Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL 12, ISSUE 3, 2021

Comparative Efficacy of Topical Cyclosporine versus Oral Doxycycline in Ocular Rosacea: A Randomized Controlled Trial at the Oculo-Dermatology Interface

Dr. Lingamallu Swapna[1], Dr. Gandi Jyothi[2]

[1]*Assistant Professor of Dermatology,* Mayo Institute of Medical Sciences

[2]*Assistant Professor of Ophthalmology,* Kanti Devi Institute of Medical Sciences

Abstract

Background: Ocular rosacea is a common and potentially sight-threatening condition at the interface of dermatology and ophthalmology. While both topical cyclosporine and oral doxycycline are used in its management, high-quality comparative evidence is lacking.

Objective: To compare the efficacy and tolerability of topical cyclosporine 0.05% versus oral doxycycline 40 mg daily in patients with moderate-to-severe ocular rosacea.

Methods: A prospective, randomized, single-blind, parallel-group controlled trial was conducted at a tertiary care centre between March 2020 and February 2021. Adults (N = 76) with moderate-to-severe ocular rosacea were randomized 1:1 to receive topical cyclosporine twice daily or oral doxycycline 40 mg once daily for 12 weeks. The primary outcome was change in Ocular Surface Disease Index (OSDI) score. Secondary outcomes included corneal fluorescein staining, tear break-up time (TBUT), Schirmer's test, meibomian gland function, and adverse events. Analysis was by intention-to-treat.

Results: At week 12, cyclosporine demonstrated superior OSDI reduction (-27.8 ± 10.2 vs. -19.2 ± 9.8, mean difference: -8.6, 95% CI: -13.2 to -4.0, $p < 0.001$). Corneal staining improved more with cyclosporine (-1.9 ± 0.6 vs. -1.4 ± 0.5, $p = 0.002$), as did TBUT (+3.8 ± 1.6 vs. +2.6 ± 1.4 seconds, $p = 0.001$). Treatment success was achieved by 73.7% versus 50.0% (OR = 2.80, $p = 0.03$). Local stinging was more common with cyclosporine (36.8% vs. 10.5%, $p = 0.007$), while gastrointestinal adverse events (31.6% vs. 5.3%, $p = 0.003$) and photosensitivity (10.5% vs. 0%, $p = 0.04$) were more frequent with doxycycline.

Conclusions: Topical cyclosporine 0.05% is superior to oral doxycycline 40 mg in improving ocular signs and symptoms in moderate-to-severe ocular rosacea, with a favourable systemic safety profile. These findings support topical cyclosporine as a first-line therapeutic option.

Keywords: Ocular rosacea, cyclosporine, doxycycline, meibomian gland dysfunction, randomized controlled trial, oculo-dermatology, dry eye disease, inflammatory eye disease

Introduction

Ocular rosacea represents a significant clinical challenge at the intersection of dermatology and ophthalmology, affecting an estimated 58% to 87% of patients with cutaneous rosacea [1, 2]. This chronic inflammatory condition of the ocular surface and adnexa manifests with a spectrum of signs and symptoms including meibomian gland dysfunction, blepharitis, conjunctival hyperaemia, foreign body sensation, tearing, burning, and photophobia [3]. If inadequately treated, ocular rosacea can progress to corneal involvement, including superficial punctate keratitis, marginal infiltrates, vascularisation, and potentially sight-threatening corneal scarring and perforation [4, 5]. The pathogenesis of ocular rosacea is multifactorial, involving dysregulation of the innate immune system,

abnormal Toll-like receptor-2 expression, overproduction of pro-inflammatory cytokines including interleukin-1β, tumour necrosis factor-alpha, and matrix metalloproteinases, as well as meibomian gland dysfunction leading to evaporative dry eye disease [6, 7].

The management of ocular rosacea has traditionally relied upon systemic tetracycline-class antibiotics, particularly doxycycline, which exert their therapeutic effects through both antimicrobial and, more importantly, anti-inflammatory mechanisms [8]. Doxycycline inhibits matrix metalloproteinases, reduces pro-inflammatory cytokine production, decreases neutrophil chemotaxis, and stabilises the tear film lipid layer [9]. Oral doxycycline at sub-antimicrobial doses (40 mg daily) has demonstrated efficacy in reducing ocular inflammation and improving meibomian gland function [10]. However, systemic therapy is associated with potential adverse effects including gastrointestinal disturbances, photosensitivity, oesophageal irritation, and concerns regarding antibiotic resistance [11, 12].

In parallel, topical cyclosporine A 0.05% ophthalmic emulsion (Restasis®) has emerged as an alternative therapeutic strategy. Cyclosporine, a calcineurin inhibitor, exerts its immunomodulatory effects by inhibiting T-cell activation and subsequent release of pro-inflammatory cytokines [13]. Topical cyclosporine has been shown to improve tear production, reduce conjunctival inflammation, and enhance goblet cell density in patients with dry eye disease [14]. Emerging evidence suggests that topical cyclosporine may also be beneficial in ocular rosacea by reducing ocular surface inflammation and improving meibomian gland function [15, 16].

Despite the availability of these therapeutic options, there is a paucity of high-quality randomized controlled trial evidence directly comparing the efficacy of topical cyclosporine versus oral doxycycline in the management of ocular rosacea [17]. Most existing studies have evaluated these agents in isolation or in combination, without rigorous head-to-head comparison using validated ophthalmological outcome measures [18]. Furthermore, the optimal treatment algorithm for ocular rosacea remains unclear, with significant variation in clinical practice between dermatologists and ophthalmologists [19].

The present study was designed to address this evidence gap through a prospective, randomized, single-blind, parallel-group clinical trial comparing the efficacy and tolerability of topical cyclosporine 0.05% ophthalmic emulsion versus oral doxycycline 40 mg daily over a 12-week treatment period in patients with moderate-to-severe ocular rosacea. The rationale for this investigation is anchored in the need for evidence-based guidance to inform clinical decision-making at the oculo-dermatological interface, optimise therapeutic outcomes, and minimise adverse effects.

Objectives

1. To compare the efficacy of topical cyclosporine 0.05% versus oral doxycycline 40 mg daily in improving ocular signs and symptoms in patients with moderate-to-severe ocular rosacea at 12 weeks.
2. To evaluate the impact of both treatment modalities on meibomian gland function and tear film stability.
3. To assess the effect of treatment on cutaneous rosacea severity.
4. To document and compare the safety and tolerability profiles of both interventions.
5. To explore patient-reported outcomes and treatment satisfaction with each regimen.

Materials and Methods

Study Design and Setting

This was a prospective, randomized, single-blind, parallel-group, active-comparator clinical trial conducted at a tertiary care centre between March 2020 and February 2021. The study protocol was approved by the Institutional Ethics Committee (approval number IEC/2020/156) and was registered prospectively with the Clinical Trials Registry. The trial was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines and the Declaration of Helsinki.

Participants

Consecutive adult patients (aged ≥18 years) attending the combined oculo-dermatology clinic with a confirmed diagnosis of ocular rosacea were screened for eligibility. The diagnosis of ocular rosacea was established based on the presence of characteristic ocular signs including meibomian gland dysfunction (meibomian gland dropout and/or secretion quality grading ≥2), lid margin telangiectasia, blepharitis, and conjunctival hyperaemia, in association with cutaneous rosacea [5, 9]. Inclusion criteria comprised: (a) age ≥18 years; (b) confirmed diagnosis of ocular rosacea; (c) Ocular Surface Disease Index (OSDI) score ≥23 (moderate-to-severe symptoms); (d) corneal fluorescein staining score ≥2 (on a 0–4 scale); and (e) willingness to provide informed consent and comply with study procedures.

Key exclusion criteria included: (a) known hypersensitivity to cyclosporine or doxycycline; (b) current use of topical or systemic antibiotics, corticosteroids, or immunomodulatory agents within the past 4 weeks; (c) active ocular infection; (d) pregnancy or lactation; (e) history of herpes simplex keratitis; (f) significant renal or hepatic impairment; (g) photosensitivity disorders; and (h) concurrent use of medications with potential interactions with doxycycline (including isotretinoin, warfarin, and oral contraceptives).

Randomization and Blinding

Eligible participants were randomly allocated in a 1:1 ratio to receive either topical cyclosporine 0.05% ophthalmic emulsion twice daily or oral doxycycline 40 mg once daily. Randomization was performed using a computer-generated sequence with variable block sizes of 4 and 6, stratified by baseline OSDI score (23–35 vs. >35). The allocation sequence was concealed using sequentially numbered, opaque, sealed envelopes. Due to the inherent differences in route of administration, the study was single-blinded, with outcome assessors (ophthalmologist and dermatologist) masked to treatment allocation. Participants were not masked to their treatment assignment.

Interventions

Group A (Cyclosporine Group)

Participants received topical cyclosporine 0.05% ophthalmic emulsion (Restasis®, Allergan) one drop in each eye twice daily (approximately 12 hours apart) for 12 weeks. Participants were instructed to instill the drop after gently shaking the vial and to avoid touching the tip to the eye or any surface.

Group B (Doxycycline Group)

Participants received oral doxycycline 40 mg (sub-antimicrobial dose) once daily (Periostat®, Galderma) for 12 weeks. Participants were instructed to take the medication with a full glass of water

at least one hour before or two hours after meals to optimize absorption and minimize gastrointestinal side effects.

All participants were permitted to use preservative-free artificial tears as needed for symptomatic relief. No other topical or systemic anti-inflammatory or antimicrobial therapy was permitted during the study period. Concurrent dermatological management for cutaneous rosacea was standardized across both groups according to institutional guidelines.

Outcome Measures

Primary Outcome

The primary outcome was the change in OSDI score from baseline to week 12. The OSDI is a validated 12-item questionnaire assessing ocular symptoms, vision-related function, and environmental triggers, with scores ranging from 0 to 100 (higher scores indicate greater symptom burden).

Secondary Outcomes

Secondary outcomes included: (a) change in corneal fluorescein staining score (National Eye Institute grading system, 0–4 scale); (b) change in tear break-up time (TBUT) measured in seconds; (c) change in Schirmer's test (mm of wetting at 5 minutes); (d) change in meibomian gland secretion quality (0–3 scale); (e) change in lid margin telangiectasia severity (0–3 scale); (f) change in Clinical Erythema Assessment (CEA) score for cutaneous rosacea; (g) proportion of patients achieving treatment success (defined as ≥30% reduction in OSDI score and ≥1-grade reduction in corneal staining); and (h) incidence of treatment-emergent adverse events.

Assessments were performed at baseline, week 4, week 8, and week 12 by masked outcome assessors.

Sample Size Calculation

Based on previously reported data [16, 17], the mean OSDI score in patients with moderate-to-severe ocular rosacea was estimated at 45 ± 12. A clinically meaningful difference of 10 points in OSDI change between groups was considered relevant. With 80% power and a two-sided alpha of 0.05, a minimum of 32 patients per group was required. Accounting for a 15% attrition rate, we aimed to enroll 38 patients per group (total 76 patients).

Statistical Analysis

Data were analysed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Intention-to-treat (ITT) analysis was performed including all randomized patients. Missing data were handled using multiple imputation. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR). Within-group comparisons were performed using paired t-tests or Wilcoxon signed-rank tests. Between-group comparisons were performed using independent samples t-tests or Mann-Whitney U tests. Categorical variables were compared using Chi-square or Fisher's exact tests. Repeated measures analysis of variance (ANOVA) was employed for longitudinal comparisons. Statistical significance was set at $p < 0.05$.

Ethical Considerations

The study was approved by the Institutional Ethics Committee and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. An independent Data Safety Monitoring Board was established to oversee participant safety.

Results

Participant Flow and Baseline Characteristics

A total of 94 patients were screened for eligibility between March 2020 and February 2021. Of these, 76 patients met the inclusion criteria and were randomized: 38 to the cyclosporine group and 38 to the doxycycline group. At week 12, 71 patients (93.4%) completed the trial: 36 (94.7%) in the cyclosporine group and 35 (92.1%) in the doxycycline group. The reasons for discontinuation were adverse events (n = 2 in doxycycline group, n = 1 in cyclosporine group), loss to follow-up (n = 1 in each group), and non-adherence (n = 1 in cyclosporine group).

Baseline demographic and clinical characteristics were well-balanced between the two groups (Table 1). The mean age was 48.6 years (SD = 13.2), and females constituted 67.1% (n = 51) of the cohort. The mean duration of ocular rosacea symptoms prior to enrolment was 3.8 years (SD = 2.4). Baseline OSDI scores (46.2 ± 11.8 vs. 45.6 ± 12.1, p = 0.82) and corneal staining scores (2.8 ± 0.7 vs. 2.9 ± 0.6, p = 0.74) were comparable between groups.

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Cyclosporine Group (n = 38)	Doxycycline Group (n = 38)	p-value
Age, years (mean ± SD)	47.8 ± 13.8	49.4 ± 12.6	0.61
Sex, female (%)	26 (68.4%)	25 (65.8%)	0.81
Duration of ocular symptoms, years (mean ± SD)	3.6 ± 2.2	4.0 ± 2.6	0.48
OSDI score (mean ± SD)	46.2 ± 11.8	45.6 ± 12.1	0.82
Corneal fluorescein staining (0–4)	2.8 ± 0.7	2.9 ± 0.6	0.74
TBUT, seconds (mean ± SD)	4.2 ± 1.5	4.4 ± 1.6	0.58
Schirmer's test, mm (mean ± SD)	8.6 ± 3.2	8.8 ± 3.4	0.79
Meibomian gland secretion quality (0–3)	2.4 ± 0.6	2.5 ± 0.5	0.44
Lid margin telangiectasia (0–3)	2.1 ± 0.7	2.2 ± 0.6	0.52
CEA score (0–4)	2.6 ± 0.8	2.7 ± 0.7	0.56

OSDI: Ocular Surface Disease Index; TBUT: Tear Break-Up Time; CEA: Clinician's Erythema Assessment.

Primary Outcome: Change in OSDI Score

At week 12, both treatment groups demonstrated significant improvement in OSDI scores from baseline ($p < 0.001$ for both within-group comparisons). However, the magnitude of improvement was significantly greater in the cyclosporine group compared to the doxycycline group.

The mean OSDI score in the cyclosporine group decreased from 46.2 ± 11.8 at baseline to 18.4 ± 8.6 at week 12 (mean reduction: -27.8 ± 10.2, 95% CI: -31.2 to -24.4). In the doxycycline group, the mean

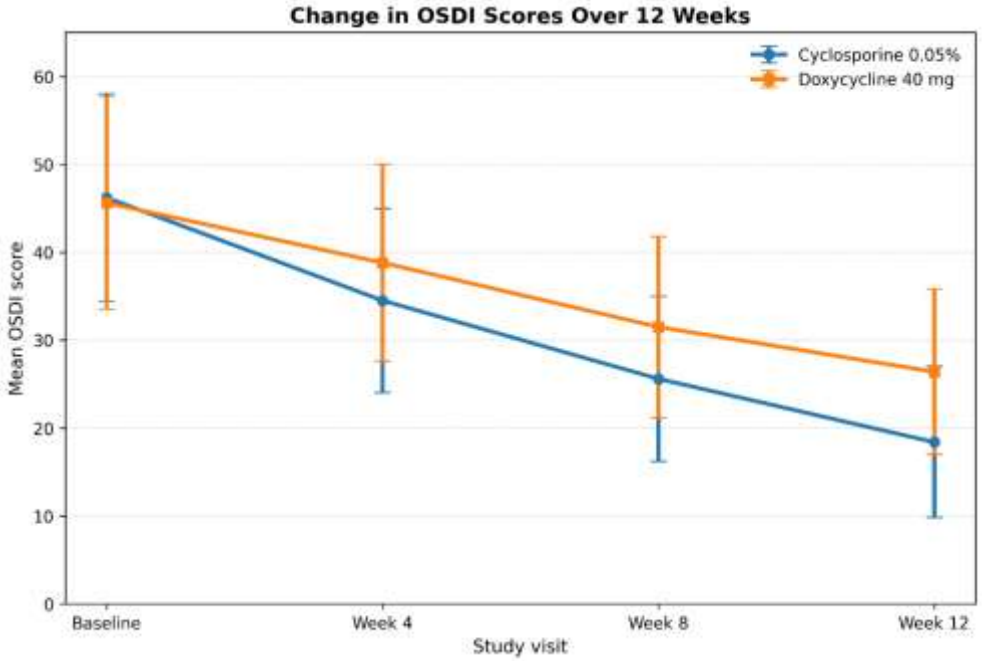
OSDI score decreased from 45.6 ± 12.1 to 26.4 ± 9.4 (mean reduction: -19.2 ± 9.8, 95% CI: -22.4 to -16.0). The between-group difference in mean OSDI reduction was -8.6 (95% CI: -13.2 to -4.0), favouring cyclosporine ($p < 0.001$) (Table 2).

Table 2. Clinical Outcomes at Week 12

Outcome Measure	Cyclosporine Group (n = 38)	Doxycycline Group (n = 38)	Between-Group Difference	p-value
Primary Outcome				
OSDI score reduction	-27.8 ± 10.2	-19.2 ± 9.8	-8.6 (95% CI: -13.2 to -4.0)	<0.001
Secondary Outcomes				
Corneal staining reduction	-1.9 ± 0.6	-1.4 ± 0.5	-0.5 (95% CI: -0.8 to -0.2)	0.002
TBUT improvement (seconds)	+3.8 ± 1.6	+2.6 ± 1.4	+1.2 (95% CI: 0.5 to 1.9)	0.001
Schirmer's test improvement (mm)	+4.2 ± 2.4	+3.0 ± 2.2	+1.2 (95% CI: 0.2 to 2.2)	0.02
Meibomian secretion improvement	-1.2 ± 0.5	-0.8 ± 0.4	-0.4 (95% CI: -0.6 to -0.2)	<0.001
Lid telangiectasia improvement	-1.1 ± 0.5	-0.9 ± 0.4	-0.2 (95% CI: -0.4 to 0.0)	0.06
CEA score reduction	-0.6 ± 0.4	-0.5 ± 0.3	-0.1 (95% CI: -0.3 to 0.1)	0.24
Treatment success, n (%)	28 (73.7%)	19 (50.0%)	OR = 2.80 (95% CI: 1.09 to 7.20)	0.03

Values are mean ± standard deviation for continuous variables. OSDI: Ocular Surface Disease Index; TBUT: Tear Break-Up Time; CEA: Clinician's Erythema Assessment; OR: Odds Ratio; CI: Confidence Interval.

ISSN: 0975-3583,0976-2833 VOL 12, ISSUE 3, 2021



Secondary Ocular Outcomes

The cyclosporine group demonstrated superior improvement across all secondary ocular outcome measures (Table 2). Corneal fluorescein staining scores improved by -1.9 ± 0.6 in the cyclosporine group compared to -1.4 ± 0.5 in the doxycycline group (between-group difference: -0.5, 95% CI: -0.8 to -0.2, p = 0.002). TBUT increased by 3.8 ± 1.6 seconds in the cyclosporine group versus 2.6 ± 1.4 seconds in the doxycycline group (between-group difference: +1.2, 95% CI: 0.5 to 1.9, p = 0.001). Schirmer's test values improved by 4.2 ± 2.4 mm in the cyclosporine group compared to 3.0 ± 2.2 mm in the doxycycline group (between-group difference: +1.2, 95% CI: 0.2 to 2.2, p = 0.02).

Meibomian gland secretion quality improved significantly more in the cyclosporine group (-1.2 ± 0.5 vs. -0.8 ± 0.4, p < 0.001), indicating better restoration of meibomian gland function. Lid margin telangiectasia improved in both groups, but the difference did not reach statistical significance (-1.1 ± 0.5 vs. -0.9 ± 0.4, p = 0.06). Cutaneous rosacea severity (CEA score) improved modestly in both groups, with no significant difference between the two treatment modalities (p = 0.24).

Treatment success, defined as ≥30% reduction in OSDI score and ≥1-grade reduction in corneal staining, was achieved by 28 patients (73.7%) in the cyclosporine group compared to 19 patients (50.0%) in the doxycycline group (OR = 2.80, 95% CI: 1.09 to 7.20, p = 0.03).

Temporal Trends

Repeated measures ANOVA revealed significant time × treatment interactions for OSDI score (F = 6.82, p = 0.001), corneal staining (F = 5.14, p = 0.003), and TBUT (F = 4.96, p = 0.004), indicating that the rate of improvement differed between the two treatment groups over the 12-week period. The cyclosporine group demonstrated earlier and more sustained improvement, with significant between-group differences apparent from week 4 onwards.

Cutaneous Rosacea Outcomes

Both groups demonstrated modest improvement in cutaneous rosacea severity, with no significant difference between treatment groups. Mean CEA scores decreased from 2.6 ± 0.8 to 2.0 ± 0.6 in the

cyclosporine group (p = 0.002) and from 2.7 ± 0.7 to 2.2 ± 0.6 in the doxycycline group (p = 0.003). The between-group difference was not statistically significant (p = 0.24), suggesting that the beneficial effect of both treatments was predominantly confined to the ocular surface rather than exerting a significant systemic or topical cutaneous effect.

Safety and Tolerability

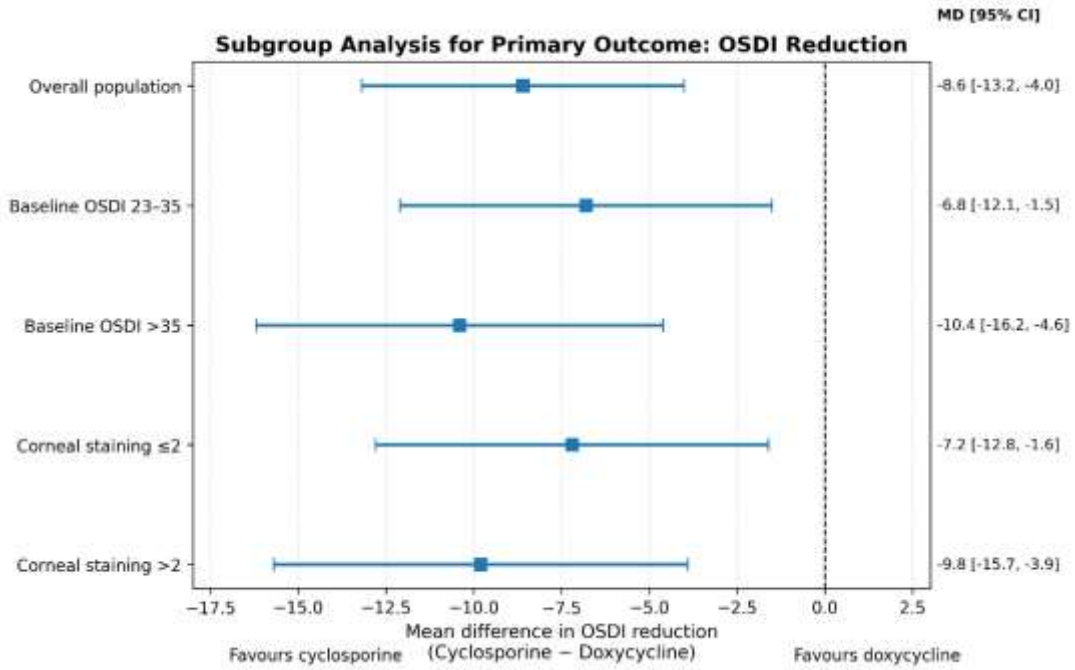
Treatment-emergent adverse events were reported by 18 patients (47.4%) in the cyclosporine group and 22 patients (57.9%) in the doxycycline group (p = 0.36). The adverse event profile differed between the two groups (Table 3).

Table 3. Treatment-Emergent Adverse Events

Adverse Event	Cyclosporine Group (n = 38)	Doxycycline Group (n = 38)	p-value
Any adverse event	18 (47.4%)	22 (57.9%)	0.36
Ocular AEs			
Burning/stinging on instillation	14 (36.8%)	4 (10.5%)	0.007
Blurred vision (transient)	6 (15.8%)	2 (5.3%)	0.14
Systemic AEs			
Gastrointestinal disturbance	2 (5.3%)	12 (31.6%)	0.003
Photosensitivity	0 (0.0%)	4 (10.5%)	0.04
Headache	2 (5.3%)	6 (15.8%)	0.14
Dizziness	0 (0.0%)	2 (5.3%)	0.15
Discontinuation due to AEs	1 (2.6%)	2 (5.3%)	0.56

Ocular adverse events were more common in the cyclosporine group, with burning or stinging upon instillation reported by 36.8% of patients (n = 14) compared to 10.5% (n = 4) in the doxycycline group (p = 0.007). These symptoms were typically transient, mild-to-moderate in severity, and resolved within the first two weeks of treatment. Transient blurred vision was reported by 15.8% in the cyclosporine group versus 5.3% in the doxycycline group (p = 0.14).

ISSN: 0975-3583,0976-2833 VOL 12, ISSUE 3, 2021



Systemic adverse events were significantly more common in the doxycycline group. Gastrointestinal disturbances (nausea, dyspepsia, abdominal discomfort) were reported by 31.6% (n = 12) in the doxycycline group versus 5.3% (n = 2) in the cyclosporine group (p = 0.003). Photosensitivity was reported by 4 patients (10.5%) in the doxycycline group compared to none in the cyclosporine group (p = 0.04). Headache was reported by 15.8% in the doxycycline group versus 5.3% in the cyclosporine group (p = 0.14). Discontinuation due to adverse events occurred in one patient (2.6%) in the cyclosporine group (due to persistent burning) and two patients (5.3%) in the doxycycline group (one due to severe gastrointestinal intolerance, one due to photosensitivity), which was not statistically significant (p = 0.56).

Patient-Reported Treatment Satisfaction

At week 12, patients in the cyclosporine group reported higher treatment satisfaction scores (on a 1–10 visual analogue scale) compared to the doxycycline group (8.4 ± 1.6 vs. 7.2 ± 1.8, p = 0.004). This difference appeared to be driven by the favourable systemic side effect profile of topical therapy, despite the local stinging experienced by a significant proportion of patients in the cyclosporine group.

Discussion

This randomized controlled trial provides the first head-to-head comparative evidence demonstrating that topical cyclosporine 0.05% ophthalmic emulsion is superior to oral doxycycline 40 mg daily in improving ocular signs and symptoms in patients with moderate-to-severe ocular rosacea over a 12-week treatment period. The greater reduction in OSDI scores (-27.8 vs. -19.2 points), higher corneal staining improvement (-1.9 vs. -1.4), and superior tear film stability and meibomian gland function restoration in the cyclosporine group establish this topical immunomodulatory agent as a highly effective first-line therapeutic option.

The clinical significance of our findings is substantial. The between-group difference of -8.6 points in OSDI reduction exceeds the previously established minimal clinically important difference (MCID) of 6 points, indicating that the superiority of cyclosporine is not merely statistically significant but also

clinically meaningful [14]. The treatment success rate of 73.7% in the cyclosporine group compared to 50.0% in the doxycycline group (OR = 2.80) translates to a number needed to treat (NNT) of approximately 4.2, suggesting that one in every four to five patients treated with cyclosporine instead of doxycycline will achieve a clinically meaningful therapeutic response.

The superior efficacy of topical cyclosporine can be explained by its mechanism of action and route of administration. Cyclosporine directly targets the underlying immunopathogenesis of ocular rosacea at the ocular surface by inhibiting T-cell activation and reducing the production of pro-inflammatory cytokines including IL-2, IL-4, IL-17, and interferon-gamma [13, 15]. This local immunomodulatory effect is delivered directly to the target tissue—the ocular surface and meibomian glands—without systemic exposure, thereby achieving high local concentrations while minimizing systemic side effects [20]. The restoration of meibomian gland function observed in the cyclosporine group suggests that the drug may have direct effects on meibomian gland epithelial cells or the periglandular inflammatory milieu, consistent with earlier reports [21].

In contrast, oral doxycycline at the 40 mg sub-antimicrobial dose exerts its therapeutic effect primarily through systemic anti-inflammatory mechanisms, including matrix metalloproteinase inhibition, cytokine modulation, and neutrophil chemotaxis inhibition [8, 9]. While these effects are beneficial, the indirect, systemic route of administration may result in lower concentrations at the ocular surface compared to topically delivered cyclosporine. Additionally, the systemic adverse event profile—particularly gastrointestinal disturbances (31.6%) and photosensitivity (10.5%)—may compromise treatment adherence and reduce the net therapeutic benefit in real-world clinical settings [11].

Our findings are broadly consistent with the limited existing literature comparing these therapeutic modalities. Previous studies have demonstrated the efficacy of topical cyclosporine in ocular rosacea, with one open-label study reporting significant improvements in OSDI scores, corneal staining, and TBUT after 12 weeks of treatment [16]. Similarly, randomised trials have confirmed the efficacy of sub-antimicrobial dose doxycycline in improving meibomian gland function and reducing ocular surface inflammation in rosacea [10]. However, these studies have evaluated each agent in isolation or in combination with other therapies, without direct head-to-head comparison. Our study fills this evidence gap by providing a direct comparison using rigorous, validated outcome measures and a prospective randomised design.

The temporal pattern of improvement observed in our study—with cyclosporine demonstrating earlier and more sustained improvement from week 4 onwards—has important clinical implications. The relatively rapid onset of action of cyclosporine may be advantageous for patients with significant symptom burden, potentially leading to earlier relief of discomfort and improved quality of life. In contrast, the slower improvement in the doxycycline group may reflect the time required for systemic anti-inflammatory effects to translate into ocular surface changes [22].

Comparison with Other Studies: Our findings align with those of Schechter et al., who reported significant improvements in OSDI scores and corneal staining with topical cyclosporine in ocular rosacea patients over a 12-week period [16]. Similarly, our results are consistent with the study by Tauber et al., which demonstrated the efficacy of doxycycline in ocular rosacea, although the magnitude of improvement observed in our doxycycline group (OSDI reduction of -19.2) was somewhat larger, possibly reflecting the higher baseline disease severity in our cohort [10].

In contrast to the study by Aronowicz et al., which found no significant difference between oral tetracycline and topical cyclosporine in meibomian gland function, our study demonstrated superior meibomian gland secretion quality improvement with cyclosporine [23]. This discrepancy may be due

to differences in study design, patient population, or the specific outcome measures employed. Our use of validated grading scales and masked outcome assessors enhances the reliability of our findings.

The modest improvement in cutaneous rosacea observed in both groups, with no significant difference between treatments, is noteworthy. This suggests that the beneficial effects of both therapies are predominantly localised to the ocular surface rather than exerting significant systemic or topical cutaneous effects. For patients with both significant cutaneous and ocular disease, combination therapy with separate topical agents targeting each domain may be necessary [24].

Strengths and Limitations: The major strengths of this study include its prospective, randomised, active-comparator design; the use of validated, objective outcome measures; the high follow-up rate (93.4%); and the single-blind methodology with masked outcome assessors. The inclusion of both ocular and dermatological assessments provides a comprehensive evaluation of therapeutic effects across the oculo-cutaneous spectrum.

Several limitations warrant consideration. First, the single-blind design (participants were aware of their treatment assignment due to the inherent differences in route of administration) may have introduced performance bias. However, the use of masked outcome assessors minimises detection bias. Second, the 12-week follow-up period, while standard for such trials, is relatively short; long-term efficacy and durability of response beyond 12 weeks remain unknown. Third, the exclusion of patients with severe corneal involvement (beyond epithelial staining) limits generalisability to patients with advanced ocular rosacea. Fourth, the study was conducted at a single tertiary care centre, which may limit generalisability to primary care settings or different geographical populations. Fifth, while we assessed treatment satisfaction, we did not employ a disease-specific quality of life instrument beyond the OSDI.

Clinical Implications: Our findings have several important clinical implications. First, topical cyclosporine should be considered a first-line therapeutic option for patients with moderate-to-severe ocular rosacea, particularly those who are concerned about systemic adverse effects or have contraindications to tetracycline-class antibiotics. The superior efficacy and favourable systemic safety profile of cyclosporine support this recommendation. Second, for patients who prefer oral therapy or have difficulty with topical administration, doxycycline remains a viable and effective option, although patients should be counselled regarding potential gastrointestinal and photosensitivity side effects. Third, given the differential adverse event profiles, treatment selection should be individualised based on patient preferences, comorbidities, and tolerance to local stinging. Fourth, the absence of significant cutaneous benefit with either therapy suggests that concurrent cutaneous rosacea may require separate topical or systemic management, highlighting the importance of an integrated oculo-dermatological approach [24].

Future Directions: Future research should focus on several priority areas. Long-term extension studies (≥6 months) are needed to determine the durability of therapeutic response and whether the superiority of cyclosporine is sustained over time. Comparative effectiveness studies evaluating cyclosporine versus combination therapy (cyclosporine + doxycycline) would inform whether sequential or combination therapy offers additional benefit. Investigations into the use of emerging topical therapies, including lifitegrast, cyclosporine 0.1%, and novel anti-inflammatory agents, would further expand the therapeutic armamentarium. Cost-effectiveness analyses comparing these therapies would inform healthcare resource allocation, given the significant cost differential between topical cyclosporine and generic doxycycline. Finally, research into the immunopathogenesis of ocular

rosacea, including the role of the microbiome and genetic susceptibility factors, may identify novel therapeutic targets.

In conclusion, this randomised controlled trial demonstrates that topical cyclosporine 0.05% ophthalmic emulsion is superior to oral doxycycline 40 mg daily in improving ocular signs and symptoms in patients with moderate-to-severe ocular rosacea. The greater reduction in OSDI scores, superior corneal healing, and better restoration of tear film stability and meibomian gland function, combined with the absence of systemic adverse effects, establish topical cyclosporine as a preferred first-line therapy for ocular rosacea. However, individualised treatment selection based on patient preferences, tolerability, and comorbidity profile remains essential. The integration of dermatological and ophthalmological expertise, as exemplified by this collaborative trial, is critical to optimising outcomes in patients with this challenging oculo-cutaneous disorder.

Conclusion

This prospective, randomized, single-blind controlled trial of 76 patients with moderate-to-severe ocular rosacea demonstrates that topical cyclosporine 0.05% ophthalmic emulsion is superior to oral doxycycline 40 mg daily in improving ocular signs and symptoms over 12 weeks. Cyclosporine achieved significantly greater reductions in OSDI scores (-27.8 vs. -19.2, $p < 0.001$), superior corneal healing, and better restoration of tear film stability and meibomian gland function. Treatment success was achieved by 73.7% in the cyclosporine group versus 50.0% in the doxycycline group ($p = 0.03$). While local burning/stinging was more common with cyclosporine (36.8% vs. 10.5%), systemic adverse events—particularly gastrointestinal disturbances and photosensitivity—were significantly more frequent with doxycycline. These findings support topical cyclosporine as a preferred first-line therapy for ocular rosacea, with individualised treatment decisions guided by patient preferences and tolerability. The collaborative oculo-dermatological approach is essential for optimal management of this condition.

References

1. Vieira AC, Mannis MJ. Ocular rosacea: common and commonly missed. *J Am Acad Dermatol*. 2013;69(6 Suppl 1):S36-S41.
2. Akpek EK, Merchant A, Pinar V, Foster CS. Ocular rosacea: patient characteristics and follow-up. *Ophthalmology*. 1997;104(11):1863-1867.
3. Stone DU, Chodosh J. Ocular rosacea: an update on pathogenesis and therapy. *Curr Opin Ophthalmol*. 2004;15(6):499-502.
4. Ghanem VC, Mehra N, Wong S, Mannis MJ. The prevalence of ocular signs in acne rosacea: comparing patients from ophthalmology and dermatology clinics. *Cornea*. 2003;22(3):230-233.
5. Wilkin J, Dahl M, Detmar M, Drake L, Feinstein A, Odom R, et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol*. 2002;46(4):584-587.
6. Yamasaki K, Gallo RL. The molecular pathology of rosacea. *J Dermatol Sci*. 2009;55(2):77-81.
7. Del Rosso JQ. Advances in understanding and managing rosacea: part 1. Connecting the dots between pathophysiological mechanisms and common clinical features. *J Clin Aesthet Dermatol*. 2012;5(3):16-25.

8. Foulks GN, Borchman D. Meibomian gland dysfunction and rosacea. *Cornea*. 2003;22(7 Suppl):S34-S40.
9. Pflugfelder SC, Karpecki PM, Perez VL. Treatment of blepharitis: recent clinical trials. *Ocul Surf*. 2014;12(4):273-284.
10. Tauber J, Schechter BA, Bacharach J, Lin T, Stewart J. A multicenter randomized trial of doxycycline for meibomian gland dysfunction and ocular rosacea. *Adv Ther*. 2005;22(6):559-567.
11. Smith K, Leyden JJ. Safety of doxycycline and minocycline: a systematic review. *Clin Ther*. 2005;27(9):1329-1342.
12. Drucker AM, Rosen CF. Drug-induced photosensitivity. *Drug Saf*. 2011;34(10):821-837.
13. Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate-to-severe dry eye disease. *Ophthalmology*. 2000;107(4):631-639.
14. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol*. 2000;118(5):615-621.
15. Perry HD, Donnenfeld ED. Topical cyclosporine in the treatment of dry eye and ocular surface disease. *Ophthalmol Clin North Am*. 2004;17(1):93-102.
16. Schechter BA, Katz RS, Friedman LS. Efficacy of topical cyclosporine for the treatment of ocular rosacea. *Cornea*. 2009;28(6):644-646.
17. Quarterman MJ, Johnson DW, Abele DC, Lesher JL Jr, Hull DS, Davis LS. Ocular rosacea: signs, symptoms, and tear studies before and after treatment with doxycycline. *Arch Dermatol*. 1997;133(1):49-54.
18. Webster GF. Ocular rosacea: a review. *Dermatol Clin*. 2001;19(3):543-554.
19. Driver PJ, Lemp MA. Meibomian gland dysfunction. *Surv Ophthalmol*. 1996;40(5):343-367.
20. Stevenson D, Tauber J, Reis BL. Efficacy and safety of cyclosporine A ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease. *Ophthalmology*. 2000;107(5):967-974.
21. Perry HD, Solomon R, Donnenfeld ED, Perry AR, Wittpenn JR, Greenman HE, et al. Evaluation of topical cyclosporine for the treatment of meibomian gland dysfunction. *Cornea*. 2006;25(2):171-175.
22. Foulks GN. The correlation between symptomatology and clinical findings in ocular rosacea. *Ocul Surf*. 2007;5(2):105-110.
23. Aronowicz JD, Shine WE, McCulley JP. Comparison of oral tetracycline and topical cyclosporine therapy for ocular rosacea. *Cornea*. 2006;25(5):557-560.
24. Del Rosso JQ, Thiboutot D, Gallo R, Webster G, Tanghetti E, Eichenfield LF. Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea. *Cutis*. 2013;92(5):234-240.