Al-Saadi, shatha234@gmail.com

Abstract

Background: Acne vulgaris is a common skin problem that is encountered in daily clinical work, affecting mostly the adolescent and young adult age group. Many topical therapies have been used in the treatment of mild to moderate types of acne vulgaris. However, none of these modalities is uniformly effective; furthermore, acne vulgaris is also associated with relapse and many topical side effects.

Objective: To compare the effectiveness and side effects of topical 2% spironolactone solution and 1.5% clindamycin solution in the treatment of mild to moderate acne vulgaris.

Material and methods: This was a single-blinded therapeutic clinical comparative study conducted at the Dermatology Center at Medical City in Baghdad, Iraq, from April 2019 to March 2020. Sixty-eight patients with mild to moderate acne vulgaris on the face were included. All sociodemographic data related to the disease were recorded for each patient. Patients were divided into two groups according to the type of therapy: group A (35 patients) used 2% spironolactone solution and group B (33 patients) used 1.5% clindamycin solution. All cases in both groups were instructed to use the solutions twice a day for 12 weeks in the same manner. Patients were seen every two weeks to evaluate the response to therapy and to report any topical side effects; then, follow-up was carried out for one month after cessation of therapy to evaluate relapse.

- **Systemic spironolactone**, a synthetic 17-lactone steroid, acts as a **non-selective mineralocorticoid receptor antagonist** for both **progesterone** and androgen **receptors**.
- It also exhibits **anti-androgen effects** through:
  - ✓inhibition of the cytochrome p450 system
  - ✓inhibition of 5 alpha-reductase activity
  - ✓increase in the hepatic synthesis of sex hormone-binding globulin
- **Topical spironolactone** has been used as a **gel formulation** of **5%** concentration, with studies revealing different cure rates.

- **Spironolactone solution 2% significantly** decreased **comedone** count ($p < 0.0001$).

- **Clindamycin solution had no effect on comedones**.

- Although **spironolactone** was **slower** than clindamycin solution in reaching the maximum therapeutic effect, the reduction in **papules** was comparable to that of clindamycin.

- But it exhibited a **greater reduction of pustules** ($p > 0.05$) and the **Acne Severity Index** (ASI; $p > 0.05$).

- Patients in the **spironolactone group** were **more satisfied** than those in the clindamycin group.

- Only **minimal local side effects** were reported in both groups that did not require cessation of therapy.

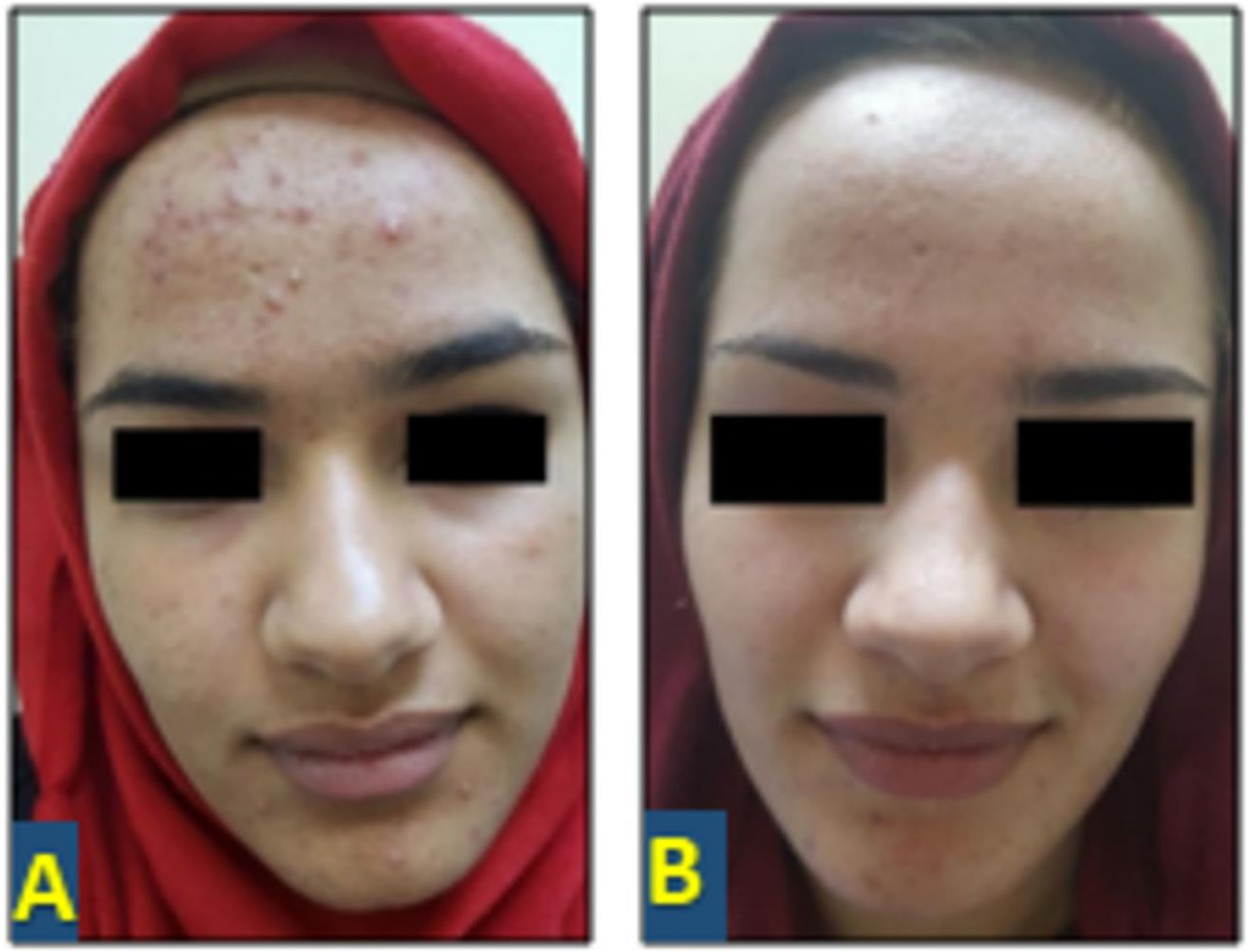


FIGURE 1: Seventeen-year-old female with moderate acne vulgaris: (A) before treatment and (B) twelve weeks after treatment with 2% topical spironolactone solution.

International Journal of Dermatology

Pharmacology and Therapeutics

Clascoterone: a new topical anti-androgen for acne management

Parvathy Santhosh, MD and Mamatha George, MD

Department of Dermatology, Malabar Medical College Hospital and Research Centre, Kozhikode, India

Correspondence
Parvathy Santhosh, MD
Department of Dermatology
Malabar Medical College Hospital and Research Centre
Kozhikode, Kerala, 673323,
India
E-mail: drparvathysanthosh@gmail.com

Conflict of interest: None.

Funding source: None.

doi: 10.1111/ijd.15752

Abstract

Clascoterone is an androgen receptor inhibitor which has been approved by the United States Food and Drug Administration for the topical treatment of acne vulgaris in patients 12 years of age and older. It competes with androgens, especially dihydrotestosterone, for androgen-receptor binding and limits their binding, thus inhibiting downstream signaling of pathways involved in the pathogenesis of acne. It inhibits androgen receptor-regulated gene transcription, and antagonizes lipid and inflammatory cytokine production in a dose-dependent manner in human primary sebocytes. Clascoterone is commercially available as 1% (10 mg/g) cream. Adverse effects of topical clascoterone are mild and infrequent, and are mostly limited to local skin reactions. Long-term safety studies have shown an absence of systemic antiandrogenic effects like reduced libido or feminization in male participants. Clascoterone seems a promising topical drug with a novel mechanism of action that could be added to the armamentarium of therapies for acne.

- **Clascoterone** is an **androgen receptor inhibitor** developed for the management of androgen-dependent skin disorders, including **acne vulgaris** and **androgenetic alopecia**.

- On August 26, 2020, **clascoterone cream 1%** received its first approval by the US-FDA (United States Food and Drug Administration) for the topical treatment of acne vulgaris in patients **12 years of age and older**.

Role of androgens in acne

- Skin can be considered an endocrine organ, as it is able to synthesize various hormones, and express receptors for those hormones.
- The **sebaceous gland** is the chief site of hormone biosynthesis in the skin, especially androgens.
- Androgen receptors (ARs) are expressed throughout the skin and are found in the **sebaceous glands and sebocytes**, **dermal fibroblasts**, and **dermal papilla cells**.

- Androgens, including testosterone, dehydroepiandrosterone sulfate (DHEAS), and dihydrotestosterone (DHT), have a role in regulating the genes responsible for sebaceous gland growth and sebum production.
- **Dihydrotestosterone (DHT)** is the **most active form**, involved in many androgen-related skin disorders like acne, hirsutism and androgenic alopecia.
- **DHT** has been demonstrated to be able to drive **immature sebocytes** to a **lipogenic differentiation process**.

Proposed mechanism of action of clascoterone in androgenetic alopecia

- Clascoterone **antagonizes dihydrotestosterone's (DHT)** negative effects on dermal papilla cells.

- It also diminishes the production of **prostaglandin D2** and **interleukin 6**, **regulates sebum secretion**, and **reduces hair miniaturization** and **dermal inflammation**.

- **Clascoterone** has been approved by the United States Food and Drug Administration for the **topical treatment of acne vulgaris** in patients **12** years of age and older.
- It competes with androgens, especially **dihydrotestosterone**, for **androgen-receptor binding** and **limits their binding**, thus inhibiting downstream signaling of pathways involved in the pathogenesis of acne.
- It inhibits androgen receptor-regulated gene transcription, and antagonizes lipid and inflammatory cytokine production in a **dose dependent manner** in human primary sebocytes.

- Clascoterone is commercially available as **1% (10 mg/g) cream**.
- Adverse effects of topical clascoterone are **mild** and **infrequent**, and are mostly limited to **local skin reactions**.
- Long-term safety studies have shown an **absence of systemic antiandrogenic effects** like reduced libido or feminization in male participants.

From The Medical Letter on Drugs and Therapeutics

Trifarotene (Aklief)—A New Topical Retinoid for Acne

The FDA has approved trifarotene 0.005% cream (Aklief – Galderma) for topical treatment of acne vulgaris in patients ≥9 years old. Trifarotene is the fourth topical retinoid to be approved in the US for treatment of acne; tretinoin (Retin-A, and others), adapalene (Differin, and generics), and tazarotene (Tazorac, and others) have been available by prescription for decades. Adapalene 0.1% gel has been available over the counter since 2016 for treatment of acne in patients ≥12 years old.[1]

Pronunciation Key

Trifarotene: trye far' oh teen **Aklief:** ack' leef

Topical Retinoids for Acne

Retinoids normalize keratinization and appear to have anti-inflammatory effects. Topical retinoids are often used for first-line treatment of acne, either alone (usually for primarily comedonal acne) or in combination with a topical antibiotic or benzoyl peroxide (usually for primarily inflammatory acne). Concurrent application of benzoyl peroxide can cause oxidation of tretinoin and loss of its effectiveness; other retinoids are more stable in the presence of benzoyl peroxide (**Table 1**). Whether any one retinoid is more effective than any other is unclear.[2,3]

Mechanism of Action

Retinoids bind to the retinoic acid receptor (RAR), which has 3 isoforms: RAR-α, RAR-β, and RAR-γ.[4] RAR activates genes that regulate immune modulation and cell differentiation, proliferation, and apoptosis. Trifarotene is the only available retinoid that is selective for RAR-γ, the most prevalent RAR isoform in the skin; whether this selectivity has any clinical significance is not known.[5]

Clinical Studies

In two 12-week, double-blind trials (PERFECT 1 and PERFECT 2), a total of 2420 patients ≥9 years old with moderate facial and truncal acne were randomized to receive once-daily treatment with trifarotene 0.005% cream or its vehicle alone. In both trials, trifarotene significantly improved the rates of facial and truncal treatment success (defined as clear or almost clear skin at week 12) and reduced

- The FDA has approved **trifarotene 0.005% cream** (**Aklief – Galderma**) for topical treatment of acne vulgaris in patients **9 years old**.
- Trifarotene is the fourth topical retinoid to be approved in the US for treatment of acne;
  - ✓Tretinoin (retin-a, and others)
  - ✓Adapalene (differin, and generics)
  - ✓Tazarotene (Tazorac, and others)

- Trifarotene 50 lg/g cream is a novel retinoid molecule approved for **once-daily** topical treatment of **facial** and **truncal** acne vulgaris.

- Trifarotene is the only available retinoid that is selective for **RAR-γ**, the **most prevalent RAR isoform in the skin**.

- Whether this selectivity has **any clinical significance** is not known.

Adverse Effects

- The most common adverse effects of trifarotene in the 12-week trials were **application-site irritation** (7.5% vs 0.3% with placebo), **sunburn** (2.6% vs 0.5%), and **application-site pruritus** (2.4% vs 0.8%).

- Most adverse effects were **mild** to **moderate** in severity.

- The *severity of skin irritation* generally **peaks during the first 4 weeks** of treatment and **declines thereafter**.

- Trifarotene 0.005% cream(Aklief) is effective and appears to be safe for treatment of **moderate** facial and truncal acne, but it is **expensive**.

- Skin irritation can occur.

- How trifarotene **compares** to other topical retinoids, including over-the-counter adapalene 0.1%gel, has not been established.

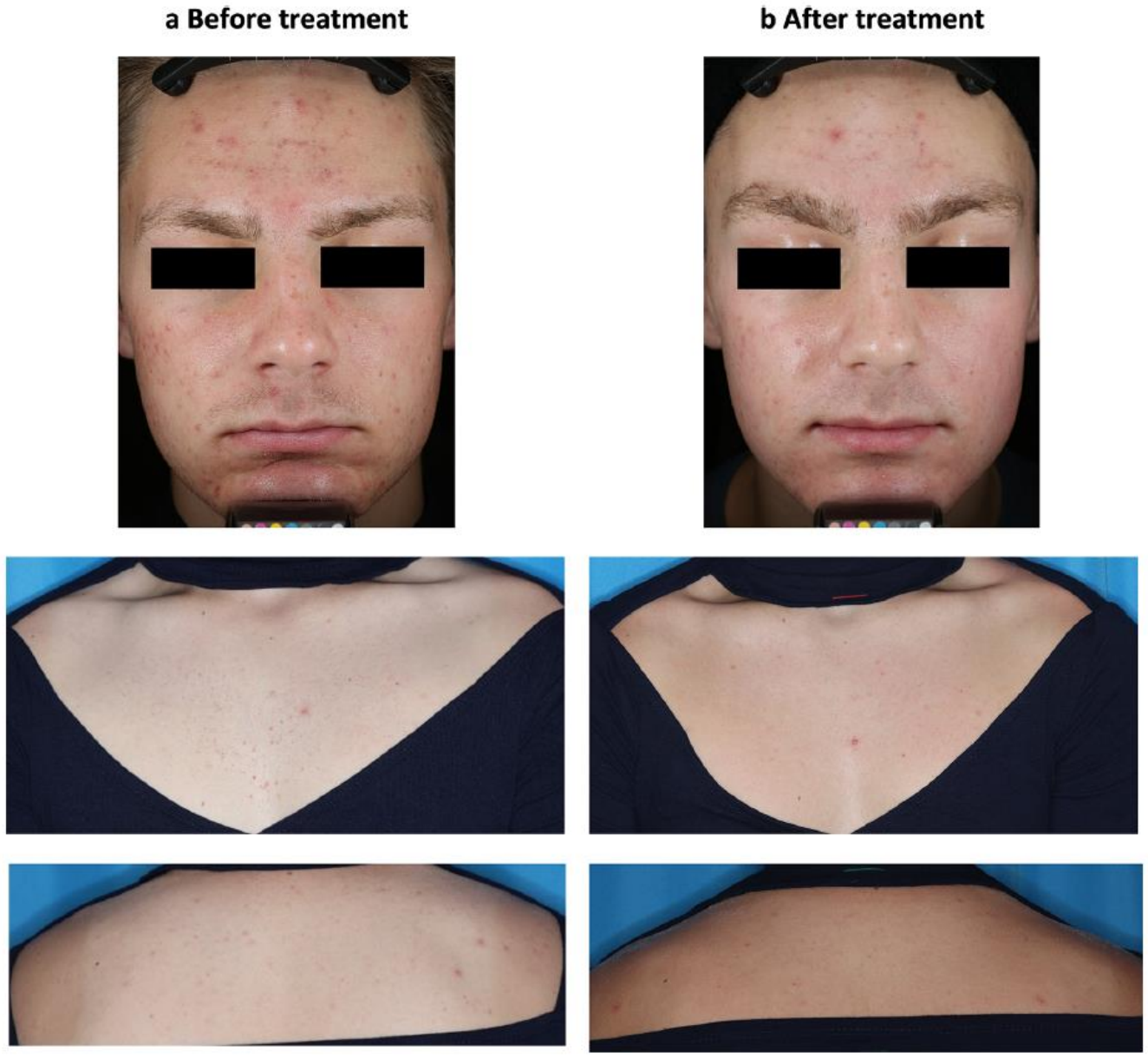


Fig. 2 Case 2: photographs of a 17-year old male subject before (**a**) and after (**b**) 12 weeks of treatment with trifarotene 50 μg/g cream on the face and trunk

ORIGINAL RESEARCH

Once-daily Dapsone 7.5% Gel for the Treatment of Acne Vulgaris in Preadolescent Patients:

A Phase IV, Open-label, 12-week Study

ABSTRACT

CLINICAL TRIALS ID: NCT02959970
BACKGROUND: Acne vulgaris in patients aged younger than 12 years is increasingly common and primarily noninflammatory (i.e., comedonal). Dapsone 7.5% gel is indicated for the topical treatment of acne vulgaris in patients nine years of age or older. **OBJECTIVE:** We sought to evaluate efficacy, safety, tolerability, and pharmacokinetics (PK) of once-daily topical dapsone 7.5% gel. **METHODS:** This was a Phase IV, multicenter, open-

by ANGELA YEN MOORE, MD; EDWARD L. LAIN, MD; AMY MCMICHAEL, MD; LEON KIRCIK, MD; ANDREA L. ZAENGLEIN, MD; ADELAIDE A. HEBERT, MD; and AYMAN GRADA, MD

Dr. Moore is with Arlington Center for Dermatology and Arlington Research Center in Arlington, Texas and Baylor University Medical Center in Dallas, Texas. Dr. Lain is with the Austin Institute for Clinical Research in Pflugerville, Texas. Dr. McMichael is with Wake Forest Baptist Health in Winston-Salem, North Carolina. Dr. Kircik is with Icahn School of Medicine at Mount Sinai in New York, New York. Dr. Grada is with Almirall, LLC in Exton, Pennsylvania. Dr. Zaenglein is with Penn State/Hershey Medical Center in Hershey, Pennsylvania. Dr. Hebert is with UTHealth McGovern Medical School in Houston, Texas.

J Clin Aesthet Dermatol. 2021;14(4):43–48.

- **Once-daily** topical **dapsone 7.5% gel** (**Aczone** gel 7.5%; Almirall, LLC, Exton, Pennsylvania) has been approved by the United States Food and Drug Administration (FDA) for acne vulgaris in patients aged nine years and older.

- In **2005**, topical dapsone **5%** gel was approved by the FDA for **twice-daily** topical treatment of acne vulgaris in patients aged **12 years and older.**

- Both topical formulations were developed because an earlier **oral formulation** of dapsone was associated with **systemic side effects**, such as **increased risk of hemolysis** in individuals with glucose-6-phosphate dehydrogenase (G6PD) defciency, which limited its usefulness for managing acne.

- The **topical formulations** have shown **lower** systemic drug absorption, **reduced potential for hemolytic anemia** in G6PD-defcient patients, and **enhanced safety and efficacy**.

- The **7.5%** concentration of topical dapsone gel was developed to offer **once-daily dosing**.

- Two pivotal, Phase III, multicenter, double-blind, randomized, vehicle-controlled trials supported the safety and efficacy of dapsone 7.5% gel for acne in patients aged **12 years and older** and led to its **2016 FDA approval** as a **once-daily** topical acne treatment in this population.

- The approval required a postmarketing study to assess safety, tolerability, and efficacy in patients aged 9 to 11 years.

- Subsequently, the indication for dapsone 7.5% gel was expanded to include patients aged **nine years and older**.

FIGURE 3. Representative photographs of an 11-year-old female patient with acne vulgaris with Fitzpatrick Skin Phototype VI; at baseline (Day 1), this patient had an IGA score of three points, with 59 total lesions, including 17 inflammatory lesions and 42 noninflammatory lesions. After 12 weeks of treatment with dapsone 7.5% gel, she had an IGA score of two points, with 38 total lesions, including 12 inflammatory lesions and 26 noninflammatory lesions. IGA: Investigator's Global Assessment, a five-point scale indicating facial acne severity (0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe)

Journal of
Medicinal Chemistry

Rational Drug Design of Topically Administered Caspase 1 Inhibitors for the Treatment of Inflammatory Acne

Jean-Francois Fournier, Laurence Clary, Sandrine Chambon, Laurence Dumais, Craig Steven Harris, Corinne Millois-Barbuis, Romain Pierre, Sandrine Talano, Etienne Thoreau, Jérome Aubert, Michèle Aurelly, Claire Bouix-Peter, Anne Brethon, Laurent Chantalat, Olivier Christin, Catherine Comino, Ghizlane El-Bazbouz, Anne-Laurence Ghilini, Tatiana Isabet, Claude Lardy, Anne-Pascale Luzy, Céline Mathieu, Kenny Mebrouk, Danielle Orfila, Jonathan Pascau, Kevin Reverse, Didier Roche, Vincent RODESCHINI, and Laurent François Hennequin

J. Med. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.jmedchem.8b00067 • Publication Date (Web): 12 Apr 2018

- Pro-inflammatory cytokines, including **TNFα**, **IL-1α** and **IL-1β** are considered to be involved for **follicular hyperkeratinisation** and the **inflammatory lesions** characteristic of acne.

- This cytokine usually exists in its pro-form which is cleaved to its active form by the aspartic cysteine protease **caspase-1** upon inflammatory stimulus.

- Recently, French and co-workers have demonstrated that the **active form of IL-1β** is abundant in human acne lesions.
- Moreover, they demonstrated that the production induced by P. Acnes of active IL-1β in monocytic lineage and in mice is dependant of the NLRP3/Caspase-1 inflammasome by P. Acnes exposed cells.
- This data indicates that **IL-1β** as a **novel potential therapeutic target in acne**, and therefore, we postulate that **inhibiting caspase-1**, could have a beneficial effect in inflammatory acne.

THANK YOU FOR YOUR ATTENTION

WWW.ARGANO.IR

TEHRAN UNIVERSITY OF MEDICAL SCIENCES

Janus