Study of the effect of combined interferon and ribavirin therapy on the hearing profile of hepatitis C virus patients

Samir Asal[a], Ossama Sobhy[a], Omneya Ismail[a], Essam Bedewy[b]

Departments of [a]Audiovestibular Medicine, [b]Tropical Medine, Faculty of Medicine, Alexandria University, Alexandria, Egypt

Correspondence to Samir Asal, MD, Faculty of Medicine, Audiology Unit, Alexandria University, Sporting Tram Station, Alexandria, 21311, Egypt
Tel: +20 122 454 9955;
e-mail: samir_asal@yahoo.com

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Objectives

This study aimed to study the effect of combined pegylated interferon and ribavirin (Peg-IFN/RBV) therapy on the hearing profile of patients with hepatitis C virus (HCV).

Materials and methods

The auditory system of a total of 74 chronic HCV patients was assessed using pure tone audiometry (conventional and high frequency) and distortion product otoacoustic emissions (DPOAEs in the form of a DP-gram) immediately before therapy and at the end of the 12th and 24th weeks. Vestibulocochlear adverse effects including hearing loss, tinnitus, vertigo, and otalgia were also considered.

Results

Significant elevations in hearing thresholds were found on comparing thresholds at the 12th and 24th weeks with those at the onset of the study. The elevations were mostly at higher frequencies (3000, 4000, 6000, 8000, 9000, 10 000, 11 200, and 12 500 Hz), and did not affect speech perception. For DPOAE, significant differences were observed at all F_2 frequencies on comparing both amplitudes and signal to noise ratios at the 12th and 24th weeks with those before therapy, with significance appearing earlier for higher F_2 frequencies. Otologic complaints were insignificant, except for tinnitus; a significant increase in tinnitus was observed from 0 to 31.1% by the end of the study.

Conclusion

Significant auditory adverse effects may result from combined Peg-IFN/RBV therapy in HCV patients, highlighting the importance of prompt monitoring of auditory functions in these patients.

Keywords:
audiometry, distortion product otoacoustic emissions, hepatitis, interferon, ribavirin

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Introduction

Chronic hepatitis C virus (HCV) affects an estimated 300 million individuals worldwide, and in Egypt, the prevalence is estimated to be the highest, somewhere between 15% and 20% of the general population [1]. Treatment of HCV with interferon-α (IFN-α) 2b and ribavirin (RBV) therapy has shown to be effective for many years now, with 41–47% of patients achieving a sustained virologic response [2–4]. With the current pegylated interferons (Peg-IFN) and RBV combination, overall sustained virologic response rates are reported to be 54–56% [5–7].

Despite the current popularity of Peg-IFN and RBV therapy, many reported side effects with standard IFN-α are also observed with Peg-IFN combination therapy. Flu-like symptoms such as fever, chills, muscle aches, nausea, vomiting, and fatigue are common side effects of treatment. Depression and related symptoms, such as anxiety, irritability, insomnia, and mental confusion, are not rare and may be significant in patients with a history. Common hematologic side effects that require monitoring include neutropenia and thrombocytopenia. Withdrawal rates in IFN-based combination studies because of side effects range from 6 to 7% [4–8].

Little is known about the effects of Peg-IFN on the auditory system. In the literature, a few patients with chronic HCV have been reported to develop sudden hearing loss because of Peg-IFN and RBV combined therapy [9–11]. It was suggested that the mechanisms of sudden sensorineural hearing loss in these patients included direct ototoxicity, autoimmunity, and hematological changes [9].

Other reports noted that auditory disability frequently developed in the later stages of IFN therapy for HCV patients in the form of tinnitus and/or hearing loss [12–14]. They described audiometry-documented SNHL, which was mostly mild and reversible after discontinuation of therapy [10,15–17].

However, other studies have reported that IFN–RBV therapy does not have any significant association with hearing loss in HCV patients, and could thus be administered safely [18,19].

Many ototoxic drugs exert their ototoxic effect at the highest frequencies first, and as the exposure continues,

lower frequencies become involved. As hearing is traditionally only tested up to 8 kHz, most initial cases of hearing loss from ototoxic drugs are never identified by standard audiometric testing [20].

OAEs reflect the functional status of the outer hair cells, which are responsible for the exquisite sensitivity, sharp frequency selectivity, and wide dynamic range of the normal auditory system, and constitute the only noninvasive means of objective cochlear investigation [21]. Few studies in the literature have evaluated the effect of the drugs used in this study on hearing and their effect on cochlear outer hair cells.

Moreover, the Egyptian Ministry of Health guidelines for HCV therapy do not specify screening of hearing by audiometry or monitoring cochlear function in their treatment and follow-up protocol.

Considering the above data, our research aimed to study the effect of dual therapy with IFN and RBV on hearing in chronic HCV patients.

Materials and Methods

This study was carried out on 74 chronic HCV patients assigned to receive IFN and RBV who were referred to the Audiology unit, Otorhinolaryngology department at the Main University Hospital. We had no age or sex restrictions for our study. All patients were diagnosed to be HCV positive on the basis of positive viral load measurements (IU/ml); HCV-RNA levels were assessed using quantitative PCR and histopathological grading of liver biopsies was a prerequisite for commencement of therapy as well. Patients were required to have no history of chronic middle ear pathology, ear operation, or otoscopic evidence of ear drum abnormalities.

Each patient was subjected to a full assessment of history including history of any otologic complaints in the form of hearing loss, tinnitus, vertigo, and otalgia, which were assessed before starting therapy and at the end of the 12th and 24th week of therapy. All patients also underwent an otoscopic examination. An audiologic evaluation was carried out before starting therapy and at the end of the 12th and 24th week of therapy, respectively. It included the following:

(1) Pure tone audiometry (PTA) (using a Madsen Astera audiometer in a sound-treated room, Part of the GN group, Denmark) in the form of standard audiometry, which included air conduction thresholds for the conventional frequencies (0.25, 0.5, 1, 2, 3, 4, 6, 8 kHz) and bone conduction thresholds in the frequency range of 500–4000 Hz at octave intervals, as well as measurement of thresholds in the sensitive five frequency ranges, generally separated by 1/6 octave (8, 9, 10, 11.2, and 12.5 kHz) [22].
(2) Speech audiometry, including speech reception threshold, using Arabic spondaic words [23], and the Word Discrimination Score (WDS), using Arabic phonetically balanced monosyllabic word lists [24]. Twenty-five words were used to test each ear and scores were expressed in percentage.
(3) Immittancemetry [using an Interacoustics (Part of William Demant group, Assens, Denmark). (AT-235) tympanometer calibrated according to ISO standards]: it included single-component, single-frequency tympanometry with a probe tone of 226 Hz and testing of the acoustic reflex threshold for the ipsilateral and the contralateral elicited reflexes using pure tones at frequencies 500, 1000, 2000, and 4000 Hz. Immittance assessments were used to show that the middle-ear function was normal at the time of the distortion product otoacoustic emissions (DPOAEs) test.
(4) DPOAEs (using the ILO-96 DP Otodynamic analyzer-version 5 in a sound-treated room): the primary tones were generated by the processor card and delivered to the ear canal by an ER-10A (Etymotic ResearchInc., 61 Martin Lane, Elk Grove Village, IL 60007) probe microphone system. Verification of the adequate quality of the probe fit was carried out using the feedback from the 'check fit' procedure of the software. The sound pressure in the ear canal was picked up by a low-level noise subminiature microphone system ER-10A, also situated inside the probe, amplified and delivered to the computer for analysis (digitizing and Fourier transformation). Patients were instructed to sit comfortably in a chair near the equipment, and they were told that no active contribution from them was required, except to sit quietly, breath regularly but as slowly and smoothly as possible, and to try not to produce any noise in the form of yawning, sneezing, or swallowing. Two pure-tone signals, F_1 and F_2 ($F_1 < F_2$; $F_2/F_1 = 1.2$), were presented simultaneously as primary tone frequencies that generate $2F_1–F_2$ DP. DP-gram points were collected at 1/3 octave steps at stimulus levels so that $L_1 > L_2$ by 10 dB. This level is customary among many centers. The levels of the primaries were 65 dB SPL for L_1 and 55 dB SPL for L_2. The parameters studied were DPOAE's amplitudes (dBSPL) and signal to noise ratios (SNR) (dBSPL) measured at different frequency bands centered at different values of F_2 (Hz) (i.e. at 1001, 1257, 1587, 2002, 2515, 3174, 4004, 5042, and 6348 Hz). Results were also classified into one of three categories: 'pass' DP-gram, where the DP

levels were above the noise floor at all frequencies by 5 dB and DP levels were more than −10 dB and the DP-gram showed replicability; 'fail' DP-gram, where all data points were embedded in the noise and did not have sufficient SNR to be considered as valid responses; and 'partial pass' DP-gram, where the DP levels were above the noise at some frequencies (four) and below at others [25].

Results

This study was carried out on 74 chronic HCV patients assigned to combined therapy (Peg-IFN + RBV). Demographic characteristics (Table 1) show that of 74 patients, 45 (60.8%) were men and 29 (39.2%) were women. Patients ranged in age from 20 to 59 years, with the majority (60.7%) in the age group of more than 40–59 years.

Before the commencement of therapy, a detailed assessment of history of any otologic complaints was performed to ensure that all patients fulfilled our prerequisites.

A detailed assessment of a history of otologic complaints was performed throughout the study (Table 2). Before the commencement of therapy, none of our patients complained of hearing loss, tinnitus, vertigo, or otalgia, thus fulfilling the selection criteria for our study. At 12 weeks of treatment, 17 patients (23%) started to develop tinnitus and 6 patients (8.1%) complained of otalgia. A further increase in the number of patients complaining of tinnitus (23 patients; 31.1%) and otalgia (12 patients; 16.2%) was observed in the 24th week of treatment. Eleven patients (14.9%) complained of hearing loss by the 24th week of treatment. A statistically significant difference was observed for tinnitus as a complaint in the time period of 0–24 weeks of treatment, with a deducted critical time period of 0–12 weeks. However, otalgia and hearing loss showed statistically insignificant differences at all time points studied throughout the 24 weeks of therapy.

Table 1 Demographic data of the patients studied (n = 74)

Demographics	*N* (%)
Sex	
Male	45 (60.8)
Female	29 (39.2)
Age (years)	
20–30	12 (16.2)
>30–40	17 (23.0)
>40–50	23 (31.0)
>50–59	22 (29.7)
Minimum–maximum	21.0–58.0
Mean ± SD	43.26 ± 10.89
Median	45.0

Table 2 Otologic complaints of the patients studied

Otologic complaint	Pretreatment [*n* (%)]	During treatment [*n* (%)]	
		12 weeks	24 weeks
HL	0 (0.0)	0 (0.0)	11 (14.9)
P_1[a]		–	0.058
P_2[a]		0.079	
Tinnitus	0 (0.0)	17 (23.0)	23 (31.1)
P_1[a]		<0.001*	<0.001*
P_2[a]		0.355	
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)
Otalgia	0 (0.0)	6 (8.1)	12 (16.2)
P_1[a]		P = 0.088[b]	χ^2 = 0.060
P_2[a]		0.208	

[a]Expressed as χ^2-test. [b]Expressed as Fisher exact test.
*Statistically significant at $P \leq 0.05$.

Audiometric results (Table 3) show that of all tested frequencies, a statistically significant difference in hearing thresholds was identified for the frequencies 3000, 4000, 6000, 8000, 9000, and 10 000 Hz in the time period of 0–24 weeks of treatment, with an apparent critical time period of 12–24 weeks. However, at higher frequencies (11 200 and 12 500 Hz), a statistically significant difference in hearing thresholds was observed in the time period 0–24 weeks of treatment, suggesting a critical time period of 0–12 weeks.

In speech audiometry, differences in Speech Reception Threshold (dB) and WDS (%) were statistically insignificant and all patients had excellent WDS throughout the 24 weeks of treatment.

For DPOAE (Tables 4 and 5), tests of significance showed statistically significant differences on comparing both amplitudes and SNRs and in the time period 0–24 weeks of treatment, at F_2 frequencies centered at 1001, 1257, 1587, 2002, and 2515 Hz. For higher F_2 frequencies centered at 3174, 4004, 5042, and 6348 Hz, statistically significant differences were also found throughout the 24 weeks of treatment, being observed as early as 12 weeks of treatment.

Qualitative results for DPOAE (Table 6) show that before the commencement of treatment, all patients (100%) had 'pass' DP-grams. This value showed a decrease throughout the study: 93.2% at 12 weeks and down to 79.9% by the end of the study at 24 weeks. However, at 12 weeks 4.1% of the patients DP-grams were considered as 'partial pass' and 2.7% considered as 'failed', showing an increase at 24 weeks to 12.2 and 8.1%, respectively. A statistically significant period was observed in the time period 0–24 weeks of treatment.

Table 3 Audiometric results of the patients studied (*n* = 74)

Frequency (Hz)	Pretreatment	During treatment		Frequency (Hz)	Pretreatment	During treatment	
		12 weeks	24 weeks			12 weeks	24 weeks
250 Hz				6000 Hz			
Minimum–maximum	0.0–25.0	5.0–25.0	5.0–25.0	Minimum–maximum	–10.0 to 30.0	-5.0 to 30.0	-5.0 to 60.0
Mean ± SD	15.34 ± 5.75	15.68 ± 5.45	15.74 ± 5.77	Mean ± SD	7.64 ± 10.38	8.38 ± 8.68	11.01 ± 13.50
Median	15.0	15.0	15.0	Median	5.0	5.0	5.0
P_1		0.197	0.058	P_1		0.078	<0.001*
P_2		0.808		P_2		<0.001*	
500 Hz				8000 Hz			
Minimum–maximum	5.0–25.0	5.0–20.0	5.0–25.0	Minimum–maximum	-5.0 to 40.0	0.0–45.0	10.0–70.0
Mean ± SD	15.14 ± 4.30	15.81 ± 4.68	15.54 ± 4.87	Mean ± SD	12.16 ± 11.82	12.97 ± 12.02	23.24 ± 13.71
Median	15.0	15.0	15.0	Median	10.0	10.0	20.0
P_1		0.059	0.234	P_1		0.173	<0.001*
P_2		0.405		P_2		<0.001*	
1000 Hz				9000 Hz			
Minimum–maximum	5.0–25.0	5.0–25.0	5.0–25.0	Minimum–maximum	-5.0 to 45.0	0.0–50.0	0.0–80.0
Mean ± SD	15.14 ± 4.61	15.27 ± 4.82	15.27 ± 4.82	Mean ± SD	14.73 ± 13.85	15.88 ± 15.56	25.24 ± 19.13
Median	15.0	15.0	15.0	Median	12.50	10.0	20.0
P_1		0.593	0.655	P_1		0.053	<0.001*
P_2		1.000		P_2		<0.001*	
2000 Hz				10 000 Hz			
Minimum–maximum	0.0–25.0	0.0–25.0	0.0–25.0	Minimum–maximum	–15.0 to 50.0	-5.0 to 55.0	0.0–75.0
Mean ± SD	13.51 ± 7.06	14.05 ± 7.06	14.12 ± 6.84	Mean ± SD	17.77 ± 16.68	18.78 ± 17.84	29.12 ± 19.26
Median	15.0	15.0	15.0	Median	17.50	10.0	25.0
P_1		0.102	0.132	P_1		0.138	<0.001*
P_2		0.901		P_2		<0.001*	
3000 Hz				11 200 Hz			
Minimum–maximum	0.0–25.0	5.0–25.0	0.0–40.0	Minimum–maximum	0.0–65.0	5.0–75.0	10.0–85.0
Mean ± SD	10.41 ± 7.57	11.15 ± 6.44	12.70 ± 8.57	Mean ± SD	22.09 ± 21.20	29.46 ± 22.85	35.81 ± 22.94
Median	10.0	10.0	10.0	Median	10.0	15.0	25.0
P_1		0.063	<0.001*	P_1		<0.001*	<0.001*
P_2		0.013*		P_2		<0.001*	
4000 Hz				12 500 Hz			
Minimum–maximum	–10.0 to 25.0	-5.0 to 25.0	-5.0 to 55.0	Minimum–maximum	0.0–80.0	5.0–90.0	20.0–90.0
Mean ± SD	11.69 ± 8.77	12.30 ± 7.86	14.66 ± 10.41	Mean ± SD	32.91 ± 26.48	40.81 ± 28.65	48.72 ± 26.68
Median	12.50	10.0	15.0	Median	22.50	30.0	35.0
P_1		0.106	<0.001*	P_1		<0.001*	<0.001*
P_2		<0.001*		P_2		<0.001*	

P_1, *P* value for the Wilcoxon signed ranks test for comparing pretreatment with 12 and 24 weeks; P_2, *P* value for the Wilcoxon signed ranks test for comparing between 12 and 24 weeks. *Statistically significant at $P \leq 0.05$.

Discussion

HCV infection is a major health problem that affects about 300 million individuals worldwide. It is estimated that three to four million individuals are infected every year [1].

The backbone of HCV treatment is Peg-IFN-α and RBV combined therapy. Treatment regimen includes a subcutaneous injection of Peg-IFN of 1.5 μg/kg once weekly, along with a daily dose of oral RBV ranging from 800 to 1200 mg, depending on the HCV genotype and bodyweight [26]. In general, a treatment duration of 48 weeks is recommended. HCV RNA measurements at weeks 4, 12, and 24 are important for a response-guided treatment approach for Peg-IFN/RBV. If, at these time points, the viral load threshold is exceeded or detected in serum, therapy should be stopped [27,28].

Although the systemic side effects of HCV combined therapy have been well documented, little is known about its effect on the hearing system. One of the proposed side effects of therapy is ototoxicity.

In the current study, we attempted to study the proposed effect through a test battery approach that included assessment of history, speech audiometry, PTA including testing frequencies in the conventional range (250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz) and in the extended high-frequency range (9000, 10 000, 11 200, and 12 500 Hz), and DPOAEs in the form of a DP-gram.

During assessment of history, we ensured that all patients fulfilled our selection criteria; none of them (0%) complained of hearing loss, tinnitus, vertigo,

Table 4 Distortion product otoacoustic emissions amplitudes (dBSPL) of the patients studied

F_2 frequencies	Pretreatment	During treatment		F_2 frequencies	Pretreatment	During treatment	
		12 weeks	24 weeks			12 weeks	24 weeks
1001 Hz				Median	3.10	3.15	3.40
Minimum–maximum	−12.10 to 11.10	−12.50 to 11.90	−14.20 to 10.50	P_1		0.389	<0.001*
Mean ± SD	2.63 ± 6.31	2.69 ± 6.26	0.90 ± 6.52	P_2		<0.001*	
Median	2.10	2.50	0.0	3174 Hz			
P_1		0.378	<0.001*	Minimum–maximum	−12.10 to 10.70	−13.0 to 9.90	−17.40 to 9.50
P_2		<0.001*		Mean ± SD	0.87 ± 6.95	−0.20 ± 6.99	−1.69 ± 7.80
1257 Hz				Median	3.20	0.90	−2.10
Minimum–maximum	−4.80 to 16.70	−4.80 to 17.0	−5.20 to 15.80	P_1		<0.001*	<0.001*
Mean ± SD	3.86 ± 5.14	3.77 ± 5.18	1.93 ± 5.68	P_2		<0.001*	
Median	2.70	2.75	1.50	4004 Hz			
P_1		0.115	<0.001*	Minimum–maximum	−12.50 to 15.70	−14.20 to 15.0	−16.10 to 14.50
P_2		<0.001*		Mean ± SD	1.41 ± 6.71	0.17 ± 6.84	−1.22 ± 7.41
1587 Hz				Median	1.30	0.0	−0.90
Minimum–maximum	−1.20 to 13.70	−2.70 to 14.0	-6.90 to 12.80	P_1		<0.001*	<0.001*
Mean ± SD	4.62 ± 4.24	4.51 ± 4.37	3.08 ± 4.97	P_2		<0.001*	
Median	4.40	4.45	3.05	5042 Hz			
P_1		0.166	<0.001*	Minimum–maximum	−16.80 to 18.30	−16.10 to 18.10	−17.0 to 17.60
P_2		<0.001*		Mean ± SD	1.75 ± 9.36	0.42 ± 9.59	1.14 ± 10.22
2002 Hz				Median	2.10	1.60	0.0
Minimum–maximum	−3.50 to 14.10	−3.30 to 15.0	-8.90 to 14.70	P_1		<0.001*	<0.001*
Mean ± SD	4.16 ± 4.48	3.88 ± 4.91	3.34 ± 5.65	P_2		<0.001*	
Median	3.30	2.85	3.25	6348 Hz			
P_1		0.056	<0.001*	Minimum–maximum	−32.90 to 10.40	−36.10 to 10.10	−39.0 to 9.50
P_2		<0.001*		Mean ± SD	−2.27 ± 9.93	−3.79 ± 10.52	−5.61 ± 11.31
2515 Hz				Median	−1.90	−2.90	−4.10
Minimum–maximum	−10.10 to 11.10	−10.80 to 11.50	−13.60 to 11.70	P_1		<0.001*	<0.001*
Mean ± SD	2.14 ± 5.55	1.88 ± 6.02	1.18 ± 7.05	P_2		<0.001*	

P_1, P value for the Wilcoxon signed ranks test for comparing pretreatment with 12 and 24 weeks; P_2, P value for the Wilcoxon signed ranks test for comparing between 12 and 24 weeks. *Statistically significant at $P \leq 0.05$.

or otalgia. By the end of the 12th week of therapy, some patients started to develop tinnitus (23%) and otalgia (8.1%), which, by the end of the 24th week of therapy, increased to 31.1 and 16.2%, respectively. The presence of a statistically significant difference in the number of patients complaining of tinnitus throughout the time period studied suggests that tinnitus might represent the subjective counterpart of ototoxicity. Tinnitus has been reported to be a common side effect of many ototoxic drugs, and there is a common assumption of tinnitus as an early indicator of ototoxicity [29]. The increase in otalgia as a complaint was found to be statistically insignificant, which may indicate that its presence may have been coincidental. An increase in patients' complaints of hearing loss (14.9%) by the end of the 24th week of therapy was found to be statistically insignificant.

Speech audiometry showed statistically insignificant changes that were expected as those complaining of hearing loss showed threshold shifts at frequencies that were not significantly impairing speech perception.

On analyzing audiometric results, therapy was found to show statistically insignificant differences in the frequencies 250–2000 Hz. Significant changes in hearing thresholds started to show at 3000–10 000 Hz on comparing the 24th week thresholds with those at pretreatment as well as on comparing those at the 24th week to thresholds at the 12th week of therapy. However, differences were found to be insignificant on comparing thresholds at the 12th week with those at pretreatment, which signifies a critical time period of 12–24 weeks during which a hearing threshold shift takes place.

Table 5 Signal to noise ratio of the distortion product otoacoustic emissions of the patients studied

F_2 frequencies	Pretreatment	During treatment	
		12 weeks	24 weeks
1001 Hz			
Minimum–maximum	−6.60 to 18.50	5.60–19.0	-6.0 to 16.10
Mean ± SD	5.63 ± 6.25	5.43 ± 5.92	4.63 ± 5.60
Median	5.90	5.35	4.90
P_1		0.060	<0.001*
P_2		<0.001*	
1257 Hz			
Minimum–maximum	−3.50 to 24.20	−3.50 to 25.0	−2.30 to 22.60
Mean ± SD	10.15 ± 6.36	9.86 ± 6.29	8.75 ± 5.61
Median	10.90	10.50	8.90
P_1		0.058	<0.001*
P_2		<0.001*	
1587 Hz			
Minimum–maximum	6.10–22.0	6.30–23.0	4.60–16.60
Mean ± SD	12.94 ± 3.70	12.57 ± 3.74	11.19 ± 3.70
Median	12.80	12.0	11.0
P_1		0.126	<0.001*
P_2		<0.001*	
2002 Hz			
Minimum–maximum	3.20–24.50	3.50–25.0	1.70–22.70
Mean ± SD	15.44 ± 6.25	15.16 ± 6.09	13.65 ± 6.16
Median	16.55	15.90	14.60
P_1		0.179	<0.001*
P_2		<0.001*	
2515 Hz			
Minimum–maximum	3.10–25.30	2.90–25.60	0.0–22.40
Mean ± SD	13.71 ± 5.72	13.49 ± 5.65	11.74 ± 5.60
Median	15.80	15.25	13.40
P_1		0.779	<0.001*
P_2		<0.001*	
3174 Hz			
Minimum–maximum	1.10–25.20	0.0–24.90	2.70–24.10
Mean ± SD	13.01 ± 6.51	12.04 ± 6.23	11.38 ± 6.13
Median	11.60	10.30	9.45
P_1		<0.001*	<0.001*
P_2		<0.001*	
4004 Hz			
Minimum–maximum	3.10–30.20	2.50–30.10	1.0–28.50
Mean ± SD	14.50 ± 7.17	13.19 ± 7.03	11.78 ± 6.48
Median	15.20	13.50	12.80
P_1		<0.001*	<0.001*
P_2		<0.001*	
5042 Hz			
Minimum–maximum	−3.20 to 31.70	−5.60 to 30.80	-8.80 to 30.0
Mean ± SD	13.42 ± 9.78	12.24 ± 9.73	10.90 ± 9.80
Median	14.80	13.80	13.10
P_1		<0.001*	<0.001*
P_2		<0.001*	
6348 Hz			
Minimum–maximum	−20.50 to 23.50	−23.0 to 22.20	−24.10 to 24.0
Mean ± SD	7.23 ± 11.17	5.94 ± 10.84	5.04 ± 11.05
Median	10.35	9.45	8.50
P_1		<0.001*	<0.001*
P_2		<0.001*	

P_1, P value for the Wilcoxon signed ranks test for comparing pretreatment with 12 and 24 weeks; P_2, P value for the Wilcoxon signed ranks test for comparing between 12 and 24 weeks.
*Statistically significant at $P \leq 0.05$.

Table 6 Qualitative results of the distortion product otoacoustic emission of the patients studied

Category	Pretreatment [*n* (%)]	During treatment [*n* (%)]		χ^2	P^a
		12 weeks	24 weeks		
Pass	74 (100.0)	69 (93.2)	59 (79.7)	19.233*	<0.001*
Partial pass	0 (0.0)	3 (4.1)	9 (12.2)		
Failed	0 (0.0)	2 (2.7)	6 (8.1)		
P_1		0.057	<0.001*		
P_2		0.072			

P_1, P value for the Monte Carlo test for comparing pretreatment with 12 and 24 weeks; P_2, P value for the Monte Carlo test for comparing between 12 and 24 weeks; χ^2, value of χ^2 for comparing between the three visits. [a]Expressed as Monte Carlo test.
*Statistically significant at $P \leq 0.05$.

At the frequencies of 11 200 and 12 500 Hz, statistically significant changes in thresholds were observed on comparing thresholds at the 12th week with those at pretreatment, and thresholds at the 24th week with those at the 12th week and with those at pretreatment. This highlights the importance of those two frequencies in the early detection of a hearing threshold shift as they were the only frequencies that were affected in the time period of 0–12 weeks.

In the literature, extended high-frequency audiometry was reported to show earlier threshold changes than conventional audiometry and was proposed as a more sensitive screening tool for ototoxicity [30]. Also, changes were reported to appear as early as the second week of therapy [31].

DPOAEs amplitudes and SNRs at F_2 frequencies centered at 1001, 1257, 1587, 2002, and 2515 Hz showed a similar pattern to the audiometric frequencies in the range 3000–10 000 Hz, where the significant critical time period occurred between the 12th and the 24th week. Results for F_2 frequencies centered at 3174, 4004, 5042, and 6348 Hz showed a pattern similar to the last two frequencies in the extended high-frequency audiometry, showing a critical time period of 0–12 weeks of therapy.

Frequency-specific DPOAEs always showed significant changes throughout the course of treatment, unlike the PTA, where lower frequencies reflecting speech (250–2000 Hz) showed no significant change at all. This would lead us to consider frequency-specific DPOAEs to be a more reliable tool in the early detection of the ototoxic effect of HCV combined therapy.

On assessing DPOAEs qualitatively using the criteria of 'pass', 'partial pass,' and 'failed', a statistically significant change in the criteria was found in the therapeutic time period of 0–24 weeks, which indicates that DPOAE, if assessed qualitatively, may be a partially less sensitive tool in the detection of ototoxicity.

In conclusion, this study indicates an ototoxic effect of Peg-IFN/RBV combined therapy on hearing, starting with a perceived complaint of patients with tinnitus, which was correlated with a shift in hearing thresholds mainly at high frequencies, in both PTA and DPOAE.

In the current study, we propose the critical time period of ototoxicity to be in the therapeutic time period of 0–12 weeks, at which the frequencies 11 200 and 12 500 Hz and DPOAE at F_2 frequencies centered at 3174, 4004, 5042, and 6348 Hz have been proven to be the most sensitive in early detection. However, qualitative DPOAE has shown to be less effective in early detection of the ototoxic effect.

Also, we should raise awareness of the importance of tinnitus as a complaint in this proposed critical time period, where it could be used as a simple screening tool.

Although patients' daily life activities were not altered by the ototoxic effect of therapy as speech perception was not affected significantly, we believe that the auditory function of patients receiving Peg-IFN/RBV therapy should be monitored periodically.

Acknowledgements

Conflicts of interest

None declared.

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