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Evaluation of oral isotretinoin effects on hearing system in patients with acne vulgaris: Reversible or not?

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Abstract

Systemic isotretinoin is commonly used for severe acne treatment. It has many side effects, one of these is about hearing system, which has rarely been reported, also previous studies reported contradictory results about systemic isotretinoin and its association with hearing system. In this study, we aimed to investigate whether systemic isotretinoin affected on the hearing system or not. The study included 32 acne vulgaris patients (64 ears) who treated with oral isotretinoin 0.5 mg/kg body weight for at least 4 months and audiometric tests including pure-tone, speech, bilateral acoustic reflexes, and tympanometric measurements were performed at baseline, in the first week, in the first month, and third month of treatment, and sixth month after treatment. Audiometric tests were performed for right and left ears separately. A significant difference was found in the pure-tone thresholds (before treatment, first week, first month, third month of treatment, and sixth month after treatment) for the both ears at 8000 Hz ($P < .001$) and a significant decrease in the sixth month post-treatment pure-tone thresholds compared to pre-treatment thresholds at 8000 Hz. Additionally, a statistically significant increase was observed in serum LDL and triglyceride levels in the third month of treatment and a significant decrease at the sixth month after treatment ($P < .001$). Systemic isotretinoin caused bilateral hearing threshold changes in acne patients during the therapy but the changes improved after discontinuation. Therefore, our findings may provide safety using for dermatologists about hearing effects of isotretinoin, which is quite effective on severe acne.

KEYWORDS

acne, hearing, isotretinoin

1 | INTRODUCTION

Systemic isotretinoin, a synthetic derivative of vitamin A (retinol), remains the most efficacious treatment of severe acne. Many cases of more moderate disease, which are unresponsive to other treatment modalities, are treatable with systemic isotretinoin.[1] It is the only therapy having impacts on all of the major etiological factors implicated in acne. By influencing various stages of the cell cycle, such as, progression, differentiation, and apoptosis, isotretinoin shows success in treatment.[1-7] It greatly reduces sebum production, influences comedogenesis, reduces the colonization of *Propionibacterium acnes*, and has anti-inflammatory properties.[2-5] Various narrative reviews and, studies on acne have discussed the efficacy and adverse events of oral isotretinoin, but studies about the side effects on the hearing system have rarely been reported.[3,8-11]

The goal of this prospective study was to investigate whether systemic isotretinoin affects hearing functions with pure-tone audiometry, speech audiometry, and tympanometry.

2 | MATERIALS AND METHODS

2.1 | Study design

In this single- center, prospective study, 32 patients with acne vulgaris (64 ears) who had an indication for systemic isotretinoin treatment at the department of dermatology were included. After receiving approval from the Local Committee of Clinical and Laboratory Research Ethics, patients between the ages of 18 and 50 years were admitted to the clinic. The study group was selected from among male and non- pregnant female patients who had severe resistant acne vulgaris, were indicated for oral isotretinoin therapy, and were informed about and consented to receive oral isotretinoin therapy. Female patients who had potential risk of pregnancy were using at least two methods of birth control. They had a negative serum pregnancy test 1 week before the initiation of the therapy. Patients who had a history of psychiatric diseases, sensitivity or allergy to drugs, inflammatory bowel diseases, metabolic and systemic diseases causing hearing loss, otoscopic evidence of a perforated tympanic membrane or other middle-ear pathology, a flat tympanogram or absence of acoustic reflexes at 1 kHz with contralateral stimulation, an air-bone gap >5 dB at any frequency, Meniere's disease, cranial trauma, presbycusis (50 years older), noise exposure, ear surgery, ototoxic agents usage, and pregnancy were excluded from the study.

Oral isotretinoin therapy was initiated at a dose of 0.5 mg/kg body weight. Treatments lasted for at least 4 months. Liver and renal function tests, complete blood count, and assessments for lipid parameters, such as, total cholesterol, triglyceride, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were performed before initiation and once a month during the treatment.

2.2 | Audiometry

The hearing status of the patients was determined according to otoscopic examination and auditory test results. Audiometric tests included pure-tone, speech, bilateral acoustic reflexes, and tympanometric measurements. Tests were performed at the beginning of treatment, and in the first week, first month, and third month of treatment, and in the sixth month after treatment.

Pure-tone and speech audiometry assessments were performed using a diagnostic audiometer (interacoustic ac40) in a sound-treated cabin. TDH-39 standard headset was used for air conduction thresholds and speech tests. Air conduction pure-tone thresholds from 250 to 8000 Hz for the right and left ears were obtained. Additionally, bone-conduction thresholds were measured at 500 and 4000 Hz. Hearing thresholds of the right and left ears were determined with the ascending method in *5*-dB steps at frequencies of 250, 500, 1000, 2000, 4000, and 8000 Hz. If the patient made two or more responses to a set of three stimuli, she/he was supposed to have heard the sound. Tympanometric measurements were performed using a TDH-39 headset and Middle Ear Analyzer (TympStar GSI). Pure-tone averages (PTAs) were used to define the degree of hearing loss at all frequencies. The degree of hearing loss was determined by averaging the pure-tone hearing thresholds (in decibels) for test frequency groups. PTAs of air conduction thresholds were calculated for the right and left ears separately.

2.3 | Statistical analysis

Results are presented as median (min-max). The distribution pattern of the data were investigated using Kolmogorov Smirnov normality test ($P < .001$). To compare the consecutive measurement results, Friedman test was used. For advanced comparison of consecutive measurements, Wilcoxon test was used as the post-hoc test. All statistical analysis was performed using the SPSS 23.0 software for Windows (SPSS Inc, Chicago, IL). A P value under .05 was considered statistically significant. Additionally, for post- hoc comparison tests, we used Bonferroni correction of five consecutive measurements (decimal combination) and a P-value less than .005 (0.05/10) was considered statistically significant.

3 | RESULTS

Fifty-one patients were enrolled in the study, but thirty-two patients were able to comply with the scheduled therapy and follow-up procedure. The attribution rate was 62.7%. The group consisted of 5 (%15.6) males and 27 (%84.3) female patients. The mean age was 32 ± 3.2 years (age range: 18-33 years). In our study population, all of the patients (100%) showed a hearing change for at least one frequency in any ear. However, all patients had a level 1 (mild) Hartwigscale score[12] since the hearing changes did not require any change in the treatment. According to the modified Schumock and Thorton scale[13] assessment, hearing changes in all patients were not preventable because none of the nine criteria of the scale were fulfilled.

The otoscopic examination was normal in all participants. The right and left ears of the patients were tested and evaluated separately. Speech discrimination scores were within normal limits in all patients. Tympanometric findings in all patients were normal for each ear. Normal acoustic reflexes, peak pressure, gradient, peak compliance, and ear canal volumes were obtained in all patients before the initiation of the treatment and in all follow-up measurements.

No statistically significant differences in the pure-tone thresholds (before treatment, the first week, first month, and third month of treatment and, the sixth month after treatment) for both ears of the patients were evident at 250, 500, 1000, 2000, and 4000 Hz. ($P = .056$, $P = .074$, $P = .105$, $P = .984$, and $P = .442$, respectively for the right ears; and $P = .365$, $P = .434$, $P = .162$, $P = .739$, and $P = .237$, respectively for the left ears) (Tables 1 and 2). However, a significant difference was found in the pure tone thresholds (before treatment, the first week, first month, third month of treatment, and the sixth month after treatment) for both the ears at 8000 Hz ($P < .001$) (Tables 1 and 2). Thus, we found that systemic isotretinoin treatment affected hearing at 8000 Hz frequency. Nevertheless, the final (the

TABLE 1 Median (min-max) pure-tone thresholds of the right ears

Right ear	250 Hz (dB)	500 Hz (dB)	1000 Hz (dB)	2000 Hz (dB)	4000 Hz (dB)	8000 Hz (dB)
Pre-treatment	10 (3-20)	10 (3-20)	8 (3-20)	8 (3-20)	9 (3-30)	8 (3-35)
First week	10 (3-20)	10 (3-18)	8 (3-18)	9 (5-20)	10 (5-20)	10 (5-20)
First month	10 (3-15)	10 (3-15)	10 (5-13)	10 (5-15)	10 (5-30)	13 (5-40)
Third month	10 (3-20)	10 (3-13)	10 (5-13)	10 (5-20)	10 (5-20)	14 (5-30)
Sixth month after stopping treatment	8 (3-15)	8 (5-12)	8 (3-15)	8 (5-12)	9 (5-20)	8 (5-20)
P-value[a]	.056	.074	.105	.984	.442	<.001

[a]of Friedman test.

TABLE 2 Median (min-max) pure-tone thresholds of the left ears

Left ear	250 Hz (dB)	500 Hz (dB)	1000 Hz (dB)	2000 Hz (dB)	4000 Hz (dB)	8000 Hz (dB)
Pre-treatment	10 (3-40)	10 (4-18)	10 (3-18)	8 (3-18)	8 (0-20)	8 (5-20)
First week	10 (3-17)	10 (3-33)	10 (3-20)	8 (4-23)	10 (3-20)	10 (5-20)
First month	10 (3-23)	10 (3-23)	10 (3-23)	8 (3-20)	10 (3-20)	12 (5-24)
Third month	10 (3-20)	10 (3-20)	10 (3-15)	8 (5-15)	10 (5-20)	14 (8-30)
Sixth month after stopping treatment	9 (5–20)	10 (3-13)	10 (5-13)	8 (5-12)	10 (5-15)	8 (5-15)
P-value[a]	.365	.434	.162	.739	.237	<.001

[a]of Friedman test.

sixth month after treatment) median speech discrimination values were within normal limits as follows: 92 (90-100) for the right ears and 95 (90-100) for the left ears.

In the advanced comparisons of the right ears, the first week pure-tone thresholds at 8000 Hz were not different from the pre-treatment thresholds (P = .16). However, we found increased pure tone thresholds in the first and third months compared with pre-treatment thresholds at 8000 Hz, but the differences were not significant (P = .047, P = .1). In contrast, we found a significant decrease in the sixth month post-treatment pure-tone thresholds compared with the pre-treatment thresholds at 8000 Hz (P = .001).

In the advanced comparisons of the left ears, the first week pure tone thresholds at 8000 Hz were not different from the pre-treatment thresholds (P = .77). However, we found increased pure-tone thresholds in the first and third months compared with the pre-treatment thresholds at 8000 Hz, but the differences were not significant (P = .021, P = .013). In contrast, we found a significant decrease in the sixth month post-treatment pure-tone thresholds compared with the pre-treatment thresholds at 8000 Hz (P = .001).

The initial median serum LDL level was 79 (49-112) mg/dL, and it was 128 (49-112) mg/dL at the end of the third month of treatment and 86 (56-99) mg/dL at the sixth month after treatment. The initial median serum triglyceride level was 79 (49-165) mg/dL, and it was 171 (62-207) mg/dL at the end of the third month of treatment and 91 (53-122) mg/dL at the sixth month after treatment. Thus, a statistically significant increase was observed in serum LDL and triglyceride levels after the third month of treatment (P < .001). However, both serum LDL and triglyceride levels significantly decreased at the sixth month after treatment (P < .001) (Table 3).

TABLE 3 Serum LDL and triglyceride levels at baseline, third month, sixth month after stopping treatment

	LDL level	Triglyceride level
Pre-treatment	79 (49–112) mg/dL	79 (49–165) mg/dL
Third month	128 (49–112) mg/dL	171 (62–207) mg/dL
Sixth month after stopping treatment	86 (56–99) mg/dL	91 (53–122) mg/dL
P-value[a]	*P*<.001	*P*<.001

[a]of Friedman test.

4 | DISCUSSION

Acne vulgaris is a common skin disorder that affects the quality of the social life of patients. Even though many therapeutic modalities have been recommended for use, oral isotretinoin is an effective, and successful first line treatment for severe acne, and the success of the treatment with oral isotretinoin seems to greatly improve the social functioning of acne patients.[3,8,14]

Oral isotretinoin has effects on cellular growth and differentiation, and the maintenance of immune modulatory function.[3,5,15] The clinical adverse effects of isotretinoin and other retinoid types can be divided into the following two groups: mucocutaneous and systemic toxic effects. Dryness and fissures on the lips, skin, and mucosae may occur due to a reduction in sebum production, slimming of the stratum corneum, and alterations in the skin barrier function. The medication may also have toxic effects on the liver, kidneys, bones,

gastrointestinal tract, central nervous system, eyes, ears, thyroid, and muscles.[15] The teratogenic adverse effects of isotretinoin increases the risk of spontaneous abortion.[8] Even though it has several side effects on multiple systems, effects on the hearing system have rarely been reported.[3,5,15,16] In 1988, Bigby et al. reported 104 suspected adverse reactions occurring in 93 patients who took isotretinoin, and they found decreased hearing in one patient who received the therapy and classified this as possibly related to isotretinoin use.[3] Karabulut et al. performed a study with 38 acne patients (76 ears) using systemic isotretinoin. The patient visits were performed at baseline and at weeks 1, 2, and 3, and the PTAs of air conduction thresholds at 250 Hz (PTA1); 500, 1000, and 2000 Hz (PTA2); 4000, 8000, and 10 000 Hz (PTA3); and 12 500, 16 000, 18 000 and 20 000 Hz (PTA4) for each ear were calculated separately. Unlike our results, they suggested that systemic isotretinoin improved the hearing levels of the patients at all audiometric frequencies in a short-period follow-up, and they did not assess the hearing status of the patients after stopping systemic isotretinoin therapy, but we did assess the hearing status of the patients at the sixth month after treatment.[8] Nikiforidis et al. performed a study with 33 severe nodulocystic acne patients before and 3 weeks after the onset of oral isotretinoin administration and, they found a marked increase in latencies and interpeak latencies and, a decrease in amplitudes for both ears in three patients (9%) after systemic isotretinoin therapy. They suggested that these subclinical changes might occur due to drug-induced synaptic malfunction or a conduction defect in the auditory nerves. The difference of our study from this study is that, they did not assess the hearing status of the patients in a long-period treatment and post-treatment follow-up.[9] Ugur et al. performed a study with 23 acne vulgaris patients (50 ears) who were treated with systemic isotretinoin 5 mg/kg (high dosage). Tests were performed before the use of isotretinoin and after 4 months of treatment. Pure-tone air and bone conduction audiometry assessments including high frequencies (250, 500, 1000, 2000, 4000, 8000, 9000, 10 000, 12 500, 14 000, and 16 000 Hz) were performed in all subjects. They found that acne patients receiving isotretinoin therapy had bilateral hearing threshold changes (especially at frequencies ≥8000 Hz) despite the absence of significant otoacoustic emissions amplitude levels in the study. This study had a smaller group than that in our study, and in this study, there were no data about the hearing status of the patients after stopping the therapy (whether these changes were reversible).[10] Boztepe et al. performed a study with 47 acne patients using 0.5 mg/kg isotretinoin and, found that isotretinoin treatment decreased PTAs at the end of the sixth month. They suggested that this might be associated with increased lipid levels, as our results indicated, but in this study also, there were no data about the hearing status of the patients after stopping therapy and whether there was a correlation with hyperlipidemia.[11] Akdağ et al. performed a study with 31 acne patients using 0.3-0.6 mg/kg/day systemic isotretinoin. They evaluated pure-tone audiometry and transient evoked autoacoustic emissions before and, 2 and 4 weeks after treatment with systemic isotretinoin. They found significant differences in hearing thresholds between pre-treatment and 2 and 4 weeks after treatment at 1000, 2000, 4000, and 6000 Hz frequencies, but this study also had no data about the hearing status of the patients after stopping treatment (whether this effect was reversible).[17] Karaosmanoğlu et al. performed a study with 30 moderate acne vulgaris patients using 0.5-0.75 mg/kg systemic isotretinoin and 25 psoriasis vulgaris patients using 0.5-0.75 mg/kg acitretin. They performed evaluations before and, at the first and third months of treatment. They found significant differences in hearing thresholds values at 500 Hz frequency between pre-treatment and, at the first and third months of treatment, which progressively decreased in the isotretinoin group ($P < .05$). The differences of our study from this study are that they did not assess the lipid changes and their associations with hearing thresholds, and in this study also, there were no data about the hearing thresholds of the patients after stopping the treatment.[18] Yaldiz et al. performed a study with 30 acne patients (60 ears) who received isotretinoin therapy. They evaluated auditory function at the beginning of the treatment and the sixth month of the treatment with liver function tests and lipid status. No statistically significant differences were found between pre-treatment and post-treatment mean pure-tone audiometry threshold and distortion product otoacoustic emissions (DPOAE) values although they found statistically significant increases in total blood cholesterol, triglyceride, and LDL levels, and decreases in HDL levels.[19] The difference of our study from this study is that they did not perform auditory function tests in the first week, first month, and third month in patients. They found no audiometry threshold changes; thus, there was no need to evaluate auditory function tests after stopping the treatment.

Published data about systemic isotretinoin effects on the hearing system seem to be conflicting as mentioned above. Moreover, it is obvious that major variables that influence the results of researches may occur at different times of hearing measurement procedures during therapy, and these audiometric tests may sometimes be subjective. To our knowledge, no published data are available, such as, evaluation of systemic isotretinoin effects on the hearing system (whether it is reversible). In addition, we did not perform the tests in the sixth month of treatment because the treatment procedure could be longer or shorter than 6 months and depends on patients; thus, some patients could not complete the 6-month treatment procedure. In our study, we found a significant hearing loss at 8000 Hz and increased serum lipid levels in the third month follow-up, like some prior literature. Additionally, all hearing threshold changes disappeared after 6 months from the end of treatment. We also found that both serum LDL and triglyceride levels significantly decreased at the sixth month after treatment when bilateral hearing threshold changes improved. We can hypothesize that hearing loss in the patients who received oral isotretinoin might be due to hyperlipidemia as explained previously.[11] Development of hyperlipidemia in the patients who received oral isotretinoin may lead to a decrease in cochlear oxygenation. The other mechanism might be a direct toxicity on the cochlea or a decrease in vascularization.

In conclusion, according to our results, it was found that systemic isotretinoin therapy does not cause irreversible hearing impairment. Additionally, the drug caused bilateral hearing threshold changes, with significantly increased pure-tone thresholds at 8000 Hz in the third

month follow-up in acne patients, but these changes improved after 6 months from the time of stopping drug use. These changes did not lead to clinical findings in acne patients during the systemic isotretinoin therapy. Furthermore, we would like to focus on the improvement of changes when the lipid levels decreased to pre-treatment levels. We thought this might be impermanent short-term ototoxicity, since the hearing threshold changes improved in long-term follow-up after discontinuation, with decreases in lipid levels. Thus, we suggest that systemic isotretinoin might not have permanent ototoxic effects and clinicians may use this very effective drug safely for the treatment of severe acne patients. Additionally, we think that routine audiometric hearing tests may not be necessary before and during the isotretinoin therapy unless patients have clinical hearing findings or high serum lipid levels.

Our study has some limitations. First, our patients were mostly younger to avoid the confounding effects of advanced age, like presbycusis. Moreover, the study did not include a control group before the treatment. Additionally, our study lacked histopathological examination of the inner ear. Although there was focus on an adverse drug reaction, our data were lacking a causality assessment.

Consequently, further research, including histopathological studies, should be performed with larger study groups to clarify the causative mechanism of systemic isotretinoin-related hearing loss and obtain more assuring results.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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