



RESEARCH ARTICLE

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Teprotumumab–Associated Deafness: A Pharmacovigilance Analysis.

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ARTICLE INFO ABSTRACT



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Introduction: Teprotumumab was approved in 2020 for the treatment of thyroid eye disease after the Food and Drug Administration (FDA) fast-tracked its review. Though the initial trial showed 10% hearing loss, the results of the Phase 3b/4 safety study will not be completed until 2025.

Objective/Methods: The objective of this analysis was to investigate whether a statistically significant signal exists between deafness and teprotumumab in the real-world phase four post-marketing safety data. Adverse event reports in FDA Adverse Event Reporting System (FAERS) and literature review were also analyzed to determine the severity of the hearing loss and whether the deafness is irreversible.

Results: Of the 53 adverse event reports containing teprotumumab as the medicinal product in FAERS, nine reports had an adverse event of deafness. Teprotumumab was listed as the suspect drug in all such adverse events reports. Disproportionality analysis showed a statistically significant signal between teprotumumab and deafness (PRR 95, chi-squared 744, ROR₀₂₅ 56 and IC₀₂₅ 2.9). Eight of the nine teprotumumab-associated deafness adverse event reports described the deafness as resulting in a serious or disabling condition. Literature review revealed 24 patient case reports of teprotumumab-induced hearing loss. 67% (4/6) of adverse events reports in FAERS and 57% (12/21) of patient case reports in literature for teprotumumab associated deafness specified that the deafness did not resolve after withdrawal of teprotumumab.

Conclusion: FDA should evaluate whether severe hearing loss should be listed under “warning and precautions” of teprotumumab.

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Introduction

Hearing loss is often thought to be a benign process that is part of aging. However, hearing loss has been found to lead to a poorer quality of life, a 13% higher risk of all-cause mortality and a 28% higher risk of cardiovascular mortality (Tan et al., 2022). A dose-response association has also been observed with a doubling of the all-cause mortality relative hazard for every 30-dB increase in audiometric threshold (Lin et al., 2019; Tan et al., 2022). Early identification and treatment of preventable causes

of severe hearing loss is vital to improve the health, quality of life, and mortality of patients.

The Food and Drug Administration (FDA) approved teprotumumab for treatment of active thyroid eye disease (TED) in adults in January 2020. Earlier, the FDA had granted the drug Fast Track designation in April 2015, Breakthrough Therapy designation in July 2016, and Orphan Designation for the treatment of TED on June 2019. This led the FDA to fast track the review of the drug and the FDA agreed to review a small Phase III clinical trial for teprotumumab involving only 84 patients



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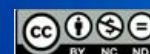
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in the treatment group. The results of this study showed hearing impairment occurring in 10% of those taking teprotumumab (Kahaly et al., 2021). In the safety data reviewed by FDA for 121 patients treated by teprotumumab (including the 84 subjects of the Phase III trial), ear and labyrinth disorders were observed in 21 subjects (17%), ear discomfort in 8 (7%), hypoacusis in 5 (4%), tinnitus in 3 (2.5%), deafness in 3 (3%) and hyperacusis in 1 (1%) (Center for Drug Evaluation and Research, n.d.; FDA Dermatologic And Ophthalmic Drugs Advisory Committee, 2019). During the advisory committee meeting held by the FDA on December 13, 2019 for assessing the efficacy and safety of the drug, committee members suggested that a clinical trial with a greater number of subjects be performed to identify any additional adverse events that may have not been identified from the limited data presented. However, the FDA ignored the suggestion (Center for Drug Evaluation and Research, n.d.). Further, the FDA noted that no risk evaluation and mitigation strategies had been considered necessary to monitor the observed adverse events (Center for Drug Evaluation and Research, n.d.). To fulfill FDA post-marketing requirements, a Phase 3b/4 trial is being conducted to evaluate the safety, efficacy, and need for re-treatment of three different teprotumumab treatment durations for TED. However, the results of this safety study in 300 proposed subjects are estimated to not be available before August 2025 (NIH Clinicaltrials.gov, n.d.).

The objective of this analysis was to investigate whether there is a statistically significant signal between deafness and teprotumumab in the real-world phase 4 post-marketing safety data. In addition, adverse event reports in the FDA Adverse Event Reporting System (FAERS) and case reports and case series in literature review were analyzed to determine the severity of the hearing loss and whether the deafness is irreversible.

Methods

The FDA maintains the database FAERS, which contains medication adverse event reports that are submitted to the FDA. These adverse event reports can be submitted by physicians, pharmacists, nurses, other health professionals, product manufacturers and consumers among others. FAERS is used for phase 4 post-marketing safety surveillance program, and based on analysis of this database, the FDA may take regulatory action including updating the drug label, restricting use of the drug, informing the public of new safety information and removing a drug from the market (U.S. Food & Drug Administration, n.d.).

Data in FAERS from January 1, 2004 to March 31, 2023 was analyzed for this study. Data was filtered to those which reported an adverse event containing the Medical Dictionary for Regulatory Activities Terminology term

“Deafness.” Adverse event reports were also filtered to those containing the medicinal product of “Teprotumumab.” Duplicates were identified and removed if they fit the following criteria: Adverse event reports that A) were created within 30 days of each other and B) contain the same age, gender and weight and C) occurred in the same country and D) contain the same adverse events, and E) based on the case narrative provided in the report.

A pharmacovigilance disproportionality analysis was performed on the remaining cases. This analysis allows for the identification of a statically significant signal between a drug and an adverse event. Disproportionality analysis consisted of proportional reporting ratio (PRR), chi-squared, lower limit of the 95% confidence interval of reporting odds ratio (ROR₀₂₅) and the lower limit of the 95% confidence interval of the information component (IC₀₂₅). A statistically significant signal is found if there are 3 or more drug-adverse event reports, the PRR is 2 or more, and chi-squared value is 4 or more (Evans et al., 2001). Another criteria used to define a statistically significant signal is a lower limit of the 95% confidence interval of the ROR greater than 1 (van Puijenbroek et al., 2001). Further, the World Health Organization (WHO) uses a Bayesian confidence propagation neural network when identifying potential signals in the database of adverse drug reactions from the Uppsala Monitoring Centre. A statistically significant signal in this Bayesian confidence propagation neural network is defined as IC₀₂₅ greater than 0 (Bate et al., 1998).

In addition, a literature review for case reports of teprotumumab induced hearing loss was performed. Medline (PubMed) (NIH National Library of Medicine, n.d.) was queried for case reports and case series that contained “teprotumumab” and “hearing loss.” These case reports are summarized in tabular form to determine the time to onset of symptoms, the severity of the hearing loss, and whether the hearing loss was reversible.

Results

FAERS analysis

Over 16 million adverse events reports were analyzed through FAERS. Of the 53 adverse event reports containing teprotumumab as the medicinal product, nine reports had an adverse event containing deafness. The earliest of these nine reports was in January 2021. Eight of these reports occurred in the United States and the remaining one report did not specify the country. A physician, pharmacist or other health professional reported seven of the cases and a consumer or non-health professional reported the remaining two. Of the nine adverse event reports with teprotumumab and deafness, six reported a gender, and in all of these six reports, the

gender was female. Age ranged from 46 years old to 77 years old. In these nine adverse reports, “deafness” was listed as the specific adverse event in four reports,

“deafness neurosensory” in four reports and “conductive deafness” in one report (Table 1).

Table 1. Characteristics of Teprotumumab-associated deafness adverse event reports in the FDA Adverse Event Reporting System

Teprotumumab associated Deafness Adverse Event Reports	
Specific Adverse Reaction	
Deafness Neurosensory	44% (4/9)
Deafness	44% (4/9)
Conductive Deafness	11% (1/9)
Resolution of Deafness	
Deafness did not abate after stopping Teprotumumab	67% (4/6)
Deafness abated after stopping Teprotumumab	33% (2/6)
Unknown	3
Severity of Deafness	
Adverse event resulted in death, a life threatening condition, hospitalization, disability, congenital anomaly or other serious condition	88% (8/9)
Adverse event did not result in death, a life threatening condition, hospitalization, disability, congenital anomaly or other serious condition	11% (1/9)

One of these reports with “deafness neurosensory” as an adverse event also listed bilateral deafness as another adverse event. Similarly, one of the four reports with only “deafness” reported as an adverse event also had adverse events reported of ear discomfort, ear hemorrhage and

tympanic membrane perforation. Disproportionality analysis between teprotumumab and deafness revealed a PRR of 95, chi-squared of 744, ROR₀₂₅ of 56 and an IC₀₂₅ of 2.9 (Table 2).

Table 2. Disproportionality analysis of Teprotumumab-associated deafness reports in the FDA Adverse Event Reporting System

	Teprotumumab associated Deafness		
	Lower 95% Confidence Interval	Value	Upper 95% Confidence Interval
Proportional Reporting Ratio	52	95	172
Chi-squared		744	
Reporting Odds Ratio	56	114	233
Information Component	2.9		

Using Evans’ criteria (Evans et al., 2001), a statistically significant signal was found between teprotumumab and deafness as the PRR was higher than two, chi-squared higher than four and the number of adverse event reports greater than three. A statistically significant signal was also found using ROR₀₂₅ (van Puijenbroek et al., 2001) as the ROR₀₂₅ was greater than one. Further, using the WHO criteria based on Bayesian confidence propagation neural

network (Bate et al., 1998), the IC₀₂₅ was greater than zero and so deemed to be a statistically significant signal.

In all nine reports with teprotumumab as a medicinal product and deafness as an adverse event, teprotumumab was listed as the suspect drug. Five of these nine adverse event reports had teprotumumab as the only suspect drug. Of the remaining four, three listed prednisone or methylprednisolone as a suspect drug in addition to teprotumumab. The remaining report included sertraline

as a suspect drug in addition to teprotumumab. Six of the nine reports provided whether teprotumumab was withdrawn, dose reduced, dose increased or dose not changed. In all six reports, teprotumumab was withdrawn.

Further, six of the nine reports listed whether the adverse event abated after stopping teprotumumab. In four of these six reports (67%), the deafness persisted, while in the remaining two (33%), the deafness resolved (Table 1). Eight of the nine reports (88%) with teprotumumab as a medicinal product and deafness as an adverse event listed that the adverse event resulted in death, a life-threatening

condition, hospitalization, disability or other serious condition and one of the nine reports (11%) stated it did not result in any of the above (Table 1). Furthermore, of the original nine adverse event reports, seven reported whether the adverse event was disabling. Of these seven, five (71%) reported the adverse event was disabling and two (29%) reported it was not disabling.

Case Reports Analysis

Literature review revealed 24 patient case reports of teprotumumab induced hearing loss (Table 3).

Table 3: Literature review of case reports and case series of Teprotumumab-associated hearing loss

Study	Age/ Gender	Symptoms/Time to Onset	Audiogram	Resolution of Symptoms	Included in FDA Adverse Event Reporting System
(Ding et al., 2022)	77/F	Hearing loss at 3 rd and 4 th infusion. Worsened after 6 th infusion. Persistent hearing loss after 7 th infusion	Moderate to severe downsloping sensorineural hearing loss (SNHL)	No resolution	Yes
(Phansalkar et al., 2023)	64/F	Hearing loss, autophony and ear popping after 4 th infusion.	SNHL	Resolved after 2-5 months from last dose of teprotumumab. Patient tolerated restarting at half dose 10mg/kg without return of hearing loss.	Yes
(Safo & Silkiss, 2021)	46/F	Hearing loss during each treatment. Also developed new ulcerative colitis	N/A	Yes	Yes
(Belinsky et al., 2022)	68/F	Bilateral hearing loss worse on left after 3 rd infusion.	Mild to moderately severe downsloping SNHL bilaterally	No resolution. Continued on treatment with slight worsening of SNHL	No
(Belinsky et al., 2022)	34/F	Hearing loss 2 months after completion of 8 th infusion	Decreased sensitivity in high frequency range (baseline audiogram prior to initiation of treatment was normal)	Unknown	No
(Belinsky et al., 2022)	48/F	Fullness in both ears after 4 th infusion	Mild bilateral SNHL in the standard range and more severe loss in high frequency range	Symptoms gradually improved	No
(Chow & Silkiss, 2022)	50s/ F	Intermittent ringing after 3 rd infusion. Hearing loss after 5 th infusion.	Bilateral moderate to severe down sloping SNHL	No resolution. Stopped teprotumumab but no improvement in hearing at 6 weeks post	No

(Lu et al., 2023)	70/F	Hearing loss in right ear as well as loss of taste 10 days after 1st infusion	Mild down sloping to moderately severe mixed conductive and SNHL	Resolved with oral prednisone. Completed full course of teprotumumab without recurrence of hearing loss	No
(Reed et al., 2022)	54/M	After initial infusion had hearing loss but did not disclose to physician. 2 months into treatment course patient developed rapid hearing loss in the setting of shooting rifle without ear protection.	Moderate to severe SNHL bilaterally	No resolution. Patient had previously fired the same rifle without ear protection but without hearing loss during those times	No
(Highland et al., 2022)	61/F	Bilateral hearing loss, sound distortion, aural pressure and tinnitus after 5 th infusion. These worsened after 6 th and 7 th infusions	Symmetric bilateral mild sloping to moderately severe SNHL	No resolution of hearing loss. Completed 8 week teprotumumab and 2 week corticosteroid taper.	No
(Yu et al., 2021)	74/F	No subjective hearing loss	After 6th infusion had symmetric and rapidly progressive worsening of SNHL on audiogram	Unknown	No
(Yu et al., 2021)	42/F	Intermittent tinnitus and low-pitched hearing difficulty after 3rd infusion	Audiogram following symptoms and after completion of therapy showed no changes from pre-treatment audiogram	Unknown	No
(Najjar & Yu, 2022)	57/F	Persistent ringing in ears after 2 nd infusion. Decrease in hearing after 5 th infusion	Bilateral sloping to mild SNHL in the high frequency range	No resolution. Infusion was stopped and audiogram at 1 month post showed no improvement.	No
(Sears et al., 2022) *Prospective Observational Case Series	-	11 out of 27 patients developed hearing loss, muffled hearing or worse word comprehension. Symptoms occurred at a mean of infusion number 3.3	6 of the 11 patients had decreased hearing threshold on audiometry. 3 of these 6 had baseline audiometry testing to compare to and all 3 were diagnosed with teprotumumab related SNHL	6 out of the 11 patients had persistent hearing loss. The other 5 patients had resolution at a mean of 29 weeks.	No

Three of these case reports were present in FAERS. Ages ranged from 34 years old to 77 years old and similar to the analysis from FAERS there was a predominance of females in these case reports. The onset of hearing loss ranged from 10 days after the 1st infusion of teprotumumab to 2 months after completion of 8th teprotumumab infusion. Eighteen of the 24 patient case reports had an audiogram performed. Seventeen (94%) showed new or worsening SNHL or decreased hearing threshold/sensitivity. Eight (44%) patients were found to have a component of moderate to severe SNHL or rapidly

progressive worsening SNHL. Several patients developed otologic symptoms, including autophony, tinnitus, fullness in both ears and tinnitus, in addition to the hearing loss. Twenty-one of the 24 patient case reports found in literature review specified whether the hearing loss resolved. Twelve patients (57%) did not have resolution of hearing loss. Eight patients (38%) had resolution of hearing loss and one patient (5%) was described as having improvement in hearing loss.

Discussion

FAERS disproportionality analysis showed a statistically significant signal between teprotumumab and deafness using three different pharmacovigilance methods. Further, teprotumumab was listed as the suspect drug in all such adverse events reports. All adverse event reports with teprotumumab and deafness that included a gender reported female patients. This may be due to females being more likely to develop thyroid eye disease and be a candidate for teprotumumab treatment as opposed to teprotumumab-associated deafness being more likely in females than males.

A majority of the patients in both the adverse event reports in FAERS and the case reports in literature review did not have resolution of the hearing loss. In addition, eight of the nine teprotumumab associated deafness adverse event reports in FAERS described the deafness as resulting in a serious or disabling condition. The post-marketing data analysis and case reports highlight that patients on teprotumumab who are developing deafness are often developing irreversible and disabling deafness as opposed to a mild hearing loss or reversible hearing loss.

The FDA drug label for teprotumumab includes hearing impairment as an “adverse reaction” alongside muscle spasm, nausea, fatigue, and dry skin. Infusion reaction, exacerbation of preexisting inflammatory bowel disease, and hyperglycemia are listed under “warnings and precautions.” Post-marketing FAERS data and case reports in literature highlight that the hearing impairment associated with teprotumumab can be severe and in many cases irreversible. As such, the FDA should re-evaluate whether hearing impairment should be listed under “warning and precautions” of teprotumumab’s drug label, instead of under “adverse events”, so that patients and physicians are made aware of the potential severity of the hearing loss. In turn, this could promote earlier detection and management. Furthermore, as highlighted previously, deafness is not only associated with morbidity but also increased mortality.

Reed et al. describe a patient who developed some hearing loss after initiation of teprotumumab and then rapid worsening of the hearing loss after shooting a rifle without ear protection (Reed et al., 2022). It is possible that teprotumumab made the patient more vulnerable to noise induced hearing loss as this patient had previously fired the same rifle without ear protection but at that time without a noticeable reduction in hearing. Yu et al. described a patient who had no subjective hearing loss but audiometry revealed symmetric and rapidly progressive worsening of SNHL (Yu et al., 2021). Therefore, it may be prudent to have routine audiometry performed for patients taking teprotumumab as they may not be aware of the hearing loss. In addition, the patient

described by Reed et al. did not disclose to the physician the mild hearing loss he developed after initiation of teprotumumab (Reed et al., 2022). Patients may not know that their hearing loss could be connected to teprotumumab use and so would be less likely to inform their physician about this symptom. As such, a routine audiometry test to provide objective data while on teprotumumab would help diagnose teprotumumab associated hearing loss earlier. Kay-Rivest et al. conducted a prospective cohort study of 35 patients receiving teprotumumab and found that 25.7% (9/35) reported hearing loss (Kay-Rivest et al., 2023). In addition, 14 of the 35 patients underwent both pre and post audiometry testing. Of these 14 patients, 11 had worsened hearing loss in the posttreatment audiometric data, with 3 having changes in standard frequency, 10 having changes in high-frequency audiometry and 2 patients having changes in both. Only 5 of these 11 patients reported subjective hearing loss, again highlighting that routine audiometry testing may allow for earlier diagnosis and treatment to prevent worsening and potentially irreversible hearing loss from developing.

Deafness associated with teprotumumab is likely due to teprotumumab’s alteration of the insulin-like growth factor 1 (IGF-1) pathway. Teprotumumab is an antagonist at the IGF-1 receptor. IGF-1 receptors are overexpressed in orbital fibroblasts and contribute to thyroid eye disease (Girmita et al., 2022). The therapeutic action of teprotumumab in thyroid eye disease is likely due to targeting of this pathway. However, IGF-1 and IGF-1 receptors are also found elsewhere in the body. Specifically, IGF-1 has an active role in the early development of cochleovestibular ganglion and aids in synapse formation between inner hair cells and spiral ganglion neurons (Phansalkar et al., 2023; Varela-Nieto et al., 2004; Yamahara et al., 2019). IGF-1 also protects the ear from noise induced damage and toxicity from medications (Ding et al., 2022; Gao et al., 2020; Yamahara et al., 2019; Yamamoto et al., 2014). Sensorineural hearing loss in Laron syndrome, Turner syndrome and Noonan syndrome is associated with low IGF-1 (Attias et al., 2012; Barrenäs et al., 2000; Bertelloni et al., 2013; Rodríguez-de la Rosa et al., 2017). Further, local administration of IGF-1 has been found to control and even reverse sensorineural hearing loss. Overall, it is possible that the teprotumumab’s therapeutic action on the IGF-1 pathway in the eyes is also responsible for its adverse effect of hearing loss and deafness when acting on the IGF-1 pathway in the ears.

FAERS is a passive reporting system and so not all adverse events associated with each drug are reported. It is a voluntary reporting system and so adverse events associated with a drug are often underreported. As such, the incidence of the adverse event cannot be calculated. The drugs that the patients are taking and the adverse

events they have had are included in the report; however, no causal association can be made between the drug and adverse event. Instead, a pharmacovigilance analysis is performed to determine whether a statistically significant signal exists between a drug and an adverse event. This signal needs to be corroborated with case reports, cohort studies and randomized controlled trials to establish causation. However, FAERS is a powerful database for analyzing post-marketing adverse events in phase 4 of clinical studies on a very large and diverse population that is difficult to achieve in randomized controlled trials. In addition, FAERS is routinely analyzed by the Center for Drug Evaluation and Research and by the Center for Biologics Evaluation and Research to add, remove or reclassify adverse events associated with drugs and biologics.

Conclusions

Pharmacovigilance analysis demonstrated a statistically significant signal between teprotumumab and deafness, and all case reports of teprotumumab associated deafness had teprotumumab listed as a suspect drug. There were 24 patient case reports of teprotumumab-induced hearing loss found in the literature. A majority of these patients that had an audiogram performed were found to have new or worsening SNHL or decreased hearing threshold. Eight of the patients were diagnosed with a component of moderate to severe SNHL or rapidly progressive worsening SNHL. Similarly, eight of the nine (88%) teprotumumab-associated deafness adverse event reports in FAERS described the deafness as resulting in a serious or disabling condition. In addition, 66% (4/6) of adverse events reports in FAERS and 57% (12/21) of case reports in literature for teprotumumab-associated deafness specified that the deafness did not resolve after withdrawal of teprotumumab. Currently, the FDA drug label for teprotumumab includes hearing impairment as an adverse reaction alongside the mild and often reversible adverse reactions of muscle spasm, nausea, fatigue, and dry skin. Post-marketing FAERS data and case reports in literature highlight that the hearing impairment associated with teprotumumab can be more severe and, in many cases, irreversible. Based on post-marketing data analysis results and case reports, the FDA should evaluate whether severe hearing loss should be listed in the label for teprotumumab under “warning and precautions” given the risk for severe irreversible hearing loss and the dose-response morbidity and mortality associated with deafness. This can make patients and physicians better aware of the hearing impairment risk and allow for earlier detection and management. Early recognition and management may also prevent the initial hearing loss from progressing to a more severe and irreversible form. Clinicians should advise patients taking teprotumumab of the risk of hearing loss and the importance of informing the physician of any hearing loss

they notice. Further, routine audiometry testing for those on teprotumumab may be needed.

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