Bevacizumab for Hearing Preservation in Neurofibromatosis Type 2: Emphasis on Patient-Reported Outcomes and Toxicities

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Abstract
Objective. Bevacizumab for hearing preservation in patients with neurofibromatosis type 2 (NF2) is an emerging practice. We set out to characterize the effectiveness and toxicity of bevacizumab in our patient group.

Study Design. Case series with chart review.

Setting. Tertiary referral center.

Subjects and Methods. Seventeen consecutive patients with NF2 received bevacizumab treatment for vestibular schwannomas, including 2 patients treated to maintain cochlear implant performance. Volumetric analysis of serial magnetic resonance imaging scans was used to evaluate radiographic response, and hearing response was evaluated with serial audiograms. Patient-reported outcomes were also assessed, including subjective hearing improvement, changes in tinnitus, vertigo, headaches, ear pain, and improvement in ability to communicate via telephone.

Results. A positive radiographic response occurred in 8 of 17 (47%) patients and the median tumor volume change was a tumor decrease of 19%. A positive hearing response was recorded in 5 of 9 (56%) patients. Two patients had a word recognition score improvement over 40%. There was an approximately 40% improvement in patient-reported outcomes. Primary toxicities included hypertension, proteinuria, dysgeusia, and amenorrhea.

Conclusion. Bevacizumab treatment was followed by hearing improvement in 56% of patients, while decreased tumor volume was noted in 47%. These outcomes agree favorably with prior reported series. There were significant improvements in patient-reported outcomes that have not been described previously.

Keywords
neurofibromatosis type 2, NF2, vestibular schwannoma, bevacizumab, patient-reported outcomes

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Neurofibromatosis type 2 (NF2) is a dominantly inherited genetic condition caused by mutations in the NF2 gene. Bilateral vestibular schwannomas are the hallmark of the disease, eventually leading to hearing loss, tinnitus, and vestibular impairment. Most patients with NF2 will experience complete hearing loss either from tumor progression or as a result of surgery or radiotherapy. Vascular endothelial growth factor (VEGF) and its receptor VEGF-1 have been identified in schwannomas, and increased levels of these factors correlate with increased rates of tumor growth. Several previous series of patients with NF2 treated with bevacizumab, a VEGF inhibitor, suggest that bevacizumab treatment could result in hearing improvement and tumor size reduction. There is now a need for clinical indicators and patient-reported outcomes that may drive decisions to continue or discontinue therapy. The aim of our study was to analyze and report data collected from our cohort of patients with NF2 treated with bevacizumab, with attention to hearing and tumor response and patient-reported outcomes. From 2009 to 2018, patients with NF2-associated vestibular schwannomas who were not considered surgical candidates were treated by the

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neurofibromatosis clinic in concert with neurotology and neurosurgery at the University of Minnesota. Radiation therapy was not offered. Since 2011, we have also offered bevacizumab to patients with NF2 with normal hearing for hearing preservation and to those with cochlear implants (CIs) in an effort to preserve CI performance.

Methods

Study Cohort

We offered bevacizumab on a compassionate care basis to patients who fulfilled diagnostic criteria for NF2, had vestibular schwannomas with progressive symptoms, and were considered poor candidates for surgery or declined surgical treatment. Seventeen consecutive patients who met the criteria and received at least 6 doses of bevacizumab were included (Table 1). Participants were treated between September 2009 and April 2018.

This study was approved by the University of Minnesota Institutional Review Board (STUDY00002922).

Treatment

Ten male patients and 7 female patients, with a median age of 30 years (15-57 years), received intravenous bevacizumab at 5 mg/kg, 7.5 mg/kg, or 10 mg/kg every 2 to 6 weeks. Dose and time interval were adjusted based on toxicity and patient preference during treatment. Duration of treatment at the time of this report is 3 months to 5 years, with a median duration of 14 months. Ten patients were treated for 1 year or longer. Before each treatment, patients received a medical evaluation including blood pressure reading, urinalysis, comprehensive metabolic panel (CMP), complete blood count (CBC), and kidney and liver function tests.

Radiographic Response

To evaluate tumor volume changes, we used axial, T1-weighted, fat-saturated (FS), postcontrast magnetic resonance imaging (MRI) with slice thickness of 3 mm. There were several scans using 4-mm slices, and 2 computed tomography (CT) scans were used when no MRI scans were available (patient with auditory brain stem implant [ABI] and a magnet in). A target lesion was specified for each patient, and this lesion was tracked on MRI scans. Volumetric analyses were performed by a blinded radiologist by contouring the target lesions on serial MRI scans and using the Velocity AI 3.1.0 (Velocity Medical Solutions, Atlanta, Georgia) software to calculate the tumor volume.

A positive radiographic response was defined as greater than 20% reduction in tumor volume15 compared to baseline (beginning of bevacizumab therapy). Radiographic progression was defined as an increase in tumor volume greater than 20% compared to baseline. Stable tumors were defined as a change in tumor volume (increase or decrease) of less than 19%.

Hearing Response

Serial audiograms were used to evaluate hearing response. Word recognition score (WRS) was our primary parameter.

### Table 1. Baseline Patient Characteristics and Imaging and Hearing Outcomes after Bevacizumab Treatment

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Sex</th>
<th>Indication for Treatment</th>
<th>Baseline Tumor Volume, cm³</th>
<th>Time Point T, mo</th>
<th>Tumor Volume Change at Time Point T, %</th>
<th>Imaging Response</th>
<th>Hearing Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>Male</td>
<td>Hearing preservation</td>
<td>0.3</td>
<td>12</td>
<td>+3</td>
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<td>N/E</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>Male</td>
<td>Hearing preservation</td>
<td>13.5</td>
<td>9</td>
<td>-17</td>
<td>Stable</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>Male</td>
<td>Hearing preservation</td>
<td>10.0</td>
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<td>-22</td>
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<td>Positive</td>
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<tr>
<td>4</td>
<td>47</td>
<td>Male</td>
<td>Hearing preservation</td>
<td>1.2</td>
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<td>-25</td>
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</tr>
<tr>
<td>5</td>
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<td>Hearing preservation</td>
<td>0.3</td>
<td>6</td>
<td>-15</td>
<td>Stable</td>
<td>Progression</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
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<td>CI function preservation</td>
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<td>-7</td>
<td>Stable</td>
<td>N/E—CNT (CI)</td>
</tr>
<tr>
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<td>Hearing preservation</td>
<td>4.5</td>
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<td>-20</td>
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<td>Positive</td>
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<tr>
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<td>Male</td>
<td>Hearing preservation</td>
<td>15.7</td>
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<td>-19</td>
<td>Stable</td>
<td>N/E</td>
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<td>9</td>
<td>37</td>
<td>Male</td>
<td>Hearing + CI function preservation</td>
<td>2.9</td>
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<td>-35</td>
<td>Positive</td>
<td>Progression</td>
</tr>
<tr>
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<td>Hearing preservation</td>
<td>0.6</td>
<td>9</td>
<td>+12</td>
<td>Stable</td>
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</tr>
<tr>
<td>11</td>
<td>30</td>
<td>Female</td>
<td>Hearing preservation</td>
<td>12.7</td>
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<td>-24</td>
<td>Positive</td>
<td>Positive</td>
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<tr>
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<td>Male</td>
<td>Hearing preservation</td>
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<td>+74</td>
<td>Progression</td>
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</tr>
<tr>
<td>13</td>
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<td>Hearing preservation</td>
<td>1.7</td>
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<td>+13</td>
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<tr>
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<td>-28</td>
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<tr>
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<td>28</td>
<td>Female</td>
<td>Hearing preservation</td>
<td>1.7</td>
<td>30</td>
<td>-48</td>
<td>Positive</td>
<td>N/E</td>
</tr>
</tbody>
</table>

Abbreviations: CI, cochlear implant; CNT, cannot test.

*Imaging response—positive: reduction in tumor volume ≥20%; progression: increase in tumor volume ≥20%; stable: increase or decrease less than 19%.

Hearing response—N/E: not eligible for hearing response (word recognition score [WRS] >94% or cannot test); positive: statistical improvement in WRS; progression: statistical decrease in WRS; stable: less than statistical change in WRS.

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Pure-tone average (PTA) was used as well and was calculated as the average of air conduction thresholds at 500, 1000, 2000, and 4000 Hz.

WRS has been previously suggested\textsuperscript{15,16} and used\textsuperscript{10,11} as a primary hearing end point in NF2 trials.

A positive hearing response was defined as an improvement in WRS over baseline that meets criteria for statistical significance ($P \leq .05$). Changes in word recognition scores were compared using the Clinical Criteria for Definition of Hearing Response table (CCDHR).\textsuperscript{15}

Patients with a baseline WRS above 94% could not achieve a statistically significant improvement and were excluded from the hearing response analysis. These patients were followed for stability of hearing. A progression in hearing deficit was defined as a decrease in WRS below the 95% critical difference threshold. All other responses were considered stable hearing. Hearing outcomes are reported in standardized American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) scattergrams.\textsuperscript{17}

**Patient-Reported Outcomes**

Patients with NF2 are frequently afflicted by additional symptoms and neurological deficits such as tinnitus, vertigo and balance problems, headaches, and ear pain, often having a significant impact on quality of life. Although it is difficult to quantify these symptoms or their improvement, we decided to systematically summarize changes in these subjective symptoms during treatment. Each symptom was assessed at follow-up appointments. Patient-reported outcomes are now becoming an important part of neurofibromatosis studies.\textsuperscript{18,19}

**Results**

**Radiographic Response**

Seventeen vestibular schwannomas were evaluated for a radiographic response. Eight of 17 (47%) had a positive radiographic response (a decrease of tumor volume greater than 20%), 8 of 17 (47%) had stable imaging (decrease or increase less than 19%), and 1 of 17 (6%) patients had a radiographic progression (volume increase of more than 20%) (Table 1).

The median tumor volume decrease was 19% (range, 48% regression to 74% growth) (Figure 1).

Response to therapy was rapid. Five of 8 patients with a positive radiographic response had tumor regression within the first 3 to 9 months on treatment (see Supplemental Figures A and B in the online version of the article).

Among patients who experienced a tumor volume decrease in the first 9 months, the tumors then either remained stable or continued to shrink slowly if they continued on uninterrupted therapy (1-5 years) (see Supplemental Figure C in the online version of the article).

Patient 8 had an initial tumor volume decrease of 19% over 9 months but returned to pretreatment tumor volume in the 6 months following treatment discontinuation at month 10. Patient 11 had an initial 24% tumor volume decrease over 15 months but took several treatment holidays and tumor volume increased to 108% of baseline volume by 48 months.

Of our 2 patients receiving therapy for CI performance preservation, patient 9 had an initial tumor regression of 35% and then stable tumor. Patient 6 has had stable tumor.

**Hearing Response**

Pre- and posttreatment hearing assessments are reported in standardized AAO-HNS scattergrams\textsuperscript{17} (Figures 2, 3, and 4; see Supplemental Figures D and E in the online version of the article).

Nine of 17 patients were considered for a hearing response evaluation. Of the excluded 8 patients, 5 had WRS above 94% and therefore could not achieve a statistically significant improvement, one had a cochlear implant ipsilateral to the target lesion, and a posttreatment audiogram was unavailable for 2 patients.

A positive hearing response was observed in 5 of 9 (56%) of patients (Table 1). Two patients had WRS improvement over 40%. Time to hearing response for 4 of these patients was 2 to 4 months and, for 1 patient, 17 months. These patients showed additional WRS improvements beyond the initial response period (additional 12-36 months) (see Supplemental Table 2 in the online version of the article).

Two of 9 patients had stable hearing during treatment and 1 of 9 had worsened WRS scores. Patient 9, whose WRS had initially improved (from 40% to 72% in 4 months and then to 80% in 7 months), then experienced a marked decline (from 80% to 4%). Of note, this patient’s therapy interval and dose were changed before the decline from 5 mg/kg/2 wk to 7.5 mg/kg/3 wk. Dose and interval were subsequently adjusted to 10 mg/kg/2 wk and the patient’s WRS improved briefly to 12% but then declined again. This patient has since received a cochlear implant.
Patients with positive hearing response had minor improvements in their pure-tone averages that are not statistically significant (see Supplemental Table 2 in the online version of the article). It appears that the patients with pretreatment PTA ~50 dB had the most notable hearing improvements (Figure 4). Hearing improvements in our patient cohort were durable; gains made in WRS were stable for at least 1 year (1–4 years).

We found no obvious association between tumor regression and hearing improvement. This outcome is illustrated in the CCDHR table (see Supplemental Table 3 in the online version of the article). Notably, the patient in our study with the greatest hearing improvement had a slight tumor progression at the same time. Two patients with the most significant tumor decrease had no improvement in their hearing.

### Hearing Stability/Decline in Patients with Normal Hearing at Treatment Initiation

Patients who started treatment with normal word recognition scores (WRS above 94%) were evaluated for stability of hearing or decline of hearing during treatment.

Of the 6 patients whose initial WRS were 100%, 2 are still receiving treatment and their hearing has been stable at 100% WRS. Patient 12 has been treated for 4 years and patient 17 for 6 years. Patient 1, who was treated for 18 months, remained stable at 100% WRS for the duration of his treatment. Two additional patients whose initial WRS were 100% ended their treatment at 8 and 9 months (patient preference). Audiograms during treatment or posttreatment were not available for these 2 patients. Patient 13, who also started treatment with 100% WRS, experienced a hearing decline to 92% WRS during 6 months of her treatment.

### Figures

**Figure 2.** American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) pretreatment scattergram. Color is used to highlight AAO-HNS classes. Only patients who could improve statistically (with baseline word recognition score [WRS] below 94%) are included. PTA, pure-tone average.

**Figure 3.** American Academy of Otolaryngology–Head and Neck Surgery posttreatment scattergram. Only patients who could improve statistically are included. PTA, pure-tone average; WRS, word recognition score.

**Figure 4.** Pre–post treatment movement scattergram. Pre-treatment patient number is in blue color and post-treatment patient number is in red. Only patients that could improve statistically (with baseline WRS below 94%) are included. AAO-HNS, American Academy of Otolaryngology–Head and Neck Surgery; PTA, pure-tone average; WRS, word recognition score.
the following 6 years posttreatment, this patient’s hearing declined further and she is now scheduled to receive a CI.

**Patient-Reported Outcomes**

**Tinnitus.** Fourteen of 17 patients reported tinnitus at the start of the study, and 6 of them reported improvement in their tinnitus within 3 months of starting treatment. Improvement generally lasted while on therapy. Two patients reported that tinnitus returned briefly for a few days just before beginning each of their treatment cycles.

**Vertigo, dizziness, and balance issues.** Eight of 17 patients reported vestibular symptoms, including vertigo, dizziness, and/or imbalance at the start of the study; 3 of them noted an improvement within 3 months.

**Headaches.** Eight of 17 patients reported headaches at the start of the treatment and 3 reported an improvement in frequency and severity of the headaches within 3 to 6 months.

**Other subjective improvements.** Two patients reported ear pain, and one of them noted an improvement with treatment.

Cell phone use became easier for 3 patients (patients 6, 9, and 10). Patient 10, who was previously unable to use a cell phone at all, regained this ability with treatment. Patients 9 and 10 had concurrently improved WRS. Patient 6 has a CI and cannot be tested.

**Adverse Effects**

We identified several adverse events occurring during bevacizumab treatment. Hypertension, proteinuria, dysgeusia, and amenorrhea were the most common.

**Hypertension.** Seven of 17 (41%) patients developed hypertension (HTN) (as defined by age-related norms). Of these 7 patients, 3 had borderline HTN prior to starting treatment. One patient had preexisting HTN that worsened after starting bevacizumab therapy. This responded to a change in his HTN treatment. Three patients developed HTN within 4 to 6 months. Hypertension was controlled with angiotensin-converting enzyme (ACE) inhibitors and, in 1 case, with clonidine.

**Proteinuria.** Nine of 17 (52%) patients developed or had worsened proteinuria (urinary protein excretion >30 mg/dL). A patient with concurrent Alport syndrome had mild proteinuria prior to starting treatment, but her proteinuria increased during treatment and bevacizumab was temporarily stopped when her protein/creatinine ratio rose over 2. The other 8 patients developed proteinuria at 6 to 36 months after initiation of treatment. Treatment holidays and ACE inhibitors were used to manage proteinuria.

**Dysgeusia.** Eight of 17 (47%) patients developed dysgeusia. Dysgeusia was described in most cases as an increased sensitivity to spicy food. This was a bothersome effect, especially for those who enjoyed spicy food as part of their regular diet. Dysgeusia developed between 2 and 24 months. After treatment interruption or discontinuation, all affected patients’ sense of taste returned to normal.

**Amenorrhea.** Amenorrhea was another adverse effect observed with bevacizumab treatment. Of 7 female patients, 1 was postmenopausal (age 52) and did not report any irregularities. Of 6 premenopausal females (ages 17-37), all experienced cycle abnormalities. Four patients reported amenorrhea within 1 to 12 months of the start of treatment. Menstrual cycles returned with treatment interruptions or discontinuation. One patient reported menorrhagia the first month of treatment. A patient who was on continuous oral contraceptives at the start of treatment continued not having menstrual periods. One patient (age 28) is now on an adjusted dose and interval of 7.5 mg/kg/5 wk and is having periods. Another patient (age 17) is on 5 mg/kg/2 wk dose and titrated oral contraceptive and is also having periods.

Several additional adverse effects were reported, including fatigue, pain, weakness, and hair thinning.

**Other effects.** Increased sensory sensitivity was also noted. One patient experienced pain when showering as the water stream hit his body. Another patient experienced auditory discomfort when hearing certain sounds (eg, xylophone). One patient had an anaphylactic reaction.

Overall, treatment was fairly well tolerated. The patient who had an anaphylactic reaction after an infusion of bevacizumab did not continue with future treatments. Four other patients took bevacizumab holidays due to proteinuria and amenorrhea. Seven patients are still in treatment.

We have not yet identified any delayed or long-term effects of bevacizumab.

**Surgery in the Setting of Bevacizumab Treatment**

Bevacizumab therapy has been associated with an increased risk of postsurgical complications such as impaired wound healing and hemorrhage. Timing of cessation of bevacizumab prior to planned surgery and reintiation post surgery are critical in preventing possible complications. Due to the long half-life of bevacizumab (≥20 days), it is currently recommended that bevacizumab therapy be discontinued 4 weeks prior to surgery and restarted 2 weeks after. In our patient group, 6 patients received a surgical intervention for their vestibular schwannomas, including resection, debulking, or both, but all of these surgeries occurred prior to starting bevacizumab treatment. The shortest time interval between a surgery and start of treatment was 3 months.

One patient received a cochlear implant during bevacizumab therapy. His treatment was discontinued 6 weeks prior to surgery and restarted 5 weeks after the surgery with no complications. Two patients underwent other types of surgery while on treatment (dental extractions and blepharoplasty). Their treatment was stopped 4 weeks prior to surgery and restarted 2 and 3 weeks after. There were no postoperative complications for either one of these patients, and they did not experience any additional hearing loss due to the treatment interruption. No surgery needed to be delayed because of proximity to bevacizumab therapy.
Discussion

In our study, treatment with bevacizumab was followed by a significant tumor volume decrease in 47% patients and hearing improvement in 56% of patients. The median tumor volume decrease was 19%. Positive radiologic, hearing, and subjective responses were rapid, with most patients having a response within the first 3 months of treatment. More modest improvements or a response plateau then followed. Patients with an initial response that continued on therapy retained their gains for the duration of treatment (1-5 years). However, we documented that bevacizumab discontinuation or significant treatment interruptions were followed by a rebound in tumor growth and decline in hearing. We found no obvious association between tumor regression and hearing improvement. This discordance has been previously reported and could be explored in future NF2 studies. Two patients treated for preservation of CI performance had stable tumor and tumor regression/stable tumor on therapy. These studies, with small cohorts of 10 to 31 patients, reported positive imaging response in 40% to 60% and positive hearing response in 25% to 60%. The follow-up periods were 19 to 41 months. Some of our patients have been followed for up to 72 months, adding to the knowledge of long-term outcomes. We also assessed patient-reported outcomes, as these have not been addressed in detail in previous studies. Notably, approximately 40% of patients reported improvement in their tinnitus, vestibular symptoms, and headaches. Furthermore, using a cell phone became noticeably easier for 3 patients. These findings emphasize the importance of patient-reported outcomes as end points in NF2 treatment trials. Bevacizumab was well tolerated overall. Hypertension and proteinuria were the most common adverse effects. Dysgeusia was also prominent in our patient group. Amenorrhea and potential ovarian failure have emerged as a serious concern for premenopausal women. All of our young female patients treated more than 3 months experienced menstrual cycle abnormalities. The long-term effects of bevacizumab on female or male fertility in this patient group are not well understood at this time.

We generally started with a bevacizumab regimen that was suggested in previous studies, 5 mg/kg/2 wk. Due to various factors, such as worsening of symptoms, adverse effects, or patient preference, the dose for some patients was adjusted from 5 mg/kg to 7.5 mg/kg or 10 mg/kg and time interval from 2 to 6 weeks. The optimal treatment regimen is not yet determined and may need to be individualized. Given that bevacizumab therapy might need to continue for an extended period of time, it is prudent that the treatment be carefully calibrated to maximize desired effect while minimizing toxicity.

There are some limitations to our study. Our sample size of 17 was small, although it compares well to similar studies. In addition, there was some heterogeneity in the treatment regimen, although this treatment heterogeneity may be more representative of a real clinical use. Furthermore, we did not use standardized forms for the collection of patient-reported outcomes. While our practice is to inquire about the symptoms analyzed in this study, collection may not have been complete.

Conclusion

Bevacizumab treatment was followed by hearing improvement in 56% of patients, while decreased tumor volume was noted in 47%. These outcomes agree favorably with prior reported series. There were improvements in patient-reported outcomes that have not been described previously. As patient-reported outcomes become more standard end points in NF treatment studies, there will be a need for a set of comprehensive measures to evaluate and score these outcomes.

Author Contributions

Pavlina Sverak, made a substantial contribution to the acquisition, analysis, and interpretation of data for the work; assisted in drafting the work and revising it critically for important intellectual content; reviewed all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved; approved the final version to be published; Meredith E. Adams, made a substantial contribution to the conception and design of the work, including the analysis and interpretation of data for the work; assisted in drafting the work and revising it critically for important intellectual content; reviewed all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved; approved the final version to be published; Stephen J. Haines, made a substantial contribution to the conception and design of the work, including the analysis and interpretation of data for the work; assisted in drafting the work and revising it critically for important intellectual content; reviewed all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved; approved the final version to be published; Samuel C. Levine, made a substantial contribution to the conception and design of the work, including the analysis and interpretation of data for the work; assisted in revising it critically for important intellectual content; reviewed all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved; approved the final version to be published; Kathryn Dusenbery, made a substantial contribution to the acquisition, analysis, and interpretation of data for the work; reviewed it critically for important intellectual content; reviewed all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved; approved the final version to be published; Katherine Sommer, made a substantial contribution to the conception and design of the work; assisted in revising it critically for important intellectual content; reviewed all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved; approved the final version.
investigated and resolved; approved the final version to be published; Tina C. Huang, made a substantial contribution to the conception and design of the work, including the analysis and interpretation of data for the work; assisted in revising it critically for important intellectual content; reviewed all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved; approved the final version to be published; Christopher Moertel, made a substantial contribution to the conception and design of the work, including the acquisition, analysis, and interpretation of data for the work; assisted in drafting the work and revising it critically for important intellectual content; reviewed all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved; approved the final version to be published.

Disclosures
Competing interests: Christopher Moertel, consultant: Recombinetics, Inc and OX2 Therapeutics.

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Supplemental Material
Additional supporting information is available in the online version of the article.

References