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A systematic review on role of Ivermectin in Rosacea

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Abstract

Rosacea is a chronic, recurrent condition that can present as a number of different cutaneous symptoms. The centrofacial inflammatory dermatosis condition has serious financial, physical, and psychological effects. There are numerous topical, oral, and systemic therapies available. However, rosacea therapy is still challenging. It is difficult for both patients and clinicians because to the complex character of the disease and the lack of a thorough grasp of the pathogenesis. Recently, three clinical trials have provided evidence for the effectiveness of topical ivermectin cream in treating rosacea. Ivermectin exhibits a broad-spectrum anti-parasitic action, specifically targeting Demodex mites residing in the pilosebaceous units of individuals with papulopustular rosacea. The application of ivermectin cream successfully eradicates these mites. Ivermectin reduces cellular and humoral immune responses and has anti-inflammatory properties as well. The formation of inflammatory lesions in rosacea appears to be mostly influenced by inflammatory processes. Additionally, there is some proof that it exhibits antimicrobial efficacy against Chlamydia trachomatis and Myobacterium tuberculosis. According to recent clinical research on rosacea, ivermectin reduced the number of inflammatory lesions more effectively than a vehicle and had excellent tolerability. Ivermectin exhibits antibacterial, antiparasitic, anti-inflammatory, and antimicrobial properties. This article offers a thorough analysis of papulopustular rosacea treatment options, including the newly popular usage of 1% ivermectin cream. Topical 1% cream has emerged as a unique treatment for papulopustular rosacea. Although ivermectin 1% is a clinically effective drug, poor adherence remains a concern owing to topical use. Finally, the agent has the potential to be a useful medicine when used alone or in combination with other agents.

Keyword: Papulopustular, Phymatous, Demox mite, Erythematotelangiectatic

INTRODUCTION

In the US, there are around 16 million people who have rosacea. Rosacea is a complicated condition that can have serious physical, mental, and financial effects. In various populations, the prevalence of rosacea ranges from 2 to 22%. [1]

Rosacea is a common chronic inflammatory skin disease that mostly affects adults over the age of 30, typically affects women, and gets worse with age [2, 3]. It is a condition that occurs on a regular basis and causes a variety of cutaneous manifestations. The most common locations are the cheeks, nose, forehead, chin, and central convexities of the face. Telangiectasias, pustules, papules, and erythema are examples of visible skin manifestations. [1]

Rosacea is known to have a negative effect on quality of life, is linked to depression, and can make social and professional life more difficult. In a recent survey of 1675 patients conducted by the National Rosacea Society, 68% of patients with mild rosacea reported that their general outlook on life had been negatively

impacted. This percentage rose to 87% and 95% for patients with moderate and severe symptoms, respectively, indicating that patients' emotional impact appears to increase as symptoms get worse. [6]

A review panel and consensus committee made up of 17 worldwide medical experts identified four kinds of rosacea. Similar patterns or clusters of symptoms or indications describe these subgroups. These are some: [4]

- **Subtype 1** –**Erythematotelangiectatic Rosacea:** The erythematotelangiectatic condition manifests with visible blood vessels, accompanied by persistent redness and flushing.

- **Subtype 2** – **Papulopustular Rosacea:** Papules and pustules that appear and disappear on the central part of the face are the primary symptom of this subtype. These lesions can also appear around the mouth, nose, and ear and may resemble acne. Telangiectases or persistent redness may also occur. The face frequently stings, burns, itches, and occasionally becomes red.

- **Subtype 3** – **Phymatous Rosacea:** Plaques, or skin thickening, and skin nodules are the primary symptoms of this subtype. The nose is typically the site of these symptoms, but the chin, forehead, cheeks, ears, and eyelids can also be affected. Telangiectases and an enlargement of the nose known as rhinophyma may also be present. Men are more likely to have this subtype, and if left untreated, it can get worse and cause severe facial disfigurement.

- **Subtype 4** – **Ocular Rosacea:** The primary regions of the eye affected by this particular subtype include the cornea, conjunctiva, and eyelids.. Eyelid crusts and scales, watery, bloodshot eyes, burning, stinging, and itching, light sensitivity, blurred vision, the sensation that something is in the eyes, and occasionally eye infections like styes are the primary symptoms.

PATHOPHYSIOLOGY

Individuals with Papulopustular Rosacea (PPR) are believed to possess an overactive innate immune system that is excessively responsive to various triggers, encompassing specific meals, UV rays, temperature fluctuations, heat, and stress. The immune response and lifestyle of individuals are also thought to influence the epidermal barrier effect and the inflammation seen in rosacea patients. It is widely acknowledged in the field that microbiological agents such as "Demodex folliculorum" and "Demodex brevis" may contribute to the development of PPR by triggering an inflammatory or immunological reaction.. [5, 6]

Combination therapy is frequently used for rosacea because of its multifactorial etiology. Each patient receives a treatment plan for rosacea that is tailored to their specific subtype or subtypes. There are medications, procedures, and ways to avoid the environment, all of which have varying degrees of efficacy. [7]. Rosacea, like other chronic diseases with varying symptoms, requires ongoing long-term treatment [5]. For rosacea there are very lees anti-inflammatory treatment choice and very few options exist with high efficacy and once daily dosing [3].

AVAILABLE TREATMENT [7]

Topical and systemic medications are currently available for rosacea treatment.

- Brimonidine and oxymetazoline can be utilized to treat refractory erythema.
- Topical azelaic acid, topical metronidazole, and topical ivermectin are all considered first-line treatments for inflammatory lesions like pustules and papules. Tragically (Unfortunately), treatment failure is normal with first-line medication. In these case, therapy like antibiotic-antibiotic combination may be beneficial. other tetracyclines and macrolides, like azithromycin, can also be used as adjuncts in the clinic. Isotretinoin is an agent that can be used as a last-line treatment.

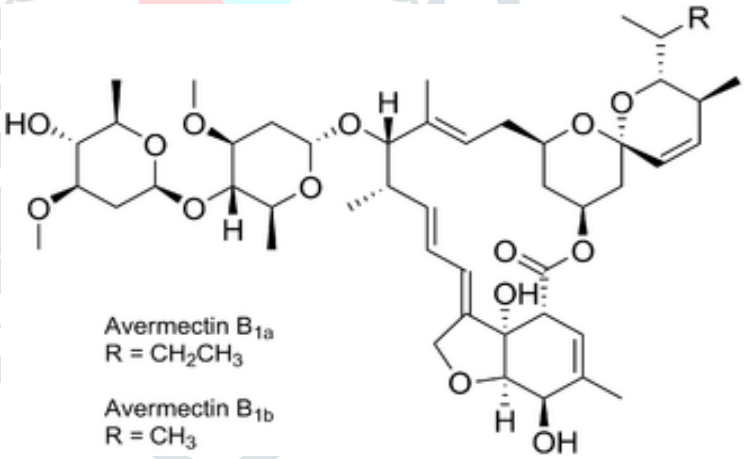
- However, phymatous rosacea should be treated with oral medications like doxycycline, tetracycline, isotretinoin.
- Visual rosacea can be treated with cyclosporine ophthalmic emulsion or oral doxycycline.
- Visual rosacea can be treated with cyclosporine ophthalmic emulsion or oral doxycycline in serious case.

IVERMECTIN

Ivermectin is a semi-synthetic macrocyclic lactone derivative of Avermectin family, which have both broad spectrum anti-parasitic activity and anti-inflammatory properties, may both contribute to its efficacy in treating rosacea [2]. A cream containing 1% ivermectin is used to treat papulopustular rosacea. Ivermectin has been shown to increase the levels of the anti-inflammatory cytokine IL-10, while simultaneously reducing the levels of the pro-inflammatory cytokines IL-1b and TNF-alpha. These cytokines are produced in response to lipopolysaccharide, which is known to cause inflammation. Similar to other macrolides, it has anti-inflammatory characteristics that are regarded to be the main cause of its therapeutic impact in rosacea. [3]

CHEMISTRY

In 1981, it was first introduced. The two B1a and B1b isoforms are the main structural components of ivermectin. Both of the isoforms are macrolides derived from Streptomyces avermitilis. Ivermectin's structural composition prevents it from passing through the blood-brain barrier in mammals and protects humans from numerous potential side effects. [7]

Structure	
Molecular Formula	$C_{48}H_{74}O_{14}$, H_2B_{1a} $C_{47}H_{72}O_{14}$, H_2B_{1b}
Molar Mass	875.106 g/mol 861.079 g/mol
Boiling point	940.4 ℃
Density	1.23 g/cm^3
Nature	Ivermectin is yellow or yellowish white crystalline powder, slightly hygroscopic

Solubility	Freely soluble in dichloromethane, soluble in ethanol, practically insoluble in water

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties [7]

Mechanism of action: Ivermectin has anti-inflammatory and anti-parasitic properties thanks to its dual mechanism of action. Prostaglandins, nitric oxide synthesis, and cytokine pathways are all affected by the anti-inflammatory effects, with IL-1b, IL-6, NF-kB, and LPS acting as major inhibitors. Ivermectin inhibits parasites by acting as an agonist on ligand-gated ion channels. Ivermectin blocks the transmission of GABA or glutamate between synapses after binding. These neurochannels are transcendently situated inside nerve and muscle cells. Through inhibition of the chloride channels that result, Demodex mites become paralyzed, and the parasite dies of starvation due to gastrointestinal dysfunction.

Pharmacokinetic properties [7]

Absorption: Ivermectin medication is available in oral and topical forms, but the most extensively researched treatment for papulopustular rosacea involves the use of topical ivermectin.

Distribution: It exhibits high lipid solubility and attaches to plasma proteins, allowing for extensive distribution across the body. Ivermectin has a half-life of around 6 days and achieves its peak plasma concentration within 10 hours when applied topically.

Metabolism: CYP3A4 metabolizes ivermectin predominantly in liver microsomes.

Elimination: Most of it is removed by feces and only 1% is excreted by the kidneys.

IVERMECTIN CREAM

Rosacea inflammation-related lesions are treated with the topical prescription drug ivermectin 1% cream.

MECHANSIM OF ACTION:

Its mode of action is uncertain, although it might involve both its anti-inflammatory and anti-parasitic effects on the Demox mite, which is found on the skin and may be a factor in the symptoms of rosacea. Ivermectin showed anti-inflammatory characteristics in immunopharmacological tests, specifically by inhibiting the production of inflammatory cytokines and increasing the production of interleukin 10, an anti-inflammatory cytokine. [5]

EFFICACY [8]

- Ivermectin 1% cream was given FDA approval in December 2014 to treat rosacea inflammation lesions. It is based on two pivotal Phase 3 trials that compared the effects of 1% ivermectin cream vs a vehicle control on patients with mild to moderate papulopustular rosacea. Significant changes included a reduction in the number of inflammatory lesions, an improvement in Investigator Global Assessment (IGA) scores, and a drop in health-related quality of life ratings.
- Once-daily ivermectin 1% cream significantly decreased the number of inflammatory lesions compared to twice-daily metronidazole 0.75% cream, which was proven to increase the number of IGA patients in a separate phase III study. Ivermectin 1% cream significantly increased patient satisfaction compared to metronidazole 0.75% cream. However, the choice to test metronidazole twice daily rather of a similarly efficient once-day regimen may have had an impact on these evaluations.

- There haven't been any efficacy studies comparing ivermectin cream 1% to common rosacea treatments like sulfacetamide/sulfur cream and azelaic acid 15% (both of which are thought to be more effective than metronidazole4), nor have there been any studies comparing ivermectin cream 1% to a common mix of oral and topical medications like metronidazole, azelaic acid, or (doxycycline or others).
- One advantage of using ivermectin 1% cream is the frequency of once-daily dose, which may increase adherence.

SAFETY [8]

- Ivermectin 1% cream was determined to have a low probability for side effects in vehicle-controlled phase III trials. There were a small number of participants who suffered mild to moderate adverse responses; these reactions were most frequently characterized by dry skin, pruritus, and skin burning.
- Comparative trials with ivermectin 1% cream and azelaic acid 15% gel or metronidazole 0.75% cream have demonstrated tendencies toward fewer side effects.
- There are no documented drug-drug or drug-food interactions with the usage of ivermectin 1% cream.

POTENTIAL IMPACT [8]

- Ivermectin 1% cream has been shown to be effective in treating papulopustular rosacea, although its comparative effectiveness to other treatment modalities for this condition is unknown.
- Ivermectin 1% cream should be taken into consideration when standard topical treatments or combinations of standard topical treatments and an oral antibiotic have failed to work or have been poorly tolerated.

TOLERABILITY [9]

Cream containing ivermectin is typically well tolerated. By 16 weeks, one in 77 patients will stop using ivermectin cream because to side effects. Less than 2% of patients will develop local side effects include dry skin, skin irritation, and burning skin sensation. Typically, these symptoms are momentary and will fade with time.

USES OF IVERMECTIN CREAM

Topical ivermectin is indicated for the treatment of inflammatory lesions of rosacea (Papulopustular) in adult patients.

DOSAGE AND ADMINISTRATION OF IVERMECTIN CREAM

Applying a thin layer of 1% Ivermectin cream to the affected facial areas (nose, forehead, chin, and cheeks) and avoiding the lips, eyes, mucosa and mouth is recommended in the USA and EU (including the UK) for the treatment of inflammatory lesions of rosacea. Ivermectin 1% cream is not intended for intravaginal, oral, or ocular usage; it should only be administered to facial skin. Ivermectin dosage does not need to be changed in elderly or renally compromised patients, although extreme hepatic impairment calls for caution. For information on the length of the treatment, the contraindications, the warnings, and other safety measures, review the local prescription information. [10]

CONCLUSIONS:

Clinically, it is challenging to treat rosacea. It is mostly a dermatosis of the face that is inflammatory and characterized by centrofacial erythema. There are currently numerous pharmacological options available for the therapy, the majority of which are given topically. Patients with rosacea are intrinsically susceptible to topical treatments and may have uncomfortable symptoms. Patient disobedience results in higher healthcare

costs. Ivermectin 1%, which can be applied once daily, is a relatively pleasant, effective, and safe medication for the treatment of rosacea. The medication is incrementally economical as a first therapeutic approach. Ivermectin 1% frequently outperforms other formulations in clinical trials.Future research should concentrate on increasing patient adherence to rosacea treatment.

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