Dermatology Practical & Conceptual

Efficacy of Topical Dapsone 5% Gel for the Treatment of Erythematotelangiectatic Rosacea: New Treatment Option With Old Drug

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ABSTRACT

Introduction: Many topical drugs are used in the treatment of erythematotelangiectatic rosacea (ETR). However, dapsone 5% gel has never been used in ETR to date.

Objectives: To evaluate the efficacy of dapsone 5% gel as a new treatment option for ETR.

Methods: Thirty-five patients with ETR were included in the study. Diagnosis was made with National Rosacea Society criteria. Dapsone 5% gel was used topically twice a day for 12 weeks. Investigator Global Assessment (IGA) 4-point scale (0 → Clean, 1 → mild, 2 → moderate, 3 → severe, 4 → very severe), Visual Analogue Scale (VAS) and Dermatology Life Quality Index (DLQI) were used for evaluation (at baseline, 2nd, 6th, and 12th weeks).

Results: IGA scores among baseline (2 → 62.9%, 3 → 34.3%, 4 → 2.9%) and 2nd (1 → 14.3%, 2 → 77, 1%, 3 → 8.6%), 6th (1 → 45, 7%, 2 → 54.3%) and 12th weeks (1 → 62.9%, 2 → 37.1%) were found to be statistically significant (P < 0.001). Median VAS scores among baseline (median = 7 [5-9]) and 2nd (median=5 [3-8]), 6th (median=5 [3-6]) and 12th weeks (median = 4 [2-6]) were statistically significant (P < 0.001). Median DLQI scores among baseline (median = 8 [6-14]) and 2nd (median = 5 [3-11]), 6th (median = 5 [3-11]) and 12th weeks (median = 4 [2-9]) were statistically significant (p<0.001). Concurrent systemic disease was a risk factor for poor treatment response (P = 0.034). Mild irritation was observed in 3 patients (8.5%) during treatment.

Conclusions: Dapsone 5% gel was effective and well tolerated in ETR treatment.

Introduction

Rosacea is a chronic, recurrent, inflammatory skin disease localized in the centrofacial region, characterized by transient flushing, persistent erythema, telangiectasia, and papulopustular lesions. Rosacea affects 5–10% of the population and is usually seen after the third decade of life [1,2]. Rosacea can be classified into four subtypes; erythematotelangiectatic, papulopustular, phymatous, and ocular rosacea [3]. Erythematotelangiectatic Rosacea (ETR) is the most common and has the most prominent vascular component among the other subtypes [4].

An exaggerated innate immune response and neurovascular dysregulation are the two main pathophysiological factors in the emergence of ETR [5]. Bacterial proteases, products of *Demodex folliculorum* and *Staphylococcus epidermidis*, heat, stress, irritants, ultraviolet B radiation, products of cellular metabolism such as reactive oxygen species (ROS), other known triggers such as spicy food, strenuous exercise activate certain specific receptors and channel over the skin. All of these triggers lead to the secretion of proinflammatory cytokines, chemokines, proteases, and pro-angiogenic factors [1,6]. These factors cause inflammation in the dermis, which play a major role in the occurrence of rosacea [6]. Density of inflammation in the dermis varies in rosacea between individuals and over time. In the ETR subtype of rosacea, inflammation is seen in both perivascular and interstitial regions [5]. Cytokines such as vascular endothelial growth factor (VEGF), and proangiogenic factors contribute to angiogenesis by both direct and indirect mechanisms [7]. Many evidences shows that there is an association between inflammation and angiogenesis [6]. The molecular mechanisms underlying the relationship between chronic inflammation and angiogenesis in rosacea have been clearly demonstrated [6].

Dapsone is an antibiotic which is a member of the sulfone family [8]. Dapsone has anti-inflammatory activity in addition to its antibiotic activity. Dapsone also blocks angiogenesis by inhibiting some molecular mechanisms such as VEGF formation [9]

In the light of this knowledge, we used topical dapsone to treat ETR by targeting chronic inflammation and angiogenesis. The absence of a study in the literature investigating the effectiveness of topical dapsone on ETR makes our study a first.

Objectives

In this study, we primarily evaluated the efficacy of dapsone 5% gel in treatment of ETR and additionally aimed to determine the side effects during treatment in this patient's group.

Methods

Study Design and Patient Population

This is a single-centre prospective experimental clinical study. A total of 35 patients with ETR who applied to the outpatient clinic between March and November 2022 were enrolled in the study.

Diagnosis, Classification, and Staging of the Disease

Rosacea diagnosis, classification, and staging was done according to the criteria of the National Rosacea Society Expert Committee [10].

Inclusion Criteria of the Patients

Patients over 16 years old diagnosed with ETR by at least two dermatologists were included in the study. The diagnosis of rosacea was made after comprehensive clinical and dermoscopic evaluation, including histopathologic evaluation when needed.

Exclusion Criteria of the Patients

The exclusion criteria included pregnancy, lactation, immunosuppression, glucose 6 phosphate dehydrogenase enzyme deficiency, anemia, and methemoglobinemia.

Ethics Committee Approval and Informed Consent

Approval of the Ethics Committee of the Non-Invasive Clinical Research was taken for this study (Decision number / year, E-60116787-020-258589 / 2022). Informed consent was taken for all of the patients. This study has been conducted in accordance with the principles of the Declaration of Helsinki.

Treatment Method

Only topical dapsone 5% gel was used in the treatment of ETR without any topical or systemic agent.

Dapson 5% Gel Application

Dapson 5% gel was applied on the facial lesion (right and left cheeks, forehead, chin and nose) as a thin layer twice a day for 12 weeks by sparing the perioral, periorbital regions.

Determination of Clinical Status and Treatment Efficacy

Patients underwent 4 visits: a baseline evaluation and visits at weeks 2, 6, and 12. Clinical status of the patients and treatment efficacy were evaluated by Investigator's Global Assessment (IGA), Visual Analogue Scale (VAS), and and Dermatology Life Quality Index (DLQI) scales.

The IGA was a grading method used by the physician to show the severity of skin disease. Zero to 4 point scale

was used for determining the severity of ETR and clinical status for each patient (Grade; 0 → Clean, 1 → mild, 2 → moderate, 3 → severe, 4 → very severe) [11-13].

To assess subjective disease perception, participants were asked to mark on a 10-cm continuous VAS how disturbing their rosacea had been during the past 4 weeks. The place of every mark on VAS was measured to 1 mm and was scored from 0 to 10 (0 = not at all disturbing; 10 = maximally disturbing) [14].

The DLQI is planned to evaluate the health-related quality of life of adult patients complaining of skin disease. The DLQI occurs 10 questions regarding patients' perception of the effect of skin diseases on different aspects of their health-related quality of life over the last week. Each question is scored on a four-point Likert scale (Very much = 3, lot = 2, little = 1, not at all = 0, not relevant = 0, question unanswered = 0). The DLQI questionnaire (10 questions, maximum 30 points) was administered to all patients at baseline and at each visit [15].

Treatment Success

Treatment success was accepted as an IGA score of 0 or 1, or a two-point reduction in score.

Adverse Events

Adverse events were recorded at each visit.

Statistical Analysis

Analyses were performed with IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp). Continuous variables were stated as median, minimum, maximum, descriptive values, while categorical variables were stated as number and frequency. In addition to qualitative statistical methods, the Wilcoxon signed-rank test was used to compare the quantitative data. The risk factors affecting the efficacy of therapy were established by using logistic regression analysis. The statistical significance was accepted as $P < 0.05$.

Table 1. Baseline demographic and clinical characteristics of the patients.

Parameters	N (%) or Median (Min-Max)
Age	38 (19-62)
Gender	
• Male	13 (37.1)
• Female	22 (62.9)
Onset age of rosacea	34 (16-57)
Disease duration, month	4 (2-10)
Rosacea involvement site	
• Cheek	35 (100)
• Forehead	15 (42.9)
• Nose	24 (68.6)
• Chin	8 (22.9)
Smoking	
• No	24 (68.6)
• Yes	11 (31.4)
Alcohol	
• No	19 (54.3)
• Yes	16 (45.7)
Triggering factors[a]	34 (97.1)
Skin type	
• Type I	15 (42.9)
• Type II	19 (54.3)
• Type III	1 (2.9)
Systemic disease[b]	11 (31.4)
Additional dermatological disease	19 (54.3)
Systemic drug use	9 (25.7)

[a]Sunlight exposure, psychological stress, warm environment, hot beverages, spicy food alcohol intake, strenuous exercise, cold weather.

[b]Cardiovascular disease, diabetes mellitus, hypertension, lung diseases, endocrine and metabolic problems… etc. Hypothyroidism is the most common (11.4%).

Results

Patient Data Analysis

The mean age of ERT onset was 34. Female patients were more common (female to male ratio:1.7). All patients had cheek involvement. Almost all patients had a triggering cause. Detailed baseline demographic and clinical characteristics of the patients have been shown in Table 1.

Response to Treatment

While all patients had an IGA score of 2 or higher at baseline, there was no patient with an IGA score of 3 or 4 at the 12th week of treatment (Table 2). The decrease in IGA score during and at the end of the treatment was statistically significant according to baseline ($P < 0.001$). Treatment success rate was 62.9% at the end of treatment. The clinical improvement in ERT with dapsone 5% gel treatment in two different patients has been shown in Figure 1.

VAS score started to decrease after the 2nd week of treatment and reached lower values at the end of the treatment (Table 3). The decrease in VAS score during and at the end of the treatment was statistically significant according to baseline ($P < 0.001$).

The increase in DLQI after using topical dapsone 5% gel treatment was statistically significant ($P < 0.001$) (Table 4).

Table 2. Investigators Global Assessment score of erythematotelangiectatic rosacea patients in Baseline and Second, Sixth and Twelfth weeks of treatment.

IGA-ETR scale		Baseline	2nd week	6th week	12th week
Clinical Grade	Score	N (%)	N (%)	N (%)	N (%)
Clean	0	0 (0)	0 (0)	0 (0)	0 (0)
Mild	1	0 (0)	5 (14,3)	16 (45,7)	22 (62,9)
Moderate	2	22 (62,9)	27 (77,1)	19 (54,3)	13 (37,1)
Severe	3	12 (34,3)	3 (8,6)	0 (0)	0 (0)
Very Severe	4	1 (2,9)	0 (0)	0 (0)	0 (0)
P		-	<0,001	<0,001	<0,001

ETR = erythematotelangiectatic rosacea; IGA = Investigators Global Assessment.

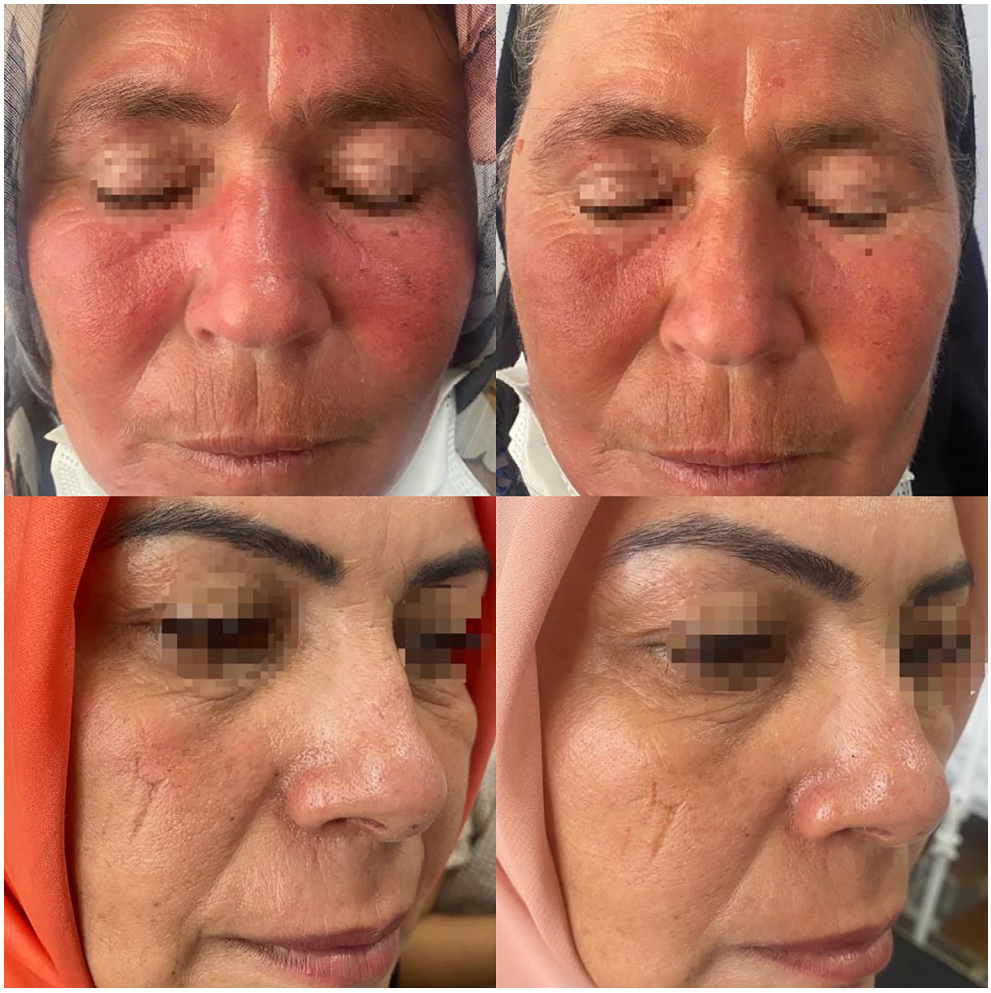

Figure 1. Clinical improvement in erythematotelangiectatic rosacea with Dapsone 5% gel treatment. Clinical improvement is seen from grade 3 to 2 in the first patient and from grade 2 to 1 in the second patient.

Adverse Events

Mild adverse events were observed in 3 patients (totally 8.5%, itching in two, burning in one) during treatment.

Risk Factor Analysis

The absence of systemic disease increased the success rate of the treatment (P = 0.034) (Table 5).

Conclusions

The current study demonstrated that dapsone 5% gel was effective in the treatment of ETR. IGA scores and patient-assessed VAS scores showed a significant improvement and good results during and after dapsone 5% gel treatment in patients with ETR.

Table 3. Visual Analog Scale scores of the patients at Baseline and Second, Sixth and Twelfth weeks of treatment.

VAS scores	Baseline Median (Min-Max)	2. week Median (Min-Max)	6. week Median (Min-Max)	12. week Median (Min-Max)
VAS	7 (5-9)	5 (3-8)	4 (3-6)	4 (2-6)
p	-	<0.001	<0.001	<0.001
VAS-burning sensation	5 (2-9)	3 (1-7)	4 (1-7)	3 (1-6)
p	-	<0.001	<0.001	<0.001
VAS-erythema	6 (4-10)	4 (2-7)	4 (2-6)	3 (2-6)
p	-	<0.001	<0.001	<0.001
VAS-pruritus	2 (1-9)	3 (0-6)	2 (0-5)	2 (0-4)
p	-	0.232	0.018	0.005
VAS-edema	2 (1-6)	2 (0-6)	2 (0-4)	2 (0-5)
p	-	0.080	0.005	0.005

VAS = Visual Analog Scale.

Table 4. Dermatology Life Quality Index (DLQI) score of the patients at Baseline and Second, Sixth and Twelfth weeks of treatment.

	Baseline Median (Min-Max)	2. week Median (Min-Max)	6. week Median (Min-Max)	12. week Median (Min-Max)
DLQI score	8 (6-14)	5 (3-11)	5 (3-11)	4 (2-9)
P	-	<0.001	0.001	<0.001

DLQI = Dermatology Life Quality Index.

Table 5. Risk factors analysis for treatment efficacy.

Variables	Odds ratio (95% CI)	P
Age	0.96 (0.90-1.02)	0.153
Gender	0.64 (0.15-2.74)	0.550
Onset age of rosacea	0.96 (0.90-1.02)	0.214
Disease duration	0.81 (0.58-1.12)	0.197
Smoking	0.53 (0.11-2.49)	0.417
Alcohol	0.63 (0.16-2.52)	0.509
Concomitant systemic disease	**5.25 (1.13-24.42)**	**0.034**
Additional dermatologic diseases	2.70 (0.64-11.47)	0.178
Skin type	0.49 (0.12-1.98)	0.316

CI = confidence interval.

Furthermore, burning sensation and erythema were significantly reduced after dapsone 5% gel treatment even in the second week compared to baseline. Moreover, the side effects of the drug were subtle, like only mild irritation. This result showed that the tolerability of dapsone 5% gel was also very well.

Rosacea treatment starts with avoidance of triggers and use of mild cleansing and moisturizing agents, as well as photoprotection [3]. Topical, oral medications, laser or light-based treatments, and injection therapies are used alone or in combination in the treatment of rosacea [3,16,17]. Metronidazole, azelaic acid; sulfacetamide/sülfür, brimonidine, oxymetazoline have been approved by FDA in the treatment of erythema in rosacea [3,18]. Vascular laser and light-based therapies (pulsed dye laser, intense pulsed light, Nd: YAG laser) can be used for erythema and telangiectasia as a second step or combined with topical therapy [3,5,18].

Various therapeutic strategies may be needed to achieve a better clinical outcome in patients with rosacea because of an overlapping clinical feature of the subtypes [3]. Physicians should individualize the treatment according to the subtype and severity of the disease, clinical grade of inflammation and erythema, presence of telangiectasia, triggering factors, and comorbidities. The efficacy of combined treatments in rosacea has been shown to be better than monotherapy [19-23]. Topical treatments are usually preferred in ETR [3]. Topical treatments were generally used for an average of 12-16 weeks in the studies [3,23,24]. We used topical dapsone 5% gel for 12 weeks. We found that the success rate of treatment was 14.3% at the end of the 2nd week, 45.7%

at the 6th week, and 62.9% at the end of the 12th week. Overall treatment success rate in rosacea has been reported to range from 31.9 to 80.3%, similar to our study result with a quite acceptable success rate at the 12th week [19-22].

In patients who recovered, treatment was discontinued at week 12, while in patients who did not improve, the duration of treatment was extended for another 4 weeks or alternative treatment was started. There is no consensus in the literature for the duration and certain algorithm of treatment. Furthermore, the expected duration of maintenance treatment still remains unclear.

Regardless of topical or systemic treatment, adverse events are inevitable. It has been reported that the rates of adverse events are observed higher in combined treatments than topical treatments alone [17,19,23].

Brimonidine tartrate gel is the first medication approved by the FDA for the topical treatment of persistent facial erythema associated with rosacea, and has been using in the first line treatment of ETR for years [5,25]. The rates of adverse events have been reported to range from 6 to 14% for various concentrations of brimonidine tartrate [17]. When its use is extended, these rates increase to 11-19% [17]. The most commonly reported side effects are irritation, flushing, worsened erythema, burning sensation, and pruritus [17]. Many case reports of contact dermatitis and rebound erythema have been documented with regard to brimonidine use [17,26-28].

Oxymetazoline side effects are reported as dryness (7%), tingling sensation (3%), and papule formation (3%) [23].

Metronidazole is generally well tolerated. Side effects such as burning and stinging, dryness, redness, pruritus, and worsening of erythema were reported to be seen less than 5% of the patients [2].

The common side effects reported during the treatment of dapsone 5% gel in acne are dryness, erythema, and burning sensation, along with systemic symptoms such as rhinitis, pharyngitis, upper respiratory tract infection, and headache [24]. In our study, adverse events were mild, transient, and skin-limited, seen with a lower rate. There was no worsening of erythema during treatment and no rebound erythema was observed after treatment in any of our patients.

Dapsone 5% gel has only been used in the papulopustular subtype of rosacea to date, and its efficacy has been reported to be as much as metronidazole 0.75% gel [29]. As far as we know, this is the first study in which dapsone 5% gel was used in the treatment of ETR.

The study has also some limitations. It was conducted in a single center. The study population was homogenous, limiting the external validity of the results. The sample size was small, the follow-up period was relatively short, and there was no control group.

To sum up, using dapsone 5% gel was safe, effective, and well tolerated in the treatment of ETR. We conclude that dapsone 5% gel treatment in ETR can be acceptable. However, we think that further multicentered, randomized, controlled, large-scale studies with longer follow-up period are needed.

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