

Comparison of dose-related ocular side effects during systemic isotretinoin administration

TONGABAY CUMURCU¹, ENGIN SEZER², RASIT KILIC¹, YUNUS BULUT³

¹Department of Ophthalmology

²Department of Dermatology

³Department of Microbiology, Gaziosmanpaşa University School of Medicine, Tokat - Turkey

PURPOSE. To compare the effects of high- (Group 1) and low-dose (Group 2) isotretinoin treatments for acne vulgaris on lacrimal functions and other ocular complications.

METHODS. Twenty-six patients receiving high-dose (>0.5 mg/kg per day) systemic isotretinoin treatment and 25 patients treated with low-dose systemic isotretinoin (<0.5 mg/kg per day) underwent complete ophthalmologic assessment of both eyes before treatment, at days 45 and 90 of treatment, and 1 month after the completion of treatment, together with a microbiologic evaluation of conjunctival flora, tear film break-up time (BUT), and anesthetized Schirmer test of the right eye of each patient.

RESULTS. When the results of the anesthetized Schirmer test for Groups 1 and 2 were compared (pretreatment, days 45 and 90 of treatment, and 1 month after treatment), there was no statistically significant difference between the groups ($p > 0.05$). Although BUT did not differ significantly between the two groups before treatment ($p > 0.05$), there was a statistically significant decrease in BUT in Group 1 when compared with Group 2 at days 45 and 90 of treatment ($p < 0.05$). One month after the completion of treatment, there was no difference in BUT between the two groups ($p > 0.05$). No difference in *Staphylococcus aureus* colonization was detected between the two groups at days 45 and 90 of treatment ($p > 0.05$).

CONCLUSIONS. During systemic isotretinoin treatment, eye dryness was related to the dose used, at least during the period of treatment. Conversely, the rate of conjunctival *S aureus* colonization was unrelated to the dose of isotretinoin. (*Eur J Ophthalmol* 2009; 19: 196-200)

KEY WORDS. High dose, Isotretinoin, Lacrimal function, Low dose, Ocular complications

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INTRODUCTION

Isotretinoin has been used for the treatment of resistant acne vulgaris for more than 20 years. Its mode of action in the treatment of acne involves the reduction of both sebum secretions and colonization by *Propionibacterium acnes* (1). It also inhibits chemotaxis, thus preventing leukocyte migration and inflammation (2). However, the systemic use of this agent has been associated with some serious adverse ocular effects. Abnormal meibomian gland secretion, blepharoconjunctivitis, corneal opacity, keratitis, dryness of the eye, intolerance of contact

lenses, blurred vision, and reduced adaptation to darkness have been the most prominent adverse effects (3-5). Because this agent potentially adversely affects the liver, skin, mucosa, musculoskeletal system, and gastrointestinal and respiratory systems, the efficacy of low-dose systemic isotretinoin treatment regimens and their adverse effect profiles have recently been investigated (6-8). Although it has been reported in these studies that the systemic adverse effects and costs are lower than those of high-dose isotretinoin treatment, we have found no studies in the literature that compare dose-dependent adverse ocular effects.

In this study, we compared dose-related ocular adverse effects during systemic isotretinoin treatments.

METHODS

Fifty-one patients were diagnosed with acne vulgaris, treated with systemic isotretinoin in the Department of Dermatology, Gaziosmanpasa a University School of Medicine, and followed up. Twenty-six (16 females, 10 males) were randomized into the high-dose treatment group (Group 1: >0.5 mg/kg per day) and 25 (15 females, 10 males) into the low-dose group (Group 2: <0.5 mg/kg per day). The cumulative dose of isotretinoin was higher than 120 mg/kg in the high-dose group, compared with a cumulative dose of isotretinoin lower than 120 mg/kg in the low-dose group. Laboratory and routine physical examination results were within the normal limits for all the patients included in the study. Patients with systemic hypertension, coronary artery disease, familial hyperlipidemia, diabetes mellitus, renal or hepatic functional disorders, severe osteoporosis, or severe pulmonary, gastrointestinal, or hematologic problems were not included in the study. Hemogram, liver enzymes, triglycerides, total cholesterol, and lipoprotein levels were measured at baseline and monthly throughout the treatment. During the treatment and follow-up periods, those patients with serious systemic or ocular adverse effects were excluded from the study and were treated for the emerging adverse effect.

A complete bilateral ophthalmologic examination was performed by the same ophthalmologist before the onset of treatment, at days 45 and 90 of treatment, and 1 month after the cessation of treatment in all patients. Patients who were identified as having dry eyes, intolerance to contact lenses, or clinical blepharoconjunctivitis during the pretreatment ophthalmologic assessment were also excluded from the study.

The right eye of each patient was evaluated for the statistical analysis of anesthetized Schirmer test (AST), for *Staphylococcus aureus* colonization, and for tear film break-up time (BUT).

To measure the basal tear secretion, a drop of topical anesthetic agent (0.5% proparacaine hydrochloride) was instilled into the inferior fornix of the right eye and excess moisture on the eyelid margin was dried with a cotton tip applicator. A Schirmer test strip (Sno strips, Chauvin Pharmaceuticals Ltd.) was placed at the inferotemporal conjunctival fornix after a few minutes. After 5 minutes,

the amount of wetting was measured in millimeters and recorded as the basal secretion. Wetness extending less than 10 mm on the test paper in 5 minutes was regarded as abnormal. Lacrimal BUT was measured with 0.125% fluorescein solution absorbed strips (Fluo strip, India). All values of 10 seconds or less were considered abnormal. Samples taken from the lower palpebral fornix of the conjunctiva were transported to the laboratory on disposable Stuart transport swabs (Dio-Transport swab). Agar was used to culture the human blood samples. The cultures were incubated at 35 °C for 24 hours in an incubator. Subjective complaints were assessed as either present or absent at the end of the trial.

A *t* test for unpaired samples was used to compare the differences between groups in the ages of the patients, the AST results, and the BUT measurements at specific times (pretreatment, day 45, day 90, and 1 month after treatment cessation), and a χ^2 test was used to compare sex, bacterial colonization, and subjective complaints.

A two-independent-sample *t* test was used to compare Groups 1 and 2. Repeated-measures one-way analysis of variance was used to analyze the differences in AST and BUT between baseline, day 45, day 90, and the follow-up periods. A least significant differences (LSD) test was used to compare baseline results with those for other time points. To emphasize the statistical importance of the change in *S aureus* colonization over time, the McNemar test (χ^2 for independent groups) was used. *p* Values less than 0.05 ($p < 0.05$) were considered statistically significant.

RESULTS

Forty-nine of the 51 patients completed the study. Two patients dropped out of the study: one patient in Group 1 because of blurred vision, and one patient in Group 2 for unrelated reasons. The age and sex distributions of the two groups were homogeneous, with no statistical differences ($p > 0.05$) (Tab. I). Although the difference in the anesthetized Schirmer test was not significant between the groups at the different time points ($p > 0.05$), there was a statistically significant reduction within the groups with time ($p < 0.05$). Whereas this reduction persisted in Group 1 one month after the discontinuation of treatment relative to the baseline value ($p < 0.05$), there was no statistically significant difference between the baseline and follow-up measures for Group 2 ($p > 0.05$) (Tab. II).

Although there was no significant difference in BUT be-

tween the two groups before treatment ($p>0.05$), the measurements made on days 45 and 90 showed statistically significant reductions in the right eyes of the Group 1 patients compared with those of Group 2 ($p<0.05$). One month after the discontinuation of treatment, the difference between the groups was not statistically significant ($p>0.05$). The BUT values decreased significantly within

the groups over time ($p<0.05$). This decrease was sustained in both groups 1 month after the cessation of treatment relative to the baseline values ($p<0.05$) (Tab. II). The results of the conjunctival cultures for *S aureus* colonization for both groups are given in Table III. No statistically significant difference in bacterial colonization was detected between the two groups at day 45 or day 90 of

TABLE I - SOCIODEMOGRAPHIC VARIABLES OF GROUPS 1 AND 2

	Group 1 (n=26)	Group 2 (n=25)	t	χ^2	p
Age, yr (MD \pm SD)	26.92 \pm 5.42	28.52 \pm 7.22	0.895	—	0.375
Gender			—	0.013	0.910
Female	16	15			
Male	10	10			

MD = mean deviation.

TABLE II - ANESTHETIZED SCHIRMER TEST (AST) AND LACRIMAL BREAK-UP TIME (BUT) RESULTS FOR PATIENTS OF GROUPS 1 AND 2 RECEIVING HIGH- AND LOW-DOSE ISOTRETINOIN, RESPECTIVELY

		Group 1 (n=26) (mean \pm SD)	Group 2 (n=25) (mean \pm SD)	t	p*
AST	Baseline	20.23 \pm 8.02	17.84 \pm 6.99	1.133	0.263
	Day 45	14.00 \pm 6.95†	16.64 \pm 6.56†	-1.393	0.170
	Day 90	13.31 \pm 5.97†	15.80 \pm 6.01†	-1.485	0.144
	Follow-up	18.42 \pm 7.04†	17.08 \pm 6.52	0.706	0.484
		F=24.840, p<0.001‡	F=11.081, p=0.001‡		
BUT	Baseline	15.23 \pm 4.95	15.60 \pm 4.55	-0.277	0.783
	Day 45	11.27 \pm 3.95†	13.64 \pm 3.77†	-2.188	0.033§
	Day 90	10.19 \pm 4.18†	13.56 \pm 4.27†	-2.846	0.006§
	Follow-up	13.73 \pm 4.38†	14.88 \pm 4.33†	-0.942	0.351
		F=19.910, p<0.001‡	F=5.196, p=0.007‡		

*Two-independent-sample t test results between Groups 1 and 2.

†According to a multiple comparisons test (LSD), a statistically significant difference was detected compared with baseline ($p<0.05$).

‡Repeated-measures one-way analysis of variance results.

§Significant.

TABLE III - COMPARISON OF STAPHYLOCOCCUS AUREUS COLONIZATION OF THE TWO GROUPS

	n	Group 1 %	p*	n	Group 2 %	p†	p‡
Patients	26			25			
Baseline	0	0		2	8.0		0.216
Day 45	10	38.5	0.004	4	16.0	0.500	0.138
Day 90	10	38.5	0.004	5	20.0	0.250	0.255
Follow-up	4	15.4	0.375	3	12.0	1.000	0.523

*McNemar test p value according to baseline within Group 1.

†McNemar test p value according to baseline within Group 2.

‡Chi square test p value between Groups 1 and 2.

treatment ($p>0.05$). One month after the cessation of treatment, there was no statistically significant difference in bacterial colonization between the two groups ($p>0.05$). Clinical blepharoconjunctivitis was detected in 5 (19.2%) patients in Group 1 and 2 (8%) patients in Group 2 during the treatment, which was statistically not significant ($p>0.05$). In Group 1, one patient experienced contact lens intolerance and another patient blurred vision, whereas there were no other ocular complaints in either group. Subjective complaints (photophobia, burning, itching, scratching) were significantly higher in Group 1 compared with baseline ($p<0.05$). However, 1 month after the discontinuation of treatment, the difference between the groups was not significant ($p>0.05$).

DISCUSSION

The effectiveness of oral isotretinoin treatment for acne vulgaris has been reported to be as high as 70–89% (9, 10). The suggested classical dose is 0.5–1.0 mg/kg per day, administered bid. The treatment period usually lasts approximately 16–30 weeks and the total cumulative dose usually exceeds 120–150 mg/kg (11, 12). The low-dose treatment is suggested to be 0.15–0.40 mg/kg per day, with a total cumulative dose of less than 120 mg/kg. With the low-dose treatment, the incidence of adverse effects is reported to be low and the cost of the treatment is reduced (6–8).

Recently, Fraunfelder et al. (13) have extensively classified the adverse ocular effects related to systemic isotretinoin use. In our study, we compared the most commonly encountered adverse ocular effects of systemic isotretinoin, when administered at different doses.

One patient experienced blurred vision, one patient had severe blepharoconjunctivitis, and one patient had contact lens intolerance, all of whom were in the high-dose group. Two patients left the study, one from each group. The most common adverse ocular effects related to systemic isotretinoin use are blurred vision, refraction problems (myopia), contact lens intolerance, and reduced accommodation (4, 13). In a study by Fraunfelder et al, 39 of 237 patients were reported to have blurred vision and four patients developed transient myopia (4). In another study by Fraunfelder et al, based on data from the National Registry of Drug-Induced Ocular Side Effects at the Casey Eye Institute, systemic isotretinoin use was associated with 473 cases of blurred vision, 85 cases of

changes in refractive error, 17 cases of reduced accommodation, and 38 cases of contact lens intolerance (13).

The second most prevalent adverse effect cited is corneal problems, such as keratitis, corneal opacity, corneal ulceration, herpes simplex virus activation, keratoconus, inflammation, and vascularization (4, 13–15). In our study, we encountered no serious corneal problems.

Another frequent adverse effect is blepharoconjunctivitis (1, 4, 13, 15). Gold et al have reported blepharoconjunctivitis rates as high as 20–50% after 3–5 weeks of systemic isotretinoin treatment (15). The most common cause of both blepharitis and blepharoconjunctivitis is reported to be *S aureus* (15–17). In animal studies, systemic isotretinoin treatment has been associated with a reduction in meibomian gland secretions, ductus and ductulus wall thickening, and peri-acinar fibrosis (18). Mathers et al hypothesized that this meibomian gland dysfunction can increase the risk of blepharoconjunctivitis by increasing lacrimal evaporation caused by a reduction in the lipid layer of the tear drops together with an increase in lacrimal osmolarity (3). This, in turn, may explain the physiopathology of the dry eye associated with systemic isotretinoin use (3, 4). We detected clinical blepharoconjunctivitis in 19.2% of patients in Group 1, which is consistent with the results of previous studies, and in 8.0% of patients in Group 2.

Although the frequency of dry eye has been reported to be as high as 30% after systemic isotretinoin treatment (4), Bozkurt et al recently stated that increased levels of eye dryness are not significant after isotretinoin treatment (17). A recent study on this topic by Aragona et al, in which 30 patients were treated with systemic isotretinoin and another 30 with topical isotretinoin, basal lacrimal secretions were evaluated with the Schirmer I test with and without anesthesia, before treatment and on days 45 and 120 of treatment. In the group using systemic isotretinoin, there was no significant reduction in lacrimal secretion when the test was performed without local anesthetic, which is consistent with the study of Bozkurt et al. However, when local anesthetic was used before basal lacrimal secretion was measured, a statistically significant reduction was seen on day 120 (19). In our study, an anesthetized Schirmer test was performed with topical anesthetic, and no significant difference was observed between the groups at each time point. However, there was a statistically significant reduction within the groups over time. In the study discussed above, there was a statistically significant increase in BUT on day 45 and a de-

crease of similar magnitude by day 120. In our study, lacrimal BUT was not significantly different between the two groups before treatment. However, on days 45 and 90 of treatment, there was a statistically significant reduction in BUT in both the left and right eyes of patients in Group 1 relative to that of Group 2. One month after the cessation of treatment, the abnormality in lacrimal function in Group 1 remained, whereas the lacrimal function of Group 2 had been restored. This can be interpreted as a recommendation for low-dose systemic isotretinoin treatment.

Symptoms such as photophobia, burning, itching, scratching, foreign object sensation, and dryness, which can be considered subjective complaints, were significantly higher in the high-dose group during treatment.

We encountered no adverse effects, other than those discussed above and cited most frequently in the literature,

in either of the groups, such as a reduction in dark adaptation, retinal problems, cataract, diplopia, iritis, and glaucoma, which are less common adverse ocular effects.

Our study demonstrates that low-dose systemic isotretinoin treatment reduces both systemic adverse effects and adverse ocular effects. However, the rate of conjunctival *S aureus* colonization seems to be unrelated to the dose of isotretinoin.

Reprint requests to:
Tongabay Cumurcu, MD
Gaziosmanpaşa University
School of Medicine
Tokat, Turkey 61100
tongabay@superonline.com
tcumurcu@gop.edu.tr

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