CASE STUDY

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Response to OKN-007 and NAC in a Patient with Unilateral Hearing Loss and Chronic Tinnitus from Vestibular Schwannoma

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ABSTRACT

Background: Tinnitus is the perception of sound in the absence of external acoustic stimulation. Being one of the most common diseases of the ear, it has a global prevalence ranging from 4.1 to 37.2%. To date, it has been difficult to treat tinnitus as its pathophysiology is poorly understood and there are limited treatment options.

Objective: To investigate the effect of OKN-007 (also known as HPN-07), a nitrone-based investigational drug, in combination with oral N-acetylcycsteine (NAC), for the treatment of hearing loss and chronic tinnitus under an individual expanded access protocol.

Patient Case: We report the case of a patient who presented with left-sided ear fullness, mild tinnitus, and mild high frequency sensorineural hearing loss with 100% word recognition. A large enhancing mass seen on MRI revealed a vestibular schwannoma. He underwent subtotal resection of the tumor resulting in a moderate-to-profound sensorineural hearing loss and catastrophic tinnitus. The patient was treated with intravenous OKN-007 at 60 mg/kg dosed three times per week and oral NAC 2500 mg twice daily.

Results: Post-treatment audiometric testing revealed an average of 16.66 dB in hearing threshold improvement in three frequencies (125, 250 and 500 Hz) with residual hearing in the affected left ear. His tinnitus loudness matching improved from 90 dB to 19 dB post-treatment. His Tinnitus Handicap Inventory improved from 86/100 (Catastrophic) to 40/100 (Moderate). He also experienced improvements in sleep, concentration, hearing, and emotional well-being, and reported significantly decreased levels of tinnitus-related distress.

Conclusions: This case report highlights the feasibility and therapeutic potential of the combination of OKN-007 and NAC in treating hearing loss and tinnitus that warrants further investigation.

Keywords: Tinnitus, Hearing loss, OKN-007.

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INTRODUCTION

Tinnitus is caused by various etiologies and is characterized by the abnormal perception of sound in the absence of an external acoustic stimulus. It is commonly associated with noise exposure, aging, and hearing loss, and may also be caused by other risk factors such as head trauma, hypertension, arthritis, smoking, obesity, and alcohol. Common conditions which can lead to tinnitus include endolymphatic hydrops, migraine-induced vestibular pathology, vestibular schwannoma, otosclerosis, labyrinthitis, ototoxicity, multiple sclerosis, meningioma, and stroke[1, 2]. Although many people habituate to the phantom sound, tinnitus can be debilitating and interfere with quality of life by causing psychological distress, with symptoms such as anxiety, depression, insomnia, and concentration difficulties[3]. A systemic review found the global prevalence of tinnitus to range from 4.1% to 37.2%[4]. To date, tinnitus has been difficult to treat and current treatments include tinnitus retraining therapy, cognitive behavioral therapy, auditory stimulation, transcranial magnetic stimulation, and pharmacologic intervention aimed primarily at relieving tinnitus distress[3]. Here, we report a patient with left-sided Sensorineural Hearing Loss (SNHL) and catastrophic tinnitus after vestibular schwannoma surgery who responded to investigational therapy with OKN-007 and N-Acetylcysteine (NAC).

CASE REPORT

A 26-year-old male presented for evaluation of chronic left-sided ear fullness associated with mild pulsatile tinnitus, mild high frequency sensorineural hearing loss, and 100% word recognition. Magnetic Resonance Imaging (MRI) of the brain in September 2019 revealed a large enhancing mass in the left cerebellopontine angle with extension into the left auditory canal and compression of the cerebellum and brainstem (Figure 1A), suspected to be a vestibular schwannoma. He underwent a left retromastoid craniotomy and subtotal removal of left vestibular schwannoma under the operating microscope with microsurgical dissection. Histopathology characterization confirmed the diagnosis of a vestibular schwannoma (Figure 1B). Prior to surgery, his mild tinnitus did not bother him or require further tinnitus evaluation or treatment. The audiogram performed prior to surgery can be seen in Figure 2. However, after surgery, he developed worsening left-sided moderate-to-profound sensorineural hearing loss leading to 0%-word recognition, which never improved, and tinnitus described as a loud waterfall next to his left ear with high-pitched ringing, chimes, and electronic beeps. The persistent hearing loss and catastrophic tinnitus caused significant anxiety, depression, and sleep disturbance. His auditory dysfunction, including left ear tinnitus and hyperacusis, also kept him housebound and prevented socialization, even after pursuing numerous sound and behavioral therapies over two years.

The Patient was started on Venlafaxine post-operatively which helped improve his mood, although his catastrophic tinnitus remained unchanged. He also tried gabapentin, lorazepam, alprazolam, NAC, and ketamine-assisted psychotherapy without significant improvement in his mood, hearing, or severity of tinnitus percept. Although his anticancer treatments of mifepristone, bevacizumab, zoledronic acid, and neoantigen dendritic cell and peptide vaccines led to interval reduction in the size of his tumor (Figure 1C-D), his debilitating tinnitus remained. This continued to disrupt his sleep, attention, emotional equilibrium, and social life, which significantly interfered with his work and daily activities.

After further evaluation and looking into the available treatment options, OKN-007 60 mg/kg intravenous

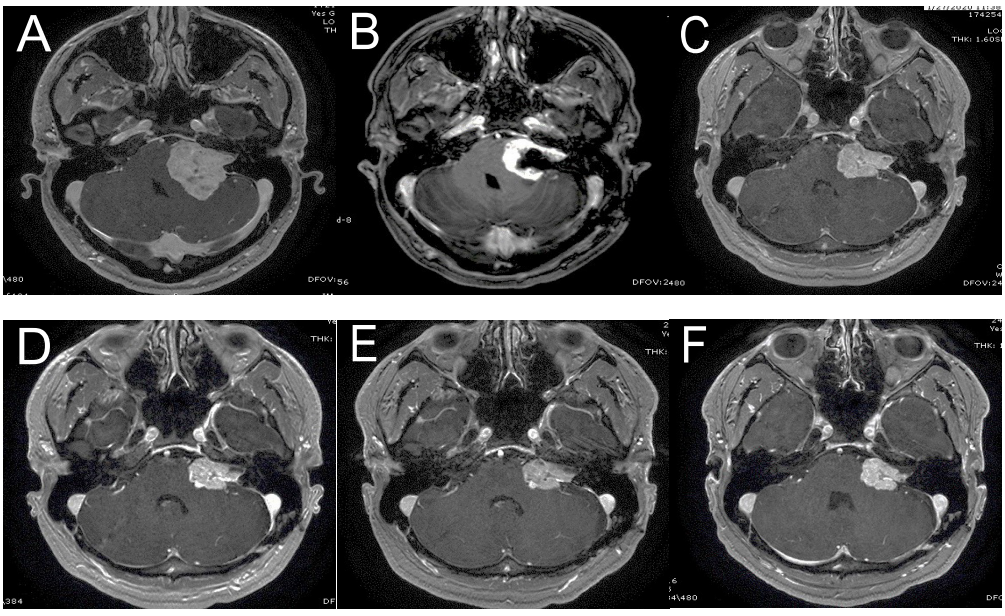


Figure 1: Imaging of Tumor. MRI showing cerebellopontine angle mass extending into the left external auditory canal before surgery (A), immediately post-craniotomy (B), baseline before bevacizumab (C), 8 months post-bevacizumab (D), with slight shrinkage of tumor, pre-OKN-007 and NAC (E), and 4 months post-OKN-007 and NAC (F) with stable disease.

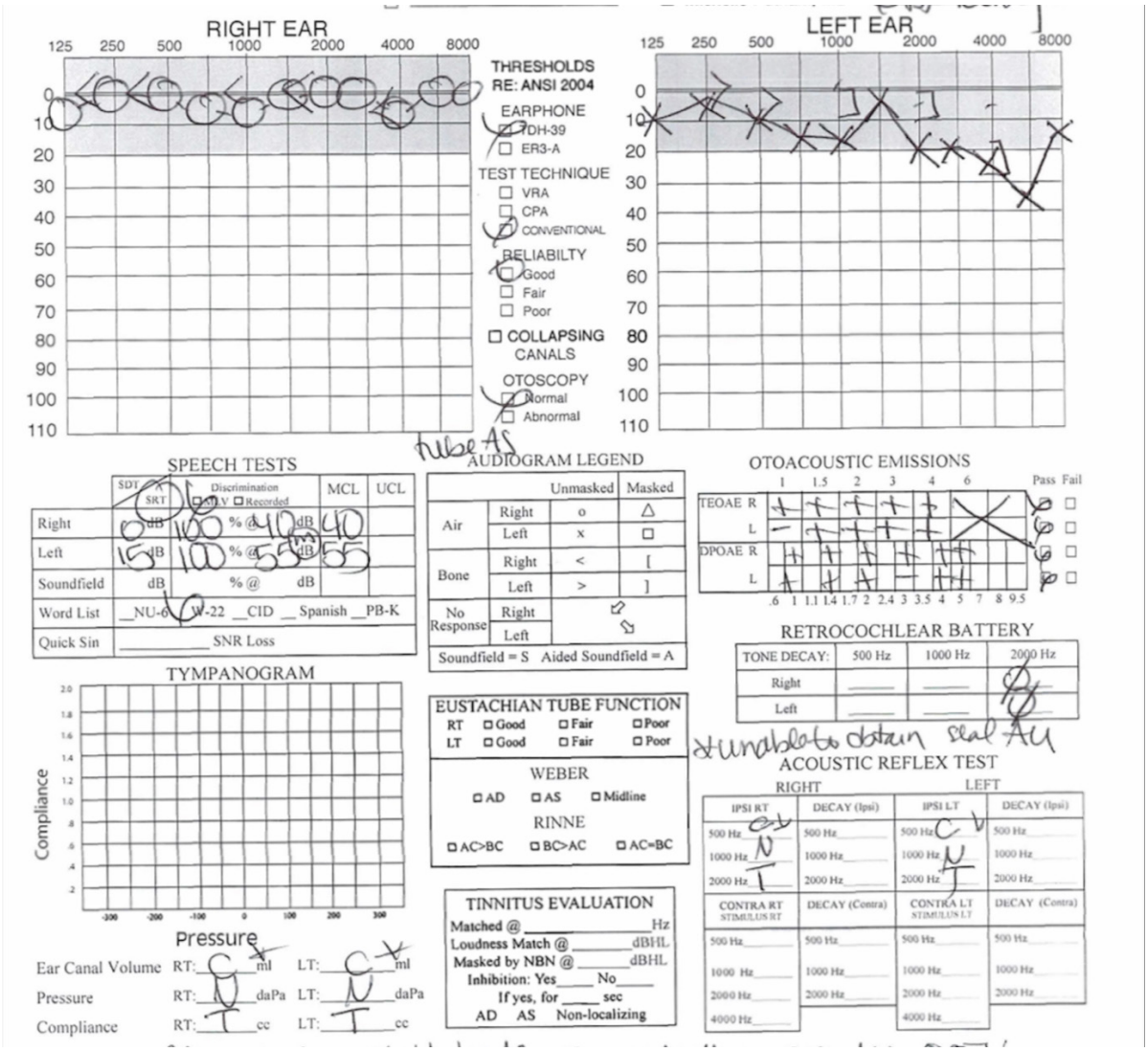


Figure 2: Pre-surgery Audiogram. Normal pure tone hearing sensitivity in the right ear and a mild high frequency sensorineural hearing loss in the left ear. Word recognition was 100% bilaterally. Present DPOAE outer hair cell responses bilaterally.

infusion was started three times per week in November 2021 and continued NAC at 2500 mg twice daily which he was taking since March 2020. He also continued his current anticancer treatment regimen which included a monthly peptide vaccine which was started in November 2020, monthly zoledronic acid injection which was started in April 2021, and Bevacizumab every two weeks which was started in May 2021.

MATERIALS AND METHODS

Protocol Oversight: This was a sponsor-investigator single-patient expanded access treatment protocol approved by the U.S. Food and Drug Administration and Providence St. Joseph's Health Institutional Review Board. Informed consent was obtained from patient prior to starting the investigational therapy.

Previous Therapeutic Approaches to Tinnitus: Studies highlighting the antioxidant activity and preclinical efficacy of OKN-007 and NAC for blast-induced tinnitus and Phase I studies that confirmed its safety and tolerability, led to compassionate use treatment with OKN-007 was proposed for this patient combined with the NAC he was concurrently receiving since March 2020[5].

Treatment: OKN-007 was provided by Oblato, Inc. (Princeton, NJ). OKN-007 (60 mg/kg) was administered intravenously three times per week for eight weeks. A second treatment course was added for OKN-007 (60 mg/kg) three times per week for four weeks, twice per week for twelve weeks, then weekly maintenance dosing. The patient was taking oral NAC 2500 mg before starting OKN-007 and continued NAC throughout treatment. Clinical laboratory assessments, vital signs, and physical exams were performed throughout treatment.

Audiology Equipment: Conventional pure-tone audiometry, speech audiometry, tinnitus loudness matching, and impedance evaluation procedures were performed with a GSI 61 Audiometer using TDH-39 earphones, and a GSI Tympstar Version 2 Middle Ear Analyzer. Distortion Product Otoacoustic Emissions (DPOAEs) were measured using the Otodynamics Echoport Model ILO288.

Audiology Evaluation: An audiological evaluation helps to determine the type, degree, and configuration of hearing loss. Pure tone audiometry is the gold standard for most auditory examinations and is used to measure auditory sensitivity. It determines the degree, type, and configuration of hearing loss at selected frequencies through either earphones, also known as air conduction, or a vibrator pressed against the mastoid portion of the temporal bone (bone conduction). The minimal level that the subject can hear (threshold) is determined for each frequency. The frequencies were tested pre- and post-surgery, and pre- and post- treatment. Impedance testing is a quick, non-invasive and objective procedure to measure the mobility of the ear drum and the ossicular chain in the middle ear. In combination with the pure tone audiogram, impedance testing helps in determining the integrity of the tympanic membrane, middle ear ossicles/ muscles, and parts of the VII and VIII nerves. Distortion Product Otoacoustic Emissions (DPOAEs) are responses which are generated by the cochlea's outer hair cells and reflect the integrity of the outer hair cells and middle ear (a normal middle ear is usually necessary to record DPOAEs).

Tinnitus Measures: Tinnitus severity and impact were assessed using the Tinnitus Handicap Inventory (THI), Tinnitus Primary Function Questionnaire (TPFQ), and the Tinnitus Reaction Questionnaire (TRQ). The THI measures the impact of tinnitus on daily living and assesses the patient's perceived tinnitus handicap, with higher scores indicating greater handicap. The TPFQ measures the impact of tinnitus on everyday functions including concentration, emotional wellbeing, hearing, and sleep, with higher scores indicating worse impact. The TRQ measures the levels of tinnitus-related distress, with higher scores indicating higher levels of distress.

RESULTS

Assessment of THI, TPFQ, and TRQ questionnaires was performed before OKN-007 treatment showed that the patient perceived his tinnitus to be a catastrophic handicap that caused a negative impact on his day-to-day life (Table 1). After three weeks of treatment with OKN-007, the patient reported subjective improvement in his tinnitus and hearing sensitivity. Pure tone audiometry one month after treatment revealed a clinically significant 16.66 dB average increase in threshold sensitivity at 125, 250 and 500 Hz with residual hearing in the affected left ear (Table 2). An average of three frequencies was used and post treatment improvement was 15 dB at 125 Hz, 25 dB at 250 Hz, and 10 dB at 500 Hz, which were all clinically significant (pure tone threshold increases or decreases greater than 5 dB are clinically significant). Tympanometry and DPOAE findings before and after surgical treatment demonstrated normal Type A patterns (Figure 3) and present DPOAEs indicating that middle ear function was normal and not associated with the improved hearing at the lower frequencies. After completing eight weeks of OKN-007 and NAC treatment, his tinnitus slightly worsened but not back to the original intensity and severity. Table 3 shows the timeline of DPOAEs measured both pre- and post-surgery and pre- and post-treatment.

Considering improvements in hearing sensitivity and severity of tinnitus percept with OKN-007 and NAC without any toxicity, a second course of OKN-007 was approved for the patient. A repeat audiogram five months after initial treatment indicated a sustained hearing sensitivity gain despite a two-month gap in treatment (Table 2). The patient also reported noticeable subjective improvement in hearing. Of note, there was a decrease in the threshold from 80 dB to 105 dB at 1000 Hz, which may be attributed to the natural course of disease from a partially treated vestibular schwannoma. The patient also had a stable brain MRI 4 months after treatment initiation (Figure 1E-F). Remarkably, the patient noted his tinnitus became unnoticeable at times within a few months of OKN-007 and NAC treatment, and he started going out to eat at noisy restaurants, which he was previously unable to do.

Table 1: Post-Treatment with OKN-007 and NAC.

A. Tinnitus Handicap Inventory scores before and after treatment.

Tinnitus Handicap Inventory	
Pre-Treatment	**6 Months Post-Treatment**
86 / 100 (Catastrophic Handicap, Grade 5)	40 / 100 (Moderate Handicap, Grade 3)

B. Tinnitus Primary Function Questionnaire scores before and after treatment.

Tinnitus Primary Function Questionnaire	
Pre-Treatment	**6 Months Post-Treatment**
Concentration: 78/100 Emotional Well Being: 100/100 Hearing: 44/100 Sleep: 90/100 Overall: 78/100	Concentration: 18 /100 Emotional Well Being: 20 /100 Hearing: 12 /100 Sleep: 0 /100 Overall: 13/100

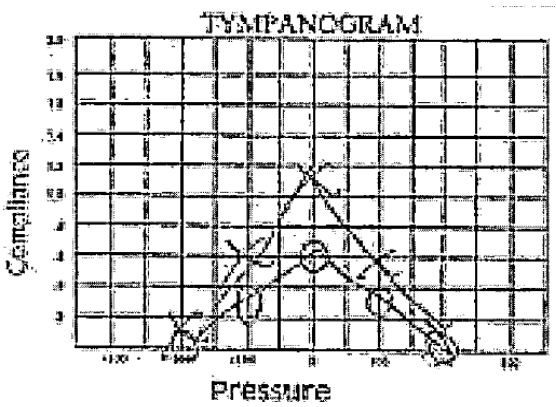
C. Tinnitus Reaction Questionnaire scores before and after treatment.

Tinnitus Reaction Questionnaire	
Pre-Treatment	**6 Months Post-Treatment**
88 / 104	13 / 104

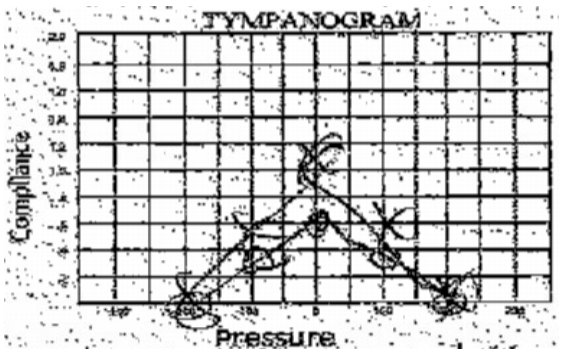
Table 2: Left Ear Audiograms.

Date	125 Hz	250 Hz	500 Hz	750 Hz	1000 Hz	1500 Hz	2000 Hz	3000 Hz	4000 Hz	6000 Hz	8000 Hz
9/23/19*	10	5	10	15	15	5	20	20	25	35	15
10/14/19	75	70	35	45	NR	NR	NR	NR	NR	NR	NR
11/1/19		55	30		30	95	115	NR	NR	NR	NR
11/8/19**	25	40	25	30	30	105	115	NR	NR	NR	NR
1/27/20	35	45	40	45	50	110	NR	NR	NR	NR	NR
4/28/21		50	40	50	80	NR	NR	NR	NR	NR	NR
6/18/21***	40	55	50	45	80	115	115	NR	NR	NR	NR
12/8/21****	35	45	40	50	80	NR	NR	NR	NR	NR	NR
3/8/22	25	35	45	55	105	NR	NR	NR	NR	NR	NR
4/20/22****	25	30	40	50	105	NR	NR	NR	NR	NR	NR

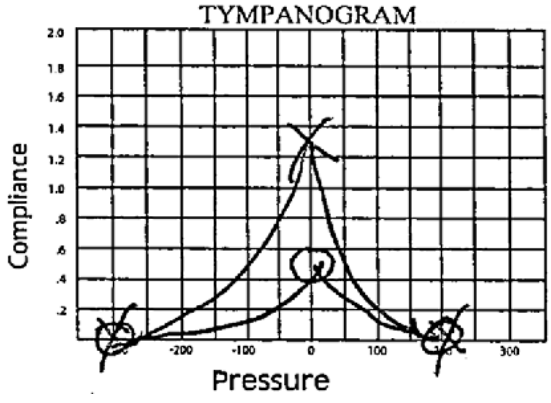
Legend:
* = Pre-Operative
** = Post-Operative
*** = Pre-Treatment
**** = Post-Treatment
NR = No Response



A. Pre-Treatment Tympanogram (June 2021).



B. Post-Treatment Tympanogram (December 2021).



C. Post-Treatment Tympanogram (March 2022).

Figure 3: Tympanogram Pre- and Post-Treatment with OKN-007 and NAC.

Table 3: Distortion Product Otoacoustic Emissions (DPOAEs).

Date	600 Hz	1000 Hz	1100 Hz	1400 Hz	1700 Hz	2000 Hz	2400 Hz	3000 Hz	3500 Hz	4000 Hz	5000 Hz	7000 Hz	8000 Hz	9500 Hz
9/23/19*	-	P	-	P	-	P	-	P	-	P	P	-	-	-
10/14/19	-	P	-	P	-	P	-	P	-	P	-	P	-	-
11/1/19	-	-	-	P	P	P	P	P	P	P	P	-	-	-
11/8/19**	P	P	P	P	P	P	P	A	A	A	P	P	A	A
1/27/20	Did Not Test													
4/28/21	-	A	A	P	A	A	A	P	P	P	P	A	-	-
6/18/21***	A	P	A	A	A	A	A	A	A	A	A	A	A	A
12/8/21****	A	A	A	A	A	A	A	A	A	A	A	P	A	A
3/8/22	Did Not Test													
4/20/22****	P	A	A	A	A	A	A	A	A	A	A	A	A	A

Legend:
* = Pre-Operative
** = Post-Operative
*** = Pre-Treatment
**** = Post-Treatment
P = Present OAE
A = Absent OAE
- = Data Not Reported

Furthermore, the 90 dB deafening waterfall sound, the chimes, and electronic beeps all subsided after treatment, and he was only left with a 19 dB tinnitus centered at 8000 Hz. Improvements in the patient's hearing and tinnitus led to improved psychosocial aspects and overall quality of life as he became able to leave the house and socialize without discomfort. Tinnitus questionnaire responses 6 months into treatment revealed remarkable improvements in tinnitus severity, distress, and handicap scores (Table 1). His perceived tinnitus handicap score dropped from a catastrophic score of 86 to a moderate score of 40. He also experienced improvements in sleep, concentration, hearing, and emotional well-being and reported significantly decreased levels of tinnitus-related distress. The patient remains on treatment with no adverse drug reactions to date.

DISCUSSION

Tinnitus can be a severe, debilitating condition that limits functional activity in day-to-day life. Vestibular schwannomas are benign tumors that originate on the cranial nerve connecting the inner ear with the brain that is responsible for transmitting sound and balance information. Mechanical compression of the adjacent auditory nerve, oxidative stress, auditory traumas, chemotherapeutics, mechanosensory damage, altered cochlear fluid chemistry, and secreted factors such as tumor necrosis factor alpha are thought to contribute to ototoxicity and excitotoxicity in the inner ear[6]. Sustained tinnitus is believed to result from central (brain) auditory processing dysfunction, and pathological effects that arise after schwannoma tumor surgery may contribute to maladaptive central neuroplasticity[7].

The severity of tinnitus in patients with vestibular schwannoma is significantly associated with subjective hearing loss and the degree of depression and anxiety, which strongly affects patients' well-being[8]. This was the case for our patient, whose debilitating tinnitus negatively impacted his quality of life and caused psychosocial distress despite multiple lines of treatment for his tumor, tinnitus, and emotional distress. With no satisfactory therapy available or clinical trials he would qualify for, the patient sought investigational treatment with OKN-007.

OKN-007 (disodium 4-[(tert-butylimino) methyl]-benzene-1,3-disulfonate N-oxide is a free radical spin trapping agent in the classes of benzenesulfonates, nitrogen oxides, small molecules, and sulfur amino acids. Although its exact mechanisms of action are largely unknown, it may exhibit these properties through inhibition of cell proliferation, migration, and angiogenesis. Large-scale clinical trials have demonstrated the safety of OKN-007 in ischemic stroke[9]. OKN-007 is currently being evaluated in clinical trials for patients with gliomas due to its anti-cancer properties. The phase I trial for recurrent glioblastoma did not reach a maximum tolerated dose and preliminary evidence of antitumor activity prompted initiation of phase II trials[10]. In light of OKN-007's potential neuroprotective effects, preclinical studies from the Hough Ear Institute demonstrated that co-administration of OKN-007 with NAC could significantly reduce both noise- and blast-induced cochlear damage and hearing loss[5, 11-13]. This drug combination has also been shown to preserve or restore afferent ribbon synapses on cochlear inner hair cells in the context of these auditory traumas and mitigate central auditory processing defects and behavioral evidence of tinnitus in rats[5, 13]. The ability to regenerate lost neurites and synapses in the cochlea and induce auditory pathway neuroplasticity centrally was an attractive therapeutic strategy to explore for our patient's tinnitus.

Through a single-patient expanded access protocol, our patient received intravenous OKN-007. The patient's report of dramatically decreased tinnitus percept and improved hearing loss was remarkable and encouraging for additional treatment. DPOAEs, which evaluate the

integrity and performed of the outer hair cells in the inner ear, were performed throughout the treatment period as they were not affected by the tumor. It is well-known and documented that if there is only damage to the auditory nerve for example from vestibular schwannoma or temporal bone fracture which result in sensorineural hearing loss, the hearing loss is neural and not cochlear (not sensory). Therefore, the DPOAE outer hair cell response will remain intact. In this patient's case, the DPOAEs were present at all frequencies prior to surgery and one month after surgery. However, they started to become absent at different frequencies until they were only present at one frequency 21 months after surgery. Additionally, the middle ear must be intact to record DPOAEs. Therefore, one can infer normal middle ear function if DPOAEs are present. In cases such as acute Tympanic Membrane (TM) perforation, or sometime chronic TM perforation, without effusion, you can sometimes record DPOAEs.

Our case study demonstrates the feasibility and therapeutic potential of OKN-007 and NAC in treating hearing loss and tinnitus that warrants further investigation. This study involved the intravenous administration of OKN-007, though future studies using an oral formulation of OKN-007 and NAC may expand treatment accessibility. It is unclear what specific dosing frequency and treatment duration are necessary to provide an optimal response. Thus, prospective studies investigating the OKN-007 and NAC treatment combination for hearing loss and tinnitus are needed as the lack of effective treatment options justifies a major investment in research in this area.

CONFLICTS OF INTEREST

This single patient expanded access treatment was funded by unrestricted departmental funds. Richard Kopke is a founder and equity-holder in Auditus, which licensed this drug technology to Oblato for further commercialization. Shinwook Kang is Vice President of Oblato, which supplied the OKN-007. Santosh Kesari is the principal investigator for a clinical trial investigating OKN-007 combined with Temozolomide in patients with recurrent glioblastoma (NCT04388475).

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