ORIGINAL ARTICLE

Isotretinoin-induced severe dry eye disease and meibomian gland alterations in patients with acne vulgaris: A noncontact ocular surface analysis

Julieana Muhammed, MMed[1,2], Syarifah Nur-Humaira Syed Mohd-Khomsah, MMed[1], Wan Noor Hasbee Wan Abdullah, MMed[3], Shahidatul-Adha Mohamad, MMed[1,2]

[1]Department of Ophthalmology and Visual Science, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, Kubang Kerian, Kelantan, Malaysia, [2]Hospital Pakar Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [3]Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan, Malaysia

ABSTRACT

Introduction: Although isotretinoin causes various potentially vision-threatening ocular side effects, it remains widely prescribed for acne vulgaris (AV) globally due to its proven efficacy, particularly in severe or treatment-resistant cases. This study evaluated the effect of isotretinoin on ocular surface parameters to elucidate the underlying mechanisms of isotretinoin-associated dry eye disease (DED).

Materials and Methods: A comparative cross-sectional observational study was conducted at two tertiary hospitals between August 2022 and May 2023. A total of 48 patients with AV were recruited and categorised into the isotretinoin-treated (n=19) and isotretinoin-naive (n=29) groups. A LacryDiag® ocular surface analyser was used to evaluate meibomian gland loss (MGL) and tear film parameters. The Ocular Surface Disease Index (OSDI) questionnaire was administered to evaluate dry eye symptom, severity and functional effects.

Results: At enrollment, the mean duration of AV was 5.26 ± 3.28 and 6.39 ± 5.63 years in the treated and naive groups, respectively. Treated participants had completed at least a minimum of 16 weeks of daily isotretinoin therapy at the time of examination (mean: 16.89 ± 3.2 weeks). The OSDI score was markedly higher in the treated group than that in the naive group (43.20 ± 18.79 vs 18.15 ± 19.24). The isotretinoin-treated group had a significantly greater MGL percentage than the naive group (p<0.001), significantly lower noninvasive break-up time (NIBUT) (p=0.046) and lipid layer thickness (p<0.001). The mean tear meniscus height was also lower in the treated group, although the difference was not statistically significant (p = 0.462). Pearson's correlation analysis revealed a significantly moderate positive correlation between the MGL percentage and OSDI score (r=0.417, p=0.003) and a significantly moderate negative correlation between MGL percentage and NIBUT (r=−0.348, p=0.015).

Conclusion: Isotretinoin therapy in patients with AV is remarkably associated with greater MGL, severe dry eye symptoms, and reduced tear film stability, supporting a lipid-deficient mechanism in isotretinoin-induced DED. Routine ocular surface evaluations are recommended for the early detection and management of ocular complications in patients receiving isotretinoin.

KEYWORDS:
Isotretinoin, meibomian gland disease, meibography, noninvasive break-up time, OSDI

INTRODUCTION

Acne vulgaris (AV) is the most common dermatological condition among adolescents, affecting approximately 85% of individuals aged 12–24 years.[1] Its pathogenesis is multifactorial, involving androgen-mediated stimulation of sebaceous glands, which promotes follicular hyperkeratinization and colonization by *Propionibacterium acnes*, leading to chronic inflammation and eventual scar formation.[2,3] The Global Burden of Disease Study 2019 documented a 47.9% increase in global cases from 1990 to 2019, culminating in 117.4 million cases worldwide.[4] Although AV is commonly observed during adolescence, it may persist into adulthood. A recent study involving 1,167 patients with acne reported that 41.3% were adults, among whom 85% were women, highlighting both the continued burden of AV beyond teenage years and its higher prevalence among adult women.[5]

Beyond cutaneous manifestations, AV may also affect the eye, particularly the ocular surface, primarily through its effect on meibomian glands (MGs).[6] Altered MG activity disrupts meibum quality and secretion, predisposing patients to MG dysfunction (MGD) and resultant evaporative dry eye disease (DED).[6] DED, previously referred to as dry eye syndromes (DES), is now classified according to TFOS DEWS II criteria, which emphasise tear film instability, hyperosmolarity, and ocular surface damage.[7] Clinically, these ocular changes are often subjectively detected through fluorescein staining, which reveals corneal or conjunctival staining and reduced tear break-up time (TBUT). However, objective evaluation is superior and currently can be performed using ocular surface analyser (OSA) to quantify MG loss (MGL) and tear film parameters, including noninvasive break-up time (NIBUT), lipid layer thickness (LLT), and tear meniscus height (TMH).[8]

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Corresponding Author: Shahidatul-Adha Mohamad
Email: shieda@usm.my

Isotretinoin, a systemic vitamin A derivative, is indicated for treating nodulocystic and severe AV, as well as moderate cases that are refractory to conventional therapies.[9,10] Although its dermatological efficacy is well established, isotretinoin has also been implicated in inducing apoptosis in sebocytes, including those within MGs, potentially leading to noncicatricial MGD and subsequent tear film instability, ocular consequences that remain underrecognized.[11] The current Malaysian guidelines for AV management exclude recommendations for ophthalmological referral or screening.[10] This study objectively evaluated MG and tear film parameters in isotretinoin-treated patients using a noncontact ocular surface analyser, providing evidence of remarkable DED and addressing a critical gap in local clinical data to support more integrated patient care.

MATERIALS AND METHODS

This comparative cross-sectional observational study was conducted at two tertiary hospitals between August 2022 and May 2023: the Ophthalmology Clinic of Hospital Pakar Universiti Sains Malaysia and the Dermatology Clinic of Hospital Raja Perempuan Zainab II. The Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/21060488] and the Medical Research and Ethics Committee of the Ministry of Health [NMRR ID-22-00453-J83] approved this study. Written informed consent was obtained from all patients.

Selection and Recruitment of the Participants

A total of 48 patients with AV were recruited via convenience sampling and categorised into two groups: the isotretinoin-treated (n=19), consisting of individuals who had completed at least 16 weeks of daily 20 mg isotretinoin therapy, and the isotretinoin-naive group (n=29), with no prior exposure to oral isotretinoin. Eligibility for the treated group required completion of at least a 16-week course of oral isotretinoin at a fixed daily dose of 20 mg. The exclusion criteria included the presence of anterior segment pathology, history of corneal or refractive surgery, chronic use of topical corticosteroid eye drops, current or prior intake of estrogen-containing medications, and diagnosis of trigeminal neuropathy. Demographic and clinical data, including age, gender, race, education level, duration of AV, and duration of isotretinoin therapy, as well as systemic and ocular history were obtained through patient interviews and review of medical records. A comprehensive ophthalmic examination, including visual acuity testing, anterior segment evaluation, and fundus assessment, was performed for all participants.

Sample Size Determination

The minimum required sample size for this study was calculated a priori for the primary outcome, MGL, using PS Power and Sample Size Software for an independent t-test (α=0.05, power=0.95). Based on a standard deviation of 0.7 and an expected difference of 1.01 between groups, [12] 14 participants per group were needed. Accounting for a 10% dropout, the total minimum sample size was 32 (16 per group).

Assessment of Dry Eye Symptoms

The severity and functional effects of dry eye symptoms were assessed using a 12-item OSDI questionnaire. Depending on participant literacy and language preference, either the original English version or the validated Malay translation was used.[13] Responses were obtained through self-completion or interviewer assistance. OSDI scores were categorised as follows: normal (0–12 points), mild (13–22 points), moderate (23–32 points), and severe (33–100 points).[14]

Noncontact Analysis of Tear Film Parameters

Tear film assessments were performed following the OSA protocol, using a LacryDiag® analyser (Quantel Medical, Cournon-d'Auvergne, France), ensuring standardised and reproducible evaluations.[8,15,16] A single masked and trained research assistant performed these procedures in the following sequence to ensure consistency, minimise potential bias, and reduce procedural variability: (1) TMH, (2) LLT, (3) NIBUT, and (4) meibography. Examinations were conducted in a temperature-controlled room with air-conditioning maintained at a comfortable level.[16] To prevent airflow-related interference, the patient's face was positioned away from direct ventilation, and no fans were used during examination.[16] Each parameter was measured three times, with the mean value used for analysis to enhance repeatability and precision.

TMH was measured at the inferior lid margin (in millimeters) to estimate the aqueous tear volume.[16,17] LLT was evaluated via interferometric analysis and categorised using a simplified version of the Guillon classification system: lipid-deficient (grades 0–2), normal lipid levels (grades 3–5), and excessive lipid presence (grade 6).[16,17] NIBUT was automatically recorded in seconds over three consecutive trials, with the median value used for analysis; readings ≤12 s were considered indicative of DED.[16,17] MG loss (MGL) was assessed using noncontact infrared meibography of the upper eyelid.[18] The captured images were automatically analysed using proprietary software to quantify the MGL percentage, defined as the proportion of gland dropout relative to the total tarsal area.[15] MGL was subsequently graded using the meiboscale system based on quantified percentage MGL: grade 0 (no loss), grade 1 (<25%), grade 2 (26%–50%), grade 3 (51%–75%), and grade 4 (>75%).[19]

Statistical Analysis

All demographic and clinical data were entered into IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA). All entries were reviewed for completeness and accuracy. The Shapiro–Wilk test was used to assess data normality, which confirmed a normal distribution.

Descriptive statistics were used to summarise the demographic characteristics, MGL percentage and clinical parameters of DED, including OSDI scores and tear film parameters (TMH, LLT, and NIBUT). Numerical variables were expressed as means and standard deviations, whereas categorical variables were expressed as frequencies and percentages.

Comparative analyses of OSDI scores, NIBUT, TMH, and MGL between isotretinoin-treated and naive participants were performed using an independent samples t-test. Differences in LLT category distribution, OSDI severity level, and meiboscale grading were evaluated using Fisher's exact test. Correlation analysis was conducted using Pearson's correlation coefficient to explore the relationships between MGL percentages and clinical parameters of DED (OSDI, NIBUT, LLT, and TMH). A p-value <0.05 was considered statistically significant in all tests, with the correlation strength interpreted on the basis of standard r-value guidelines.

RESULTS

The participants' demographic characteristics are summarised in Table I. The cohort was predominantly Malay (n = 45), with a smaller proportion of Chinese participants (n = 3). The mean age of the patients was 21.6 ± 3.15 and 25.7 ± 9.89 years in the isotretinoin-treated and isotretinoin-naive groups, respectively. Although statistically remarkable, the wide standard deviation in the naive group indicates age variability and potential overlap between cohorts. There was higher female than male, with a ratio of 1.82:1. Most patients (79.1%) were nonsmokers. Almost half (47.9%) of the patients were students. The mean duration of AV at baseline enrollment was 5.26 ± 3.28 and 6.39 ± 5.63 years in the treated and naive groups, respectively. The isotretinoin-treated participants had completed at least a minimum of 16 weeks of isotretinoin therapy at a daily dose of 20 mg at the time of examination (mean: 16.89 ± 3.2 weeks).

The objective profiles of MG and dry eye parameters are presented in Table II. The isotretinoin-treated group had a considerably higher mean OSDI score than the naive group (43.20 ± 18.79 vs 18.15 ± 19.24). The isotretinoin-treated group had lower mean values of NIBUT (p=0.046), LLT (p< 0.001), and TMH (p=0.462). A threefold higher mean MGL percentage was observed in the isotretinoin-treated group (p<0.001), with a more frequent higher dropout, meiboscale grade 2–3 in this group (p<0.001), consistent with more advanced structural compromise than in the isotretinoin-naive group (Figure 1).

Post-hoc analysis using observed means and pooled SDs demonstrated high statistical power for the primary outcomes (MGL: Cohen's d=2.02, Power (1–β)=1.00; OSDI: Cohen's d=1.31, Power (1 – β) = 0.99). For the secondary outcomes, power was lower (NIBUT: Cohen's d=0.71, Power (1–β)=0.62; TMH: Cohen's d=0.12, Power (1–β)=0.06), indicating that non-significant findings should be interpreted cautiously. These results support the robustness of significant findings while highlighting limited power for certain parameters.

The relationships between MGL and clinical parameters of DED were analysed using Pearson's correlation (Table III). There was a significant moderate positive correlation between the MGL percentage and OSDI score (r=0.417, p=0.003) and a significant moderate negative correlation between the MGL percentage and NIBUT (r=–0.348, p=0.015) (Fig. 2).

Table I: Demographic Profile of Patients with Acne Vulgaris

Variables	Total (n=48)	Isotretinoin-Treated (n=19)	Isotretinoin-Naïve (n=29)	p-value
Age (years)				
(Mean ± SD)		21.6 ± 3.15	25.7 ± 9.89	0.008[a]
Gender (n, %)				0.653[b]
Male	17 (35.4)	6 (31.6)	11 (38)	
Female	31 (64.6)	13 (68.4)	18 (62)	
Race (n, %)				0.148[b]
Malay	45 (93.8)	19 (42.2)	26 (57.8)	
Chinese	3 (6.2)	0 (0.0)	3 (100)	
Smoking (n, %)				0.276[b]
Yes	10 (20.9)	2 (10.5)	8 (27.6)	
No	38 (79.1)	17 (89.5)	21(72.4)	
Occupation (n, %)				0.452[b]
Student	23 (47.9)	12 (63.2)	11 (37.9)	
Government	4 (8.4)	1 (5.3)	3 (10.3)	
Others	16 (33.3)	5 (26.3)	11 (37.9)	
Unemployed	5 (10.4)	1 (5.3)	4 (13.8)	
Duration of acne (years)				
(Mean ± SD)		5.26 ± 3.28	6.39 ± 5.63	0.385[a]
Duration of oral isotretinoin (years)				
(Mean ± SD)		16.89 (3.2)		

[†] [a]Independent t-test; [b]Chi-square test, p-value < 0.05 significant

Table II: Meibomian Gland Loss and Clinical Parameters of Dry Eye Disease in Patients with Acne Vulgaris

Variables	Isotretinoin-Treated (n=19)	Isotretinoin-Naïve (n=29)	p-value
Meibomian Gland Loss			
Percentage Loss (Mean ± SD)	33.89 ± 16.1	11.21± 6.4	<0.001[a]
Meiboscale (n, %)			
Grade 0 (No MGL)	0 (0.00)	3 (10.3)	<0.001[b]
Grade 1 (< 33% MGL)	5 (26.3)	26 (89.7)	
Grade 2 (33% – 66% MGL)	11 (57.9)	0 (0.00)	
Grade 3 (> 66% MGL)	3 (15.8)	0 (0.00)	
OSDI Score			
Overall score (Mean ± SD)	43.20 ± 18.79	18.15 ± 19.24	<0.001[a]
Severity (n, %)			
Normal (0 – 12 points)	0 (0.00)	3 (10.3)	<0.001[b]
Mild (13 – 22 points)	5 (26.3)	26 (89.7)	
Moderate (23 – 32 points)	11 (57.9)	0 (0.00)	
Severe (33 – 100 points)	3 (15.8)	0 (0.00)	
NIBUT			
Overall score (Mean ± SD)	10.64 ± 2.96	13.02 ± 3.62	0.046[a]
TMH			
Overall score (Mean ± SD)	0.22 ± 0.10	0.23 ± 0.07	0.462[a]
Lipid Layer Thickness (n, %)			<0.001[b]
Grade 0 – 2 (Deficient)	13 (68.4)	1 (3.4)	
Grade 3 – 5 (Normal)	6 (31.6)	26 (89.7)	
Grade 6 (Excessive)	0 (0.0)	2 (6.9)	

† Abbreviations: OSDI, Ocular Surface Disease Index; NIBUT, non-invasive break-up time; TMH, tear meniscus height; MGL, meibomian gland loss
‡ [a]Independent t-test; [b]Fisher's exact test. p-value < 0.05 significant

Table III: Correlation Between Meibomian Gland Loss and Clinical Parameters of Dry Eye Disease Among Patients with Acne Vulgaris

	Meibomian Gland Loss	
	(r value)	p-value
Clinical Parameters of DED		
OSDI Score	0.417	0.003
NIBUT	0.348	0.015
TMH - 0.201	0.171	

† Abbreviations: OSDI, Ocular Surface Disease Index; NIBUT, non-invasive break-up time; TMH, tear meniscus height; DED, dry eye disease.
‡ Pearson correlation: r, correlation coefficient (r > 0.75 strong-perfect correlation). p-value < 0.05 significant

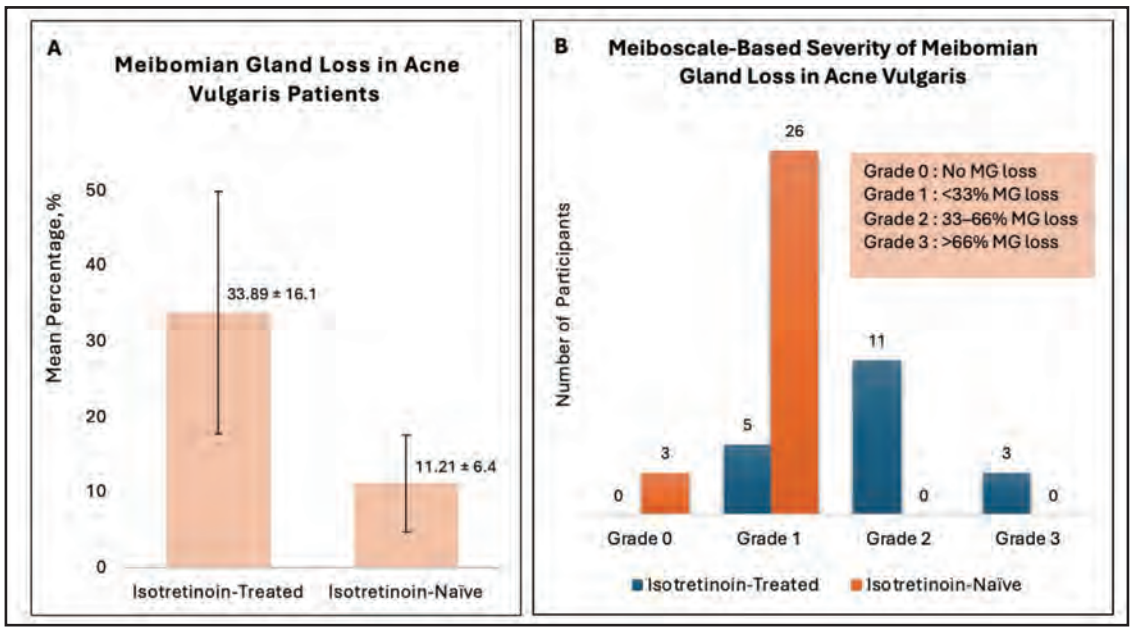

Fig. 1: Quantitative and qualitative assessment of meibomian gland loss in isotretinoin-treated vs. isotretinoin-naïve groups. (A) Mean percentage of meibomian gland loss was significantly greater in the treated group (p<0.001, independent t-test). (B) Meiboscale[29] scores indicated more severe dropout in the treated group (p<0.001, Fisher's exact test)

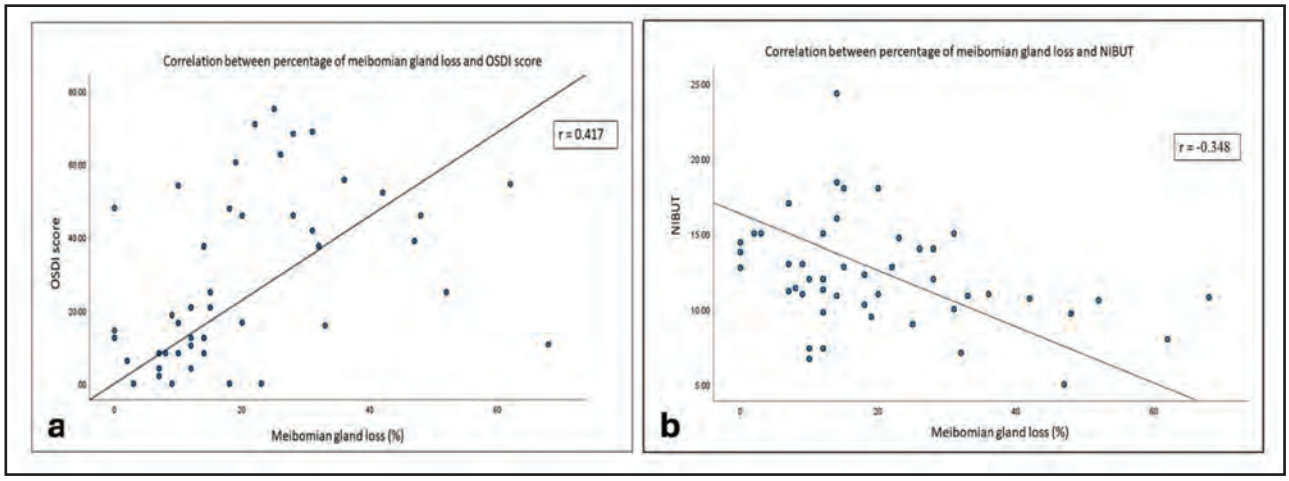

Fig. 2: Scatter plots showing (a) a moderate positive correlation between meibomian gland loss and OSDI score (r=0.417, p=0.003) and (b) a moderate negative (inverse) correlation between the meibomian gland loss percentage and NIBUT (r=–0.348, p=0.015)

DISCUSSION

Malaysian authorities and regulatory advisories emphasise that isotretinoin should be prescribed only by registered dermatologists,[10] with safety communications primarily focused on psychiatric and sexual complications.[20] However, its potential effects on ocular and visual functions remain largely overlooked, despite mounting evidence of MGD, evaporative DED, blepharitis, conjunctival irritation, contact lens intolerance, optic neuropathy, and isotretinoin-associated intracranial hypertension with papilloedema.[21–23] This gap in awareness presents a critical blind spot, particularly as isotretinoin prescriptions, commonly marketed as Accutane, continue to rise across dermatologic, aesthetic, and general practice settings.[24–26] To address this oversight, our study investigated the impact of isotretinoin on MG integrity and tear film stability in a Malaysian patient cohort.

AV predominantly affects adolescents and young adults, a trend reflected in our study cohort. Although a statistically remarkable age difference was observed between the isotretinoin-treated and naive groups, both cohorts largely overlapped in age and were composed primarily of individuals in their teenage and early adulthood years, consistent with global demographic patterns.[27] A recent Malaysian study involving high school and university students in Sarawak reported an AV prevalence of 75.8% among 441 subjects, with the highest rates among those aged 16–18 years.[28] Females accounted for 65.8% of the cases,[28] as observed in our cohort. These findings underscore the importance of early AV intervention with routine ocular screening in adolescents and young adults undergoing isotretinoin therapy, particularly among females, who often seek timely acne treatment to prevent scarring and address appearance-related concerns.

It is well established that isotretinoin alters sebaceous glands, and MG, being of the same histological type, are similarly affected, leading to MGD and associated DED.[23,29] In our study, isotretinoin-treated patients exhibited greater MGL, substantially reduced NIBUT, and deficient LLT consistent with classic MGD features and previous literature.[11,30] A correlation between greater MGL and reduced TBUT, as well as thinner LLT, has also been documented.[30] Isotretinoin reduces wax ester production in sebaceous glands, which likely disrupts lipid secretion from MGs.[31] Because MG lipids, known as meibum, form the nonpolar sublayer of the tear film, a deficiency in these lipids accelerates tear evaporation and contributes to the development of evaporative DED.[31]

Objective MG assessment and tear film measurements using a noncontact OSA provided reliable and reproducible data that strongly support the diagnosis of MGD and tear film instability.[8,16] However, symptom assessment using the OSDI remains essential for evaluating patient-reported discomfort and exploring correlations between MG changes and DED.[32] In our study, isotretinoin-treated individuals exhibited substantially elevated OSDI scores, with a positive correlation between symptom severity and MGL, indicating a greater symptom burden associated with increased gland dropout. These findings are consistent with previous reports of heightened OSDI scores during isotretinoin therapy.[32,33] Notably, each 10-mg increase in isotretinoin dose was associated with a 0.20-point increase in the OSDI score,[32] reinforcing the need for routine symptom monitoring.

Our findings underscore the urgent need to update and strengthen current management guidelines and treatment frameworks for AV by incorporating DED screening using the OSDI, a widely accessible tool that can be easily administered by patients, general practitioners, pharmacists, or other healthcare personnel.[37–40] With the rising number of isotretinoin prescriptions issued by general practitioners and aesthetic physicians globally, including in Malaysia, ocular health vigilance is essential.[24–26] Individuals initiating isotretinoin therapy should be promptly referred for ophthalmology assessment to mitigate potential ocular complications. Although dermatologic outcomes are rightly prioritized, particularly in appearance-conscious adolescents, ocular side effects and dry eye complications from

isotretinoin therapy can significantly impact quality of life.[4,34,35] Even at a relatively low daily dose (20 mg/day)[36] and brief 16-week treatment duration, features consistent with MGD and evaporative DED were already evident, suggesting that ocular effects may manifest rapidly and potentially persist with prolonged use.

This study has several limitations. Its cross-sectional design captured only the short-term ocular effects of isotretinoin on MGs and tear film parameters. Longitudinal data would better characterize the persistence of these changes, particularly given reports of sustained NIBUT reduction up to one-year post-treatment.[11] Baseline ocular surface parameters prior to isotretinoin initiation were unavailable, limiting the precision in attributing observed changes solely to isotretinoin, as AV itself may cause MGD. Cumulative and weight-adjusted doses were not analyzed, and treatment adherence relied on patient interviews rather than verified records, introducing possible recall bias. The convenience sampling and relatively small, uneven sample size between groups may also introduce selection bias, however consecutive recruitment of eligible participants helped reduce this risk. Lastly, as most participants were Malay, generalizability to other ethnic groups may be limited. Future studies should include baseline assessments, verified dosing and adherence data, longitudinal follow-up, and more diverse sampling to clarify isotretinoin's long-term ocular effects.

CONCLUSION

Oral isotretinoin therapy in patients with AV is associated with substantial structural and functional changes in MGs, contributing to tear film instability, MGD, and evaporative DED. Early recognition of dry eye symptoms and ophthalmologic assessments should be integrated into acne management to preserve vision, ocular comfort, and overall quality of life.

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ETHICAL APPROVAL

USM Human Research and Ethical Committee [USM/JEPeM/21060488] and the National Medical Research Registry [NMRR ID-22-00453-J83].

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