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Effects of Acitretin Treatment on Hearing in Patients with Psoriasis Vulgaris

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ABSTRACT

Objective: In this study, we aimed to compare the hearing thresholds and outer hair cell functions of patients with psoriasis vulgaris (PV) with healthy individuals and to investigate the ototoxic effects of acitretin treatment (AT) in patients with PV.
Materials and Methods: This study included 23 patients with PV who required treatment with acitretin as well as 23 healthy individuals. Conventional and extended high-frequency pure-tone audiometry and transient-evoked otoacoustic emission tests were performed at regular intervals during the 24 weeks of acitretin treatment.
Results: During the acitretin treatment for the PV group, the hearing thresholds of 4,000 Hz (right ear, p=0.004) presented a significant difference that did not have a worsening effect. The signal-to-noise ratios of TEOAE did not show a significant difference. At 24 weeks of AT, the changes in the hearing thresholds (4,000 Hz) and TEOAE signal-to-noise ratios did not indicate any worsening owing to acitretin. According to the ASHA criteria, there was no significant evidence of ototoxicity related to acitretin. According to the TUNE ototoxicity grading system, it was seen that at 24 weeks of AT, all the patients with psoriasis were scored as grade 0 (no hearing loss).
Conclusion: This study showed that acitretin does not have an ototoxic effect when it is used to treat PV in the recommended treatment doses.

Keywords: Acitretin, high-frequency hearing, ototoxicity, psoriasis vulgaris

INTRODUCTION

Psoriasis vulgaris (PV) is a T-lymphocyte mediated chronic inflammatory disease that is characterized by the focal formation of inflamed, swollen plaques, which is caused by excessive growth of skin epithelial cells and leads to the continuous shedding of scales. It affects approximately two to three percent of adults (1). PV, which has been considered cutaneous for a long time, is now considered a systemic inflammatory disorder that shares pathogenic pathways with many other chronic and progressive diseases (2).

Retinoids (acitretin, isotretinoin, alitretinoin, and bexarotene) are a group of drugs that are used to treat multiple dermatological diseases. Acitretin is a second-generation oral aromatic retinoid and has been effective in treating severe keratinizing skin lesions, such as PV and ichthyosis since the early 1980s (3). Some studies have mentioned that the metabolism of acitretin could cause dose-dependent adverse effects (4-8), such as sensorimotor neuropathy and some ototoxic effects; however, this is unclear (9, 10).

In the literature, there are studies that mention the ototoxic side effects of acitretin. Hearing loss has been reported with tinnitus and bilateral sudden hearing loss during the first week of using acitretin, but the symptoms disappeared after the decrement of acitretin dose (11). In a group of 12 patients with

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hydradenitis suppurativa who were treated with acitretin, one patient had tinnitus in the fourth month of treatment, and the complaint disappeared with dose reduction (12). In another study, the side effects of the retinoid group (oral isotretinoin and acitretin) on hearing were evaluated with audiometric tests and did not present any significant changes to the hearing thresholds. In the isotretinoin group, the 500 Hz air-conduction hearing thresholds declined significantly in the third month of treatment (13).

The ototoxicity assessment has two purposes: to detect the otologic effect that is caused by the drug regimen as early as possible and adjust the dose of the drug accordingly and to plan the patient's auditory rehabilitation to support the verbal communication capacity of the patient when ototoxicity occurs permanently (1, 2, 14). Although there are many studies on the ototoxic effects of isotretinoin, a member of the retinoid group, the presence of relatively few studies on the ototoxic effects of acitretin led to the planning of this study. In this study, we aimed to investigate the ototoxic effects of acitretin treatment in patients with PV and to compare their hearing thresholds and outer hair cell functions with healthy individuals.

MATERIALS AND METHODS

This prospective interdisciplinary longitudinal study was performed after getting ethical approval from the local clinical research ethics committee (Date: 27.06.2018, no: 2018/0197). Written informed consent was obtained from all the patients.

This study included 23 patients with PV who required treatment with acitretin along with 23 healthy individuals. The inclusion criteria were as follows: older than 18 years, the presence of moderate to severe PV (plaque-type psoriasis) for longer than six months, and no history of prior acitretin use. The exclusion criteria were determined as follows: younger than 18 years, pregnant, lactating, the presence of systemic or local infections, history of head or ear trauma, barotrauma, ototoxic drug usage, history of otologic surgery, patients with psoriatic arthritis, history of ear diseases (such as otosclerosis, Meniere's disease, or suppurative labyrinthitis), and a flat tympanogram. In addition, if the patient had a history of previous treatment, including phototherapy, immunosuppressive, and/or immunomodulating drugs and biological agents within the last 12 weeks, they were excluded from the study. If the hearing evaluations were not completed, the patients were excluded from the analysis. The control group in this study consisted of 23 healthy individuals. The healthy individuals were selected from volunteers who had normal hearing thresholds and no history of dermatologic and/or otologic problems.

Acitretin therapy and clinical assessments

Acitretin at a dose of 0.25–0.5 mg/kg per day was orally administered to patients with PV. The basic biochemical measurements were performed at baseline and after three months of acitretin treatment These included: the complete blood count; liver and kidney function tests; and triglyceride, total cholesterol, and low-density lipoprotein. The clinical improvement was measured by the Psoriasis Area and Severity Index (PASI). Accordingly, acitretin treatment (AT) was started at low doses (0.25–0.30 mg/kg/day), with the patients being evaluated monthly. The dose was gradually increased according to the patients' ability to tolerate the mucocutaneous side effects of the drug, such as dryness and cheilitis, and the severity of the disease. In patients who did not develop side effects and a had more severe disease, the dose was increased every month to reach 0.5 mg/kg/day.

Audiological measurements

All the participants underwent a detailed otorhinolaryngological examination. Before the audiological evaluation, a detailed medical history was taken from all the participants. Audiological tests were performed in the PV group before treatment as a baseline as well as in the second, fourth, sixth, eighth, 12th, and 24th week of AT. In the control group, all audiological assessments were performed once. The audiological results of the controls were compared with those of the PV group before AT.

An acoustic immitancemetry test was performed to evaluate the integrity of the external ear canal, tympanic membrane, flexibility of the middle ear, and the acoustic reflex arc using the Interacoustics AT235h clinical tympanometer (Interacoustics, Assens, Denmark). The pure-tone air-conduction thresholds were measured at the decibel hearing level (dB HL) at 250-8,000 Hz. In addition, the bone-conduction hearing thresholds were evaluated at 500-4,000 Hz. The degrees of hearing loss were calculated as the average of four frequencies (500–4000 Hz) (Pure tone average-PTA) (15). The high-frequency hearing thresholds were evaluated at 9.0-14.0 kHz. All audiometric measurements were performed with a calibrated Astera 2 clinical audiometer (Madsen-Otometrics, Denmark). The TDH 39 supra-aural headphone (Telephonics, Farmingdala, NY, USA) was used for determining the air conduction. The Radio-ear B-71 bone vibrator was used for the bone-conduction threshold. The high-frequency hearing thresholds were determined using the Sennheiser HAD 200 circum-aural headphones (Sennheiser Electronic GmbH & Co. KG, USA). The transient-evoked otoacoustic emissions (TEOAEs) were recorded and analyzed using the Madsen Capella Oto-acoustic Emissions System Model: 8-03-460 (Otometrics/ Natus Medical ApS, Denmark). TEOAEs were obtained using rectangular clicks at an intensity of 80±2 dB sound pressure level (SPL). The signal to noise ratios were analyzed at 1,000, 1,500, 2,000, 3,000, and 4000 Hz. Six dB peak-equivalent SPL (peSPL) SNR for at least three frequencies were accepted as normal TEOAEs.

High-frequency hearing was evaluated with high-frequency audiometry test in both groups, the patients with psoriasis and the control group. All audiological tests were performed in a double-walled, sound-isolated audiometric booth by two audiologists.

The ototoxicity decision was made according to the American Language Speech Hearing Association (ASHA) criteria (1994)

and the TUNE grading system (2014). The ASHA criteria have been developed to identify ototoxicity as early as possible by comparing the deterioration to the baseline pre-drug tests (16). According to the ASHA criteria, the presence of one of the following three conditions is sufficient to decide on ototoxicity: (a) a decline of the air-conduction hearing threshold at any test frequency ≥ 20 dB, (b) a decline of the hearing threshold of ≥ 10 dB at any two consecutive frequencies, and/or (c) a loss of response at any consecutive three frequencies that were previously detected.

The TUNE grading system uses air conduction measurements to evaluate speech intelligibility (17). According to the TUNE grading system: grade 0 indicates no hearing loss, grade 1a corresponds to 10 dB or more threshold shift at high frequencies (pure tone average of 8-10-12.5 kHz) or subjective complaints, grade 1b corresponds to 10 dB or more threshold shift at conventional frequencies (pure tone average of 1-2-4 kHz), grade 2a corresponds to 20 dB or more threshold shift at high frequencies (pure tone average of 8-10-12.5 kHz), grade 2b corresponds to 20 dB or more threshold shift at conventional frequencies (pure tone average of 1-2-4 kHz), grade 3 corresponds to 35 dB or more hearing level at conventional frequencies pure tone average of 1-2-4 kHz, and grade 4 corresponds to 70 dB or more hearing level at conventional frequencies (pure tone average of 1-2-4 kHz).

Statistical Analyses

A sample size was calculated using G* Power version 3.1.9.2 based on the ability of mean difference between two dependent means (matched pairs) for the post hoc test. The power of the study was found to be 93% according to the total sample size of 51 participants, with a confidence level of 95% (p<.05) and an effect size of 0.5. The sample size of our study was decreased by 10% to address the possibility that nonparametric statistics might have to be used because of non-normality of the dependent and independent variables, giving an overall sample size of 46 participants (23 with PV and 23 controls). Descriptive data were provided as means and standard deviations for numeric variables and as percentages for categorical variables. The Shapiro-Wilk normality test was used to assess the normality of the distribution for each finding, and it was decided that using a non-parametric test would be appropriate for modeling the data. The chi-squared test was used to compare the nominal and ordinal data. To test the differences between the repeated measurements, the Friedman's two-way analysis of variance by ranks test and Kendall's coefficient of concordance calculations were used, which are non-parametric alternatives of the repeated measures analysis of variance test. The independent samples of the Mann-Whitney U test was used to identify the differences between the PV and control groups. A p value of <0.05 was considered statistically significant.

RESULTS

The demographic data of the PV group are presented in Table 1. The study and control groups were matched for gender. There was no significant difference between the groups in terms of mean ages (p=0.664). The mean duration of the disease was 7.86±9.2 years. All the participants had normal acoustic reflexes. The distributions of the tympanogram types between the groups were similar (p>0.05) (Table 1).

Table 1. Demographics of the psoriasis vulgaris and the control groups

		PV group	Control group
N		23	23
Age (years)		34–67 (52.4±9.5)	30–64 (51.1±8.7)
Gender	**Male (n, %)**	10, 43.5	10, 43.5
	Female (n, %)	13, 56.5	13, 56.5
Duration of disease (years)		7.9±9.2	-
Tympanograms			
Type A		19 (82.6%)	20 (86.9%)
Type As		4 (17.4%)	3 (13.1%)
Acoustic reflexes Yes/No		23/0	23/0

PV: Psoriasis vulgaris

The pure-tone hearing thresholds and the TEOAE signal-to-noise ratios of the PV group before acitretin treatment and the control group are presented in Table 2. Accordingly, the air-conduction hearing thresholds at 2,000 (left ear, p=0.017), 3,000 (bilaterally, p<0.001), and 4,000 Hz (bilaterally, p<0.001) were significantly worse in the PV group than in the control group. Furthermore, the right and left ear four-frequency PTA (bilaterally p<0.001) values were significantly worse in the PV group. However, in both the PV and control groups, the PTA values were within the audiological normal hearing limits (18). The high frequency audiometry findings were similar between the groups except 14,000Hz of the left ear (p=0.036). The TEOAE signal-to-noise ratios of the PV group were also significantly lower at 3,000 (bilaterally, p<0.05) and 4,000 Hz (bilaterally, p<0.05) than the control group (Table 2).

In the PV group, after 24 weeks of AT, the air-conduction hearing thresholds of conventional pure-tone and extended high-frequency audiometry were significantly different at 4,000 Hz right ear (Tables 3 and 4). During the AT hearing thresholds of 4,000 Hz, (right ear, p=0.004) presented a significant difference, however it did not present a worsening effect and was below the 10 dB audiological error level (10 dB). The signal-to-noise ratios of TEOAE did not show any significant difference (Table 5).

At 24 weeks of AT, the changes in the hearing thresholds (4,000 Hz) and TEOAE signal-to-noise ratios did not indicate any worsening owing to acitretin. The findings of patients with PV did not present a declining 10 dB hearing threshold at two or more consecutive frequencies nor an over 20 dB decline for one frequency. According to the ASHA criteria, there was no significant evidence of ototoxicity related to acitretin.

According to the TUNE grading system, when PTAs (both

Table 2. Hearing thresholds and TEOAE signal to noise ratios of the psoriasis vulgaris and control groups before acitretin treatment

		PV group Mean±SD	Control group Mean±SD	*p* values	Effect size (Hedges' g)
Pure-tone Audiometry (dBHL)					
PTA	Right	16.07±5.85	9.06±3.03	**< .001**	1.504
	Left	15.65±6.05	8.62±4.47	**< .001**	1.321
250 Hz	Right	11.91±4.60	9.75±3.79	.094	0.512
	Left	11.42±6.91	9.75±6.97	.371	0.299
500 Hz	Right	12.62 ±7.84	8.5±4.89	.068	0.630
	Left	10.95±7.35	9.25±4.94	.329	0.271
1000 Hz	Right	13.57±7.44	10.25±3.43	.279	0.573
	Left	11.91±8.29	9.5±4.83	.48	0.355
2000 Hz	Right	11.91±9.01	8.25±5.19	.183	0.497
	Left	13.09±8.28	7.5±5.73	**.017**	0.785
3000 Hz	Right	19.04±7.84	8.75±5.34	**< .001**	1.534
	Left	19.88±7.96	7.87±5.57	**< .001**	1.748
4000 Hz	Right	26.19±10.82	9.25±4.93	**< .001**	2.014
	Left	26.66±12.87	8.25±7.82	**< .001**	1.728
6000 Hz	Right	16.66±9.66	16±14.74	.461	0.052
	Left	19.04±10.07	14.25±12.38	.088	0.424
8000 Hz	Right	18.33±12.68	16.5±14.78	.645	0.132
	Left	20.71± 8.41	18.00±14.90	.324	0.223
High Frequency Audiometry (dBHL)					
9 kHz	Right	24.5±13.26	18.5±19.41	.114	0.360
	Left	30.01±16.14	25.52±24.14	.351	0.218
10 kHz	Right	39±17.29	26±29.63	.081	0.535
	Left	36.25±20.7	26.32±27.38	.158	0.409
11.2 kHz	Right	45.75±18.44	33±32.13	.277	0.486
	Left	43.75±17.68	28.94±30.84	.134	0.589
12.5 kHz	Right	54.64±16.46	33.52±28.05	.059	0.918
	Left	53.92±14.43	33.75±30.08	.052	0.855
14 kHz	Right	56.87 ±5.3	36.42±29.38	.238	0.968
	Left	55±10.00	33.46±27.71	**.036**	1.034
Transient-evoked otoacoustic emissions (dBpeSPL)					
1 kHz	Right	10.41±2.96	10.91±2.62	.773	0.178
	Left	10.53±2.74	11.09±2.31	.751	0.221
1.5 kHz	Right	11.38 ±3.73	11.17±4.1	.84	0.053
	Left	11.48±3.59	12.05±3.6	.665	0.158
2 kHz	Right	9.74±4.36	10.41 ±4.68	.729	0.148
	Left	10.24±3.87	11.16 ±4.2	.506	0.227
3 kHz	Right	8.61±3.01	11.29±4.29	**.049**	0.723
	Left	8.89±2.89	11.21±3.75	**.037**	0.693
4 kHz	Right	7.72±3.25	9.91±3.63	**.043**	0.635
	Left	8.23±2.92	10.22±3.62	**.043**	0.605

PV: Psoriasis vulgaris, dBHL: Decibel hearing level, dBSPL: Decibel sound pressure level, PTA: 500–4000 Hz pure-tone average

Table 3: Pure-tone hearing thresholds of the psoriasis vulgaris group before and during acitretin treatment

	Hearing Thresholds (dBHL)							
Right Ear	**250 Hz**	**500 Hz**	**1000 Hz**	**2000 Hz**	**3000 Hz**	**4000 Hz**	**6000 Hz**	**8000 Hz**
Before AT	11.91±4.60	12.62±7.84	13.57±7.44	11.91±9.01	19.04±7.84	26.19±10.82	16.66±9.66	18.33±12.68
Second week of AT	13.81±8.2	11.19±8.64	12.85±8.30	11.42±8.96	18.92±9.5	26.42±13.79	17.61±11.68	22.14±16.16
Fourth week of AT	11.42±7.76	10.23±7.98	11.66±8.26	10.47±8.64	17.02±9	23.57±13.4	16.91±10.66	20.71±16.61
Sixth week of AT	10.47±9.34	10.95±8.89	11.66±7.12	11.19±9.21	17.02±9.44	22.85±12.99	17.38±10.07	18.57±15.9
Eighth week of AT	11.91±8.13	10±8.36	12.85±9.02	11.66±9.26	18.09±8.97	24.52±12.33	18.81±12.33	19.76±16.84
12th week of AT	12.61±9.82	10.23±8.72	11.91±8.87	10.95±8.45	18.69±8.46	26.42±12.56	19.05±11.35	20.1±15.57
24th week of AT	10.75±10.67	11±8.52	11.25±8.09	10.5±9.02	18.75±9.44	27±13.41	18.75±10.98	18.25±15.75
Friedman's two-way analysis of variance by ranks	0.096	0.173	0.536	0.593	0.077	**0.004**	0.114	0.442
Kendall's coefficient of concordance	0.009	0.075	0.042	0.038	0.095	**0.157**	0.085	0.049
Effect Size (partial eta squared)	0.911	0.788	0.805	0.693	0.915	**0.929**	0.808	0.709
Left Ear	**250 Hz**	**500 Hz**	**1000 Hz**	**2000 Hz**	**3000 Hz**	**4000 Hz**	**6000 Hz**	**8000 Hz**
Before AT	11.42±6.91	10.95±7.35	11.91±8.29	13.09±8.28	19.88±7.96	26.66±12.87	19.04±10.07	20.71±8.41
Second week of AT	10.95±8.3	9.76±7.66	12.38±8.61	10.71±8.11	19.28±7.37	27.85±12.41	21.91±14.35	23.81±18.96
Fourth week of AT	9.28±7.62	9.52±7.05	11.42±7.61	11.66±8.11	19.41±8.69	27.14±13.09	19.04±13.47	21.42±17.68
Sixth week of AT	9.76±8.72	9.76±8.28	11.91±7.32	10.95±7.84	18.92±8.49	26.91±13.17	20.47±12.33	24.05±19.41
Eighth week of AT	11.91±8.13	10±8.36	12.85±7.51	11.66±8.26	19.64±8.63	27.61±13	20.71±13.34	24.28±19.76
12th week of AT	10.71±8.25	10±8.51	12.14±7.34	11.19±8.2	20.11±9.43	29.04±14.54	20.47±13.77	25.47±20.11
24th week of AT	9.75±8.95	10.25±8.02	12.5±6.58	10.75±8.62	20.37±9.84	30±14.23	21.5±13.86	25.25±19.7
Friedman's two-way analysis of variance by ranks	0.506	0.715	0.343	0.193	0.864	0.407	0.53	0.162
Kendall's coefficient of concordance	0.044	0.031	0.056	0.072	0.021	0.051	0.043	0.077
Effect Size (partial eta squared)	0.868	0.745	0.868	0.759	0.932	0.881	0.829	0.882

AT: Acitretin treatment, dBHL: Decibel hearing level

Table 4: High-frequency hearing thresholds of the psoriasis vulgaris group before and during acitretin treatment

	Hearing Thresholds (dBHL)				
Right Ear	**9000 Hz**	**10000 Hz**	**11200 Hz**	**12500 Hz**	**14000 Hz**
Before AT	24.5±13.26	39±17.29	45.75±18.44	54.64±16.46	56.87±5.3
Second week of AT	25±12.77	39±18.68	45.51±18.77	54.06±16.75	56±6.51
Fourth week of AT	23.75±12.65	38.5±18.07	46.75±17.18	55±17.08	55±7.07
Sixth week of AT	24±14.56	38.75±19.92	45.75±17.71	53.33±16.65	55±7.07
Eighth week of AT	24.75±12.41	39.75±18.31	46±16.98	53.12±15.37	53.33±7.63
12th week of AT	25±11.92	39±19.37	46.75±18.37	54±16.61	53.33±7.63
24th week of AT	24.47±12.34	39.21±19.23	45.52±16.49	52.5±16.49	50±7.07
Friedman's Two-Way Analysis of Variance by Ranks	0.831	0.612	0.871	0.515	0.423
Kendall's Coefficient of Concordance	0.025	0.039	0.022	0.079	0.5
Effect Size (partial eta squared)	0.855	0.891	0.896	0.945	0.990
Left Ear	**9000 Hz**	**10000 Hz**	**11200 Hz**	**12500 Hz**	**14000 Hz**
Before AT	30.00±16.14	36.25±20.7	43.75±17.68	53.92±14.43	55±10.00
Second week of AT	30.25±16.73	38.25±19.75	43±17.27	54.64±14.21	50±7.07
Fourth week of AT	31.5±17.92	38.75±19.25	45.75±17.34	53.75±14.16	52±8.36
Sixth week of AT	28.25±17.18	35±19.6	43.25±18.93	50.83±14.27	48.75±6.29
Eighth week of AT	28.75±17	36.75±20.20	43±17.87	53.33±13.04	51.66±2.88
12th week of AT	27.63±15.39	36.05±19.61	42.63±18.05	62.63±20.3	51.66±2.88
24th week of AT	27.89±17.02	35.52±18.84	43.15±16.93	50.45±13.12	50±7.07
Friedman's Two-Way Analysis of Variance by Ranks	0.425	0.215	0.761	0.592	0.423
Kendall's Coefficient of Concordance	0.052	0.073	0.03	0.086	0.5
Effect Size (partial eta squared)	0.786	0.845	0.904	0.979	0.992

AT: Acitretin treatment, dBHL: Decibel Hearing Level

Table 5: Transient-evoked otoacoustic emissions in the psoriasis vulgaris group before and during acitretin treatment

	TEOAE Signal Noise Ratios (dBpeSPL)				
Right Ear	**1000 Hz**	**1500 Hz**	**2000 Hz**	**3000 Hz**	**4000 Hz**
Before AT	10.41±2.96	11.38±3.73	9.74±4.36	8.61±3.01	7.72±3.25
Second week of AT	10.35±2.87	11.11±3.64	9.61±4.31	8.73±2.68	8.07±3.39
Fourth week of AT	11.1±3.01	12±3.73	10.08±4.22	8.97±3.17	7.83±3.33
Sixth week of AT	10.43±3.06	11.25±3.53	9.77±4.3	9.04±2.81	8.17±3.42
Eighth week of AT	11.02±3.17	12.01±3.71	10.51±4.29	9.45±3.37	8.31±3.67
12th week of AT	11.01±3.31	12.12±3.76	10.74±4.41	9.66±3.59	8.67±3.98
24th week of AT	10.23±3.35	11.84±3.58	10.15±4.46	8.92±3.31	7.82±3.29
Friedman's two-way analysis of variance by ranks	0.224	0.148	0.05	0.379	0.496
Kendall's coefficient of concordance	0.072	0.083	0.116	0.056	0.047
Effect Size (partial eta squared)	.932	.944	.88	.94	.869
Left Ear	**1000 Hz**	**1500 Hz**	**2000 Hz**	**3000 Hz**	**4000 Hz**
Before AT	10.53±2.74	11.48±3.59	10.24±3.87	8.89±2.89	8.23±2.92
Second week of AT	10.41±2.69	11.55±3.47	10.47±3.88	9.02±2.81	7.99±3.43
Fourth week of AT	11.06±2.57	12.01±3.38	11.06±3.64	8.78±2.77	7.94±3.26
Sixth week of AT	10.77±2.53	11.75±3.34	10.54±3.88	9.55±2.98	8.35±3.37
Eighth week of AT	11.11±2.72	11.58±3.67	10.59±3.95	8.65±2.96	8.41±3.6
12th week of AT	11.58±2.81	12.1±3.46	11.38±3.88	9.18±3.32	8.78±3.91
24th week of AT	10.88±3.47	12.02±3.47	10.71±3.92	9.05±3.23	7.98±3.22
Friedman's two-way analysis of variance by ranks	0.089	0.462	0.779	0.184	0.577
Kendall's coefficient of concordance	0.096	0.05	0.028	0.077	0.042
Effect Size (partial eta squared)	.961	.951	.92	.938	.907

AT: Acitretin treatment, TEOAE: Transient-evoked otoacoustic emission, dBpeSPL: Decibel peak equivalent sound pressure level

Table 6: Results of the TUNE ototoxicity grading system in the psoriasis vulgaris group before and after acitretin treatment

	Pre-treatment	Post-treatment
HFR	34.04±12.34	34.04±13.47
HFL	34.76±12.03	34.24±14.68
CFR	17.22±6.46	16.25±8.09
CFL	17.22±6.54	17.75±7.95

HFR: Right ear pure tone average of high frequencies (8-10-12.5 kHz), HFL: Left ear pure tone average of high frequencies (8-10-12.5 kHz), CFR: Right ear pure tone average of conventional frequencies (1-2-4 kHz), CFL: Left ear pure tone average of conventional frequencies (1-2-4 kHz).

conventional and high frequencies) were calculated, it was seen that at 24 weeks of AT, all the patients with psoriasis were scored as grade 0 (no hearing loss) (Table 6).

DISCUSSION

Ototoxicity is one of the most important topics in the field of audiology because of its almost irreversible damage to the inner ear. It requires an examination of the side effects of drug therapy, such as hearing loss, tinnitus, hyperacusis, aural fullness, or balance problems (19). Several ototoxicity classification systems have been published to allow a simple, reliable, and valid interpretation of the audiometric results (20). In this study, the ASHA criteria and TUNE grading system were used for the ototoxicity decision making. The ASHA criteria can be applied to the air-conduction hearing thresholds at both conventional or high frequencies and sensitive to ototoxicity and minimize variability with the use of adjacent test frequencies. A baseline assessment and repeat testing is recommended to confirm that the changes in the threshold are related to ototoxicity (16). The TUNE grading system is a newly developed system for ototoxicity in adults. This system evaluates both the frequencies related to speech intelligibility and higher frequencies. The main difference in our study was the use of two different ototoxicity classification or grading systems. In other studies, there was not an acceptable ototoxicity classification protocol to evaluate the ototoxicity owing to acitretin or isotretinoin. Statistically significant changes in hearing thresholds should be interpreted using an ototoxicity classification system.

For comprehensive ototoxicity monitoring, acoustic immitancemetry, transient-evoked, and/or distortion product oto-acoustic emissions were suggested to combine with the conventional and high-frequency pure-tone audiometry (20).

The TEOAEs are more sensitive to ototoxic changes than the pure-tone hearing threshold; however, the most sensitive test for ototoxic changes is high-frequency audiometry (14). In this study, the TEOAE tests were combined with the conventional and high-frequency audiometry tests for ototoxicity monitorization.

Acitretin, etretinate, isotretinoin, and tretinoin are aromatic retinoid analogues of vitamin A. Acitretin toxicity has generally been described as dose-dependent and has been reported to cause transaminitis, pseudotumor cerebri, hyperostosis, and hyperlipidemia (21). Etretinate, a metabolite of acitretin, has also been reported to cause peripheral neuropathy (11).

Studies on the effects of acitretin on hearing are few (11-13), and the mechanism of ototoxicity has not been defined yet. The effect of oral acitretin intake on hearing was reported for the first time in a 31-year-old patient using acitretin for psoriasis. Tinnitus and hearing loss were described in the patient one week after starting acitretin. The averages of 500–2,000 Hz were 47 dBHL in the right ear and 33 dBHL in the left ear. Tinnitus was more severe in the right ear. As soon as otological complaints began, acitretin was discontinued, and prednisolone at a dose of 1mg/kg/day was initated. In the audiological evaluation of the patient two years later, it was determined that the tinnitus disappeared, and the mean of 500–2,000 Hz was obtained as 35 dBHL on the right and 30 dBHL on the left. In this study, the daily dose of orally administered acitretin was not specified. No baseline evaluation was made in this case report, and only conventional frequencies were evaluated with pure tone audiometry tests after the patient's complaints started, with high frequency audiometry and otoacoustic emission tests not being performed (11). In the second study reporting hearing impairment with the use of acitretin, four-year follow-up findings of 12 patients with hidradenitis suppurativa were presented. These patients were treated with acitretin at a dose of 0.59 mg/kg/day for nine to 12 months. Bilateral tinnitus was observed in one patient four months after the onset of acitretin, but hearing loss was not described. When the drug was discontinued, the complaint disappeared. When acitretin was restarted three weeks later, tinnitus, headaches, and concentration impairment reappeared, resulting in the patient stopping acitretin completely (12). In this study, no findings regarding hearing assessment were given. Karaosmanoglu et al. reported the average hearing thresholds of 30 patients with PV at 250–10,000 Hz frequencies at baseline at the first and third months during 0.5–0.75 mg/kg/day oral acitretin use (13). Hearing thresholds in the acitretin group did not change significantly after treatment. The audiological findings presented in this study are those obtained after three months of follow-up. In that study, considering that otologic complaints emerged after using acitretin for four months, the adequacy of a three-month follow-up period is controversial. Otoacoustic emission assessments were not performed (13). Important points that distinguish our study from others include the six-month follow-up period, the evaluation of frequencies above 10,000 Hz, and the otoacoustic emission findings.

Isotretinoin, like acitretin, is a member of the retinoid group and has similar action and side-effect mechanisms to acitretin (13). However, its ototoxicity has been more studied than that of acitretin. In the literature, clinical studies and case reports suggest that isotretinoin affects hearing (22-27). Akdağ et al. have reported a case with permanent bilateral sensorineural hearing loss after isotretinoin treatment (22). A 15-year-old male who was treated with isotretinoin displayed bilateral mild to moderate sensorineural hearing loss on the fifth day of treatment, which did not improve even after ceasing isotretinoin. The mechanism of ototoxicity-related inner ear damages was explained by the decreased microcirculation and oxidative stress related apoptosis (22). However, a clear definition of the ototoxic mechanism of acitretin has not been made, and longitudinal studies with different dose applications are required.

Rosende et al. have reported a 15-year-old boy who displayed hypoacusia and tinnitus during the six weeks of isotretinoin treatment (23). After withdrawing isotretinoin, he improved. In another study, Akdağ et al. have stated that the 1–6 kHz air-conduction hearing thresholds got significantly worse after isotretinoin treatment, whereas the otoacoustic emissions did not decline (24). Uğur et al. have reported a clinical study consisting of the audiological results of 25 patients who were treated with isotretinoin (25). After treatment, the conventional and high-frequency hearing thresholds were better than the pre-treatment thresholds. Otoacoustic emission amplitudes did not present a significant change after treatment. Karabulut et al. evaluated 38 patients with conventional and high-frequency pure-tone audiometry and found in the third week of isotretinoin treatment, the hearing thresholds were better than the pre-treatment thresholds (26). There are also experimental studies that report that retinoic acid stimulates the *in vitro* regeneration of auditory hair cells in ototoxic-poisoned rat organs of Corti (27, 28). In this study, after 24 weeks of AT, the audiologic findings of patients with PV did not present a 10 dB hearing threshold decline at two or more consecutive frequencies or over a 20 dB decline for one frequency. According to the ASHA criteria, there was no significant evidence of ototoxicity related to acitretin. Similarly, according to the TUNE grading system, it was seen that at 24 weeks of AT, all the patients with psoriasis were scored as grade 0 (no hearing loss).

PV is considered an autoimmune and dermatological disease. It was reported that the vascular or autoimmune effects of PV on the inner ear may increase the chance of sensorineural hearing loss (29). Vir et al. compared the patients with PV and the healthy control group in terms of cochlear function and hearing evaluation (30). They found statistically significant differences between the two groups regarding the pure-tone thresholds at high frequencies and distortion product otoacoustic emission (DPOAE) responses at all frequencies. In their study, they explained that these significant differences were caused by the damage to the outer hair cells of the cochlea in patients with PV, which resulted in high-frequency hearing loss. Yen et al. reported that the risk of sudden sensorineural hearing

loss in patients with psoriasis was 1.51 times higher than in healthy individuals (31). Possible causes of this finding are the systemic effects (microvascular or cellular) of psoriasis on the cochlea. In their study, Borgia et al. have evaluated the hearing function of patients with PV and compared it with the healthy controls (32). The comparison of the audiometric tests between the groups revealed pronounced hypoacusis in patients with PV than in the control group with a clear prevalence of sensorineural hearing loss. Furthermore, SNHL increased in patients with PV proportionally to their age, which was at a higher rate than in healthy individuals and could be linked to metabolic syndrome (32). In two different studies, the pure-tone audiometry and DPOAE findings of patients with PV were compared with healthy individuals, and no significant differences were observed between the groups (33-34). In this study, the pre-treatment two (left ear), three, and 4,000 Hz hearing thresholds of the pure-tone audiometry test and three and 4,000 Hz TEOAE signal-to-noise ratios of the PV group were significantly worse than those of the healthy controls. Although the hearing thresholds were within normal limits, except for 4,000 Hz, the significant difference between the PV and control group may be related to a subclinical autoimmune involvement. Therefore, an audiological follow-up of PV patients is important.

This study had some limitations. As the study population was small, the dose-dependent effects of acitretin were not evaluated. In addition, the patients were only followed for 24 weeks because the sale of acitretin in Turkey was stopped temporarily at that time. Another limitation was that the otoacoustic-emission assessment was made with the TEOAE test instead of DPOAE, owing to a technical failure of the DPOAE probe.

In conclusion, six months of AT has no significant ototoxic effects on patients with PV. As ototoxicity causes irreversible damage to the inner ear, it is important to collaborate between the dermatology, ear-nose-throat, and audiology departments to analyze the risk of ototoxicity with treatment methods as early as possible.

Ethics Committee Approval: This study was approved by Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (Date: 27.06.2018, No: 2018/0197).

Informed Consent: Written informed consent was obtained.

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