Treatment of Corticosteroid-Responsive Autoimmune Inner Ear Disease With Methotrexate
A Randomized Controlled Trial

Jeffrey P. Harris, MD, PhD
Michael H. Weisman, MD
Jennifer M. Derebery, MD
Mark A. Espeland, PhD
Bruce J. Gantz, MD
A. Julianna Gulya, MD
Paul E. Hammerschlag, MD
Maureen Hannley, PhD
Gordon B. Hughes, MD
Richard Moscicki, MD
Ralph A. Nelson, MD
John K. Niparko, MD
Steven D. Rauch, MD
Steven A. Telian, MD
Patrick E. Brookhouser, MD

Prior reports suggested that rapidly progressive, bilateral, asymmetric inner ear dysfunction may be caused by immunological attack or may be associated with autoimmune disorders. McCabe\textsuperscript{4} renewed interest in this disorder as a distinct clinical entity and motivated investigators to identify the most efficacious treatment regimens for management of this potentially reversible form of deafness. Initial experience with this disorder has underscored the risk of developing bilateral profound deafness and vestibulopathy if patients are left untreated or treated inadequately.

On empirical grounds, glucocorticoids and cytotoxic agents were initially proposed as treatments. In a fol-

Context A number of therapies have been proposed for the long-term management of corticosteroid-responsive, rapidly progressive, bilateral sensorineural hearing loss (autoimmune inner ear disease [AIED]). Methotrexate has emerged as the benchmark agent but has not been rigorously evaluated for hearing improvement in patients with AIED.

Objective To assess the efficacy of long-term methotrexate in maintaining hearing improvements achieved with glucocorticoid (prednisone) therapy in patients with AIED.


Intervention Randomization to either oral methotrexate (15 to 20 mg/wk; n=33) or placebo (n=34), in combination with an 18-week prednisone taper. Follow-up examinations, including audiometric evaluation, were performed at 4, 8, 12, 24, 36, 48, and 52 weeks, or until hearing loss was documented.

Main Outcome Measure Maintenance of hearing improvement achieved from prednisone treatment.

Results Sixty-seven patients (57.8%) enrolled in the prednisone challenge experienced hearing improvement. Twenty-five patients (37%) experienced hearing improvements in both ears. Of the individuals who reached study end points, 24 (80%) of 30 end points were because of measured hearing loss in the methotrexate group and 29 (93.5%) of 31 end points were because of measured hearing loss in the placebo group (P=.15). Methotrexate was no more effective than placebo in maintaining the hearing improvement achieved with prednisone treatment (hazard ratio, 1.31; 95% confidence interval, 0.79-2.17; P=.30).

Conclusion Methotrexate does not appear to be effective in maintaining the hearing improvement achieved with prednisone therapy in patients with AIED.

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low-up report, McCabe\(^3\) recommended high-dose prednisone with the addition of cyclophosphamide for prolonged periods. Although this regimen appeared to be effective, the potential adverse effects and long-term morbidity and mortality risks of cyclophosphamide limited its use, especially in younger patients.

Subsequently, several reports proposed the use of less toxic agents for autoimmune inner ear disease (AIED), including methotrexate,\(^6,7\) plasmapheresis,\(^8\) azathioprine,\(^9,10\) and intravenous gamma globulin.\(^11\) Low-dose oral methotrexate (7.5 to 20 mg/wk) was reported to improve hearing and balance in patients with AIED and Méniere disease.\(^6,7\) Furthermore, methotrexate is currently regarded as the gold standard of care for patients with rheumatoid arthritis.\(^13\) In view of its tolerability, efficacy, and ease of use, methotrexate has emerged as the benchmark agent to which other agents are compared in clinical trials.\(^11\) Its introduction in the 1980s as a once-weekly agent in the treatment of patients with rheumatoid arthritis has led to its acceptance as the most widely prescribed agent for rheumatoid arthritis; adherence to guidelines for careful monitoring of hematologic, renal, hepatic, and pulmonary adverse reactions produces a very low incidence of potential serious adverse effects.\(^15\)

Although many physicians have thought that high-dose prednisone (60 mg/d) was effective in reversing hearing loss and maintaining hearing at improved, albeit diminished levels, this treatment effect was not maintained once the prednisone was tapered. The appeal of methotrexate was its potential prednisone-sparing effects and long-term safety. Prior studies of methotrexate in patients with AIED have been small, open-labeled, and uncontrolled.

In this article, we report the results of a prospective, multi-institutional, double-blind, placebo-controlled study designed to assess the efficacy of long-term methotrexate in the maintenance of initial hearing improvement in patients with AIED.

**METHODS**

**Study Population**

The AIED study population was defined by inclusion and exclusion criteria designed to limit enrollment to individuals with idiopathic, progressive, bilateral sensorineural hearing loss; to ensure appropriate candidates for treatment with study medications; and to identify those with a high likelihood of complying with the study protocol. The sensorineural hearing loss had to be 30 dB or more in both ears at 1 or more frequencies (250, 500, 1000, 2000, 3000, 4000, 6000, or 8000 Hz). Hearing must have actively deteriorated in at least 1 ear within 3 months of entering the study and the hearing loss had to be determined by the study otologists to be idiopathic based on clinical evaluation, blood tests, or radiographic imaging.

All patients underwent a retrocochlear evaluation that included a brainstem evoked response audiogram and a computed tomographic scan or magnetic resonance imaging. By protocol, participants were aged 18 to 70 years, had no more than 30 days of prednisone treatment (at therapeutic doses) in the previous 3 months, and had no more than 30 days of methotrexate therapy for AIED at any time in their history.

Patients with the following conditions were excluded: insulin-dependent or brittle diabetes; history of tuberculosis or prophylactic isoniazid treatment for a positive tuberculin skin test result; serious psychiatric disease; history of psychiatric reaction to corticosteroids; active malignancy within the past 5 years (excluding nonmelanomatous skin cancer); prior treatment with chemotherapy agents, immunosuppressive drugs, or cyclosporine; pancreatitis or active peptic ulcer disease; positive result for human immunodeficiency virus or hepatitis B or C; renal insufficiency; alcohol abuse; herpes zoster; fluctuations in hearing associated with episodic vertigo, without episodes of rapid progression; cochlear otosclerosis defined by radiographic evidence; luetic deafness; idiopathic, sudden sensorineural hearing loss occurring less than 24 hours as atypical for the diagnosis of AIED; Cogan syndrome; or perilymph fistula.

The study protocol and consent forms were approved by institutional review boards at each of the 10 clinical sites and the coordinating center.

**Study Design**

The study involved 2 phases (FIGURE 1); all participants were fully informed and provided separate signed consent before entering each phase. In the prednisone challenge phase, all enrolled participants were prescribed a 1-month open-label regimen of prednisone therapy (60 mg/d). The primary goal of this phase was to identify participants who were responsive to therapy according to the following: pure-tone air conduction thresholds at 8 frequencies (250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz) and word identification scores at 40-dB sensation level. Participants were recruited to the randomized trial of methotrexate vs placebo if they demonstrated improved hearing, defined as (1) an improvement of sensorineural hearing from baseline, in at least 1 ear, of 15 dB or more in the pure-tone air conduction thresholds at any of the 8 frequencies, or at 10 dB at 2 consecutive frequencies; or an increase of more than 12% in word identification score; and (2) no significant additional pure-tone air conduction threshold loss at any frequency and no significant additional loss in word identification score in either ear.

Improvement could have taken place in either ear (ie, not necessarily the ear in which the rapid hearing loss was demonstrated in order for the participant to enter the study) but there could be no further hearing loss in either ear.

In phase 2, participants whose hearing stabilized in response to prednisone therapy were tapered from prednisone and followed up by study personnel. Participants who experienced further hearing loss were also followed up by study personnel but their treatment was organized by their own physicians and not governed by study
protocol. Participants and study personnel were blinded to which group the participants were assigned. Audiologists were also blinded to previous audiological results obtained on each participant.

Enrollment

Of the 959 volunteers who were screened, 681 were found to be ineligible. The major reasons for ineligibility were audiologic criteria (n=329), medical history (n=199), and age (n=125); however, an additional 28 were excluded for other reasons (eg, refusal to accept randomization and factors judged by clinic staff to compromise adherence). An additional 162 individuals declined further participation at some time during the screening process.

Of the 116 patients who enrolled in the prednisone challenge, 18 refused further participation in the study. Of the remaining 98 individuals, 67 responded to prednisone and accepted randomization into the methotrexate clinical trial. Randomization was governed by a masked variable-length blocking scheme (block lengths 2 or 4), which was stratified by clinical site to promote balance within each center, and administered by computer and maintained at the coordinating center that automatically checked all eligibility criteria.

Treatment and Follow-up

At the end of the prednisone challenge and at the beginning of the prednisone taper, participants were randomly assigned, with equal probability, to either methotrexate at 7.5 mg/wk or placebo. An oral methotrexate regimen was used in which 2.5-mg tablets of methotrexate or placebo were given at 12-hour intervals for 3 doses. If no toxicity had occurred after the first 4 weeks, dosage for both was escalated to 6 tablets or 15 mg/wk for the second 4 weeks. After 8 weeks, the dosage for both was increased to 8 tablets or 20 mg/wk and remained at this level for the remainder of the trial. The dosage of the blinded medication could be adjusted to 15 mg/wk for the remainder of the trial in response to symptoms of intolerance. All participants took 1 mg/d of folic acid for prevention of folate depletion and prophylactic avoidance of adverse effects associated with chronic methotrexate administration.

Prednisone taper, at the end of 1 month at 60 mg/d, was accomplished by a dose reduction to 40 mg for 1 month, reduction of 10 mg for 2 successive months each, and then by 5 mg every 2 weeks (× 3) until the goal of no prednisone was reached after an 18-week taper. Participant follow-up consisted of regularly scheduled clinic visits to assess current medication use, symptoms, and safety. Adherence to study medication was monitored through pill counts at each clinic visit. Audiometric examinations were performed at 4, 8, 12, 24, 36, 48, and 52 weeks into follow-up to identify study end points. All patients were given prescriptions for ranitidine to be used for gastrointestinal symptoms associated with chronic prednisone therapy.

Primary and Secondary End Point Criteria

Participants who were documented at any time during the 52 weeks of planned follow-up to have lost hearing relative to the point of randomization into the trial (ie, after a 1-month course of prednisone therapy) were defined to have reached end point. The primary end point for the trial was both clinically meaningful and sensitive to medical therapy. Hearing loss criteria were based on changes from the time of randomization in either the pure-tone air conduction thresholds or word identification scores, in either ear, as a deterioration in pure-tone air conduction threshold relative to randomiza-

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treatment values, by 15 dB at an individual frequency or 10 dB at 2 consecutive frequencies; or a worsening of word identification score of at least 12%. Word identification score was based on the ability to repeat correctly an open set of monosyllabic words at suprathreshold intensity. Word lists were phonetically balanced and percentage was based on the number of words repeated correctly. End point status was declared if these criteria were confirmed at 2 consecutive examinations, 2 to 4 weeks apart, and at least 1 criterion was met.

To control for the possibility of differential follow-up between treatment groups, individuals who were lost to follow-up or who did not complete the scheduled 52-week closeout visit were also declared to have reached study end point at the time of their last visit. This approach prevented differential rates of end points to be attributable to differential rates of follow-up. Participants who were not scheduled to have a 52-week closeout visit because of the early termination of the trial were censored at the time of their last visit, unless clinic staff reported that follow-up had already been lost. This approach allowed end point status to be defined for all participants except those censored because of early termination of the trial.

The secondary end point evaluated hearing loss in comparison with baseline values (before prednisone treatment) in the event of a primary end point, which was based on hearing loss in comparison with the phase 1 close-out audiogram. If a participant continued to exhibit some hearing gains, this additional evaluation checked for a deterioration in pure-tone average (500 to 3000 dB) by 5 dB or a worsening of word identification score of at least 12% (both relative to baseline values).

In the absence of these criteria and physician approval, participants were permitted continued treatment on blinded study medication. A secondary end point was declared if these criteria were demonstrated on consecutive visits, if the physician or the participant elected to discontinue treatment, or if the participant was lost to follow-up. For a treatment failure occurring before 52 weeks, regardless of treatment assignment, a participant was offered an additional month of prednisone and open-label methotrexate in similar doses.

### Statistical Methods

All analyses were based on the intention-to-treat principle. Times to events were measured from the date of randomization to the date of the first audiometric analysis that triggered end point. Although a second audiogram was used to confirm end point 2 to 4 weeks later, it was not used for hearing data analysis or timing the end point. Kaplan-Meier method plots were used to portray the distribution of times until end points. Log-rank tests served as the primary comparisons between treatment groups. Cox proportional hazards regression model was used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for participant subgroups and to identify predictors of end points. The proportionality assumption inherent in this model was supported by analysis of residuals. $\chi^2$ Test was used to compare frequencies. Mean levels of the longitudinal audiometric data over time between the treatment groups were compared using generalized linear models fitted by maximum likelihood, which allowed for varying patterns of follow-up among participants. Poisson regression was used to compare rates of adverse events; Fisher exact test was used to compare the percentage of individuals experiencing any adverse event. SAS statistical software version 6.06 was used for all analyses (SAS Institute Inc, Cary, NC). $P<.05$ was considered statistically significant.

### Table 1. Characteristics of Participants at the Time of Randomization

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Methotrexate (n = 33)</th>
<th>Placebo (n = 34)</th>
<th>Entire Cohort (N = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12 (36)</td>
<td>17 (50)</td>
<td>29 (43)</td>
</tr>
<tr>
<td>Male</td>
<td>21 (64)</td>
<td>17 (50)</td>
<td>38 (57)</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-49</td>
<td>16 (48)</td>
<td>17 (50)</td>
<td>33 (49)</td>
</tr>
<tr>
<td>50-70</td>
<td>17 (52)</td>
<td>17 (50)</td>
<td>34 (51)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not high school graduate</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>High school graduate</td>
<td>7 (21)</td>
<td>7 (21)</td>
<td>14 (21)</td>
</tr>
<tr>
<td>Some post–high school education</td>
<td>12 (36)</td>
<td>8 (24)</td>
<td>20 (30)</td>
</tr>
<tr>
<td>College graduate</td>
<td>13 (39)</td>
<td>17 (50)</td>
<td>30 (45)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>0</td>
<td>2 (6)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>1 (3)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hispanic American/Latino</td>
<td>2 (6)</td>
<td>2 (6)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>White (not Hispanic)</td>
<td>30 (91)</td>
<td>30 (88)</td>
<td>60 (90)</td>
</tr>
<tr>
<td><strong>No. of ears responding to prednisone†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>18 (55)</td>
<td>24 (71)</td>
<td>42 (63)</td>
</tr>
<tr>
<td>2</td>
<td>15 (45)</td>
<td>10 (29)</td>
<td>25 (37)</td>
</tr>
<tr>
<td><strong>Prednisone response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in air conduction, mean (SD)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean of both ears</td>
<td>7.5 (8.7)</td>
<td>6.9 (6.8)</td>
<td>7.2 (7.7)</td>
</tr>
<tr>
<td>Maximum across ears</td>
<td>10.7 (11.3)</td>
<td>9.3 (7.5)</td>
<td>10.0 (9.5)</td>
</tr>
<tr>
<td>Change in word identification score, mean (SD)§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean of both ears</td>
<td>14.6 (15.7)</td>
<td>12.0 (14.0)</td>
<td>13.2 (14.8)</td>
</tr>
<tr>
<td>Maximum across ears</td>
<td>22.3 (19.9)</td>
<td>18.8 (16.8)</td>
<td>20.5 (18.4)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%) unless otherwise specified. Because of rounding, percentages may not all total 100.
†Response to prednisone is defined as an improvement of 10 dB or higher at 2 consecutive frequencies or 15 dB or higher at 1 frequency in pure-tone air conduction thresholds or an improvement of 12 units or more in word identification score.
‡Change observed during 1-month administration of prednisone: mean across 8 frequencies (omitting dead ears [pure-tone average on prestudy and both baseline audiograms ≤90 dB]).
§Change observed during 1-month administration of prednisone (omitting dead ears).
**Data and Safety Monitoring**

This trial was designed to detect, with 90% statistical power, whether methotrexate therapy might lead to a 3-fold increase (from an expected 20% in the placebo group) in the success rates of maintaining hearing improvement associated with prednisone therapy at 52 weeks. To accomplish this, a goal of randomizing 130 participants was set. Trial monitoring guidelines for early stopping for success were based on approximate o’brien-fleming boundaries to control for multiple testing. 16 Stopping for futility was based on interim analyses of conditional power. These interim power projections were developed through computer simulations in which the current observed data were augmented with randomly imputed data generated from probabilities for adherence, compliance, and success detailed in the study protocol (and determined before the start of the trial) and the targeted sample size. Each interim power was estimated by using 10,000 simulations. Results from these simulations were accumulated and the proportion of times a significant result was achieved based on the primary analysis described in the protocol was computed. This size of simulation approach was sufficient to yield an SE for estimated power of ≤ .005.

Trial monitoring for early stopping was conducted semi-annually by an independent data and safety monitoring committee charged to protect the safety of the participants and the integrity of data. Each clinical site underwent an audit for compliance with the study protocol by members of the data coordinating center, a physician member of the study steering committee, and/or a member of the National Institutes of Health clinical trials staff.

**RESULTS**

**Trial Monitoring and Early Stopping**

Enrollment of the trial began February 3, 1998, with formal monitoring of the trial in November 1998. Assignment to methotrexate therapy was associated with an increased rate of study end points (relative to placebo) at every interim analysis. On October 31, 2001, the data and safety monitoring committee recommended termination of recruitment and the orderly closure of the trial, based on no apparent benefit of methotrexate over placebo and projections indicating that continuation would be unlikely to alter this finding. At that time, the probability of detecting a significant benefit for methotrexate (should the trial continue to its planned completion) was 0.016 at the current estimated HR for methotrexate therapy and 0.146 at the lower bound of a 95% CI for this HR. It was thus quite unlikely that the unfavorable trend observed for methotrexate would be reversed. Study data were collected up to November 5, 2001.

**Trial Findings**

Figure 1 illustrates that 116 (12%) of 959 patients screened were entered into the trial and participated in the prednisone challenge. Table 1 describes the 67 participants who qualified and enrolled in the trial. The randomization process yielded similar distributions of these characteristics between the trial groups. Twenty-five participants (37%) experienced hearing improvements in both ears. In their most responsive ears, the mean (SD) change in air conduction threshold across the 8 measured frequencies was 10.0 (9.5) and in word identification scores was 20.5 (18.4).

Figure 2 shows the distribution of times until study end points by treatment assignment. Differences between these distributions did not reach statistical significance (log rank P = .29).

**Table 2. Reasons for Primary End Points**

<table>
<thead>
<tr>
<th>End Points</th>
<th>Treatment Assignment, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Audiometric end points</td>
<td></td>
</tr>
<tr>
<td>Only air conduction threshold</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>Only word identification</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Both air conduction and word identification</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>Total</td>
<td>24 (80.0)</td>
</tr>
<tr>
<td>Nonaudiometric end point*</td>
<td>6 (20.0)</td>
</tr>
</tbody>
</table>

*Participant had not met an audiometric end point at earlier visits but did not appear for the closeout (52-week examination).
cause of audiologic criteria, 24 (47.1%) were because of drug discontinuation by the AIED physician, and 12 (23.5%) were because of participant dropout or refusal. There were no statistically significant differences in times until secondary end point status between individuals assigned to methotrexate vs placebo (log rank $P=.51$) (FIGURE 3).

TABLE 3 lists results from Cox proportional hazards regression model to identify predictors of primary end points. Patients assigned to methotrexate were at slightly, but not significantly, higher risk for end points than those assigned to placebo (fitted HR, 1.31; 95% CI, 0.79-2.17; $P=.30$). The rates of end points were similar across sexes and age groups and were not significantly related to the response to prednisone therapy (all $P>.10$).

FIGURE 4 shows the mean changes in pure-tone air conduction thresholds and word identification scores by treatment assignment. These are limited to ears that initially responded to prednisone and to examinations through primary end point determination. There were no significant differences between treatment groups with respect to these measures ($P=.21$ and $P=.59$, respectively).

Participant Safety

TABLE 4 lists serious and other adverse events that occurred during the prednisone challenge and trial, and provides rates per 100 person-years. Very few adverse events occurred. Two patients (1 in each group) experienced severe adverse events; the most serious included the patient in the placebo group diagnosed with lung cancer at the beginning of the blinded portion of the trial. Most of the other adverse events were predictable based on exposure to prednisone and methotrexate, elevated blood glucose levels and weight gain (prednisone), and abnormal liver function (methotrexate). In total, 10 (14.9%) of 67 patients discontinued participation in the trial for adverse events.

COMMENT

This study demonstrated that methotrexate was no more effective than placebo in maintaining hearing improvement in patients with AIED, who demonstrated initial benefit from high-dose corticosteroids. The study was halted when conditional power calculations and analyses revealed that further recruitment of patients would be futile given the decline in hearing that was observed in both groups.

An early reported clinical trial on the use of methotrexate in immune-mediated inner ear disease was retrospective and uncontrolled. In that study of 25 participants treated with methotrexate, 69.6% were reported to have improved hearing and 80% showed improvement of vestibular symptoms. In a subsequent retrospective clinical trial of methotrexate for treatment of bilateral immune-mediated Meniere disease ($N=18$), hearing improvement was observed in 5 participants (28%) and stabilization of hearing was observed in 7 participants (39%). The major benefit appeared to be resolution of vertigo observed in 14 participants (78%).

In a prospective open-label study, 25 individuals with several forms of presumed immune-mediated sensorineu-
ral hearing loss (bilateral Meniere disease, Cogan syndrome, and progressive sensorineural hearing loss responsive to prednisone) were treated with a 3-week high-dose prednisone taper; 18 participants responded with partial improvement in at least 1 ear (72%). This compares to 57.8% in our study, although participants with Cogan syndrome and typical Meniere disease were specifically excluded.

Allowing for a larger hearing loss change than permitted in our study and only using a single audiological evaluation at 52 weeks, Matteson et al found at the end of the 12-month study period that 11 (65%) of 17 participants improved, 2 participants (12%) had worse hearing, and 4 participants (23%) remained the same compared with the pretreatment values. Both pure-tone and speech discrimination improved in at least 1 ear in only 4 (23%) of 17 participants. In our study, however, the comparisons were made with postprednisone levels to determine if hearing improvements could be maintained. Matteson et al used baseline levels before any treatment, which means that they also incorporated the effect of prednisone in their analysis. When data from our study was reexamined adopting the end point definition used by Matteson et al, there were still no detectable significant differences associated with the addition of methotrexate with prednisone therapy ($P = .32$).

Several factors may have influenced these findings. Strict audiologic and clinical criteria were necessary to confirm AIED and protect patient safety but clearly resulted in a low enrollment rate of 12% of those screened. Despite this, it is possible that our study cohort contained individuals who did not have an autoimmune or an immunological cause of deafness. Prednisone respon-
siveness, the primary diagnostic criterion for entry into our study, likely did not offer complete specificity in identifying patients with an autoimmune basis for their hearing loss. In addition, entry criteria required all participants to have experienced hearing loss within the previous 3 months.

Appropriate selection of participants was further addressed by excluding those individuals in whom a nonimmunological etiology could be established (eg, a strong familial/genetic history of hearing loss, chronic otitis media, otosclerosis), and by including individuals with a coexisting autoimmune condition and with rapidly progressive hearing loss. As a result of these selection criteria, 57.8% of the participants enrolled in the prednisone challenge experienced hearing improvement.

It is also possible that our study design did not allow for sufficient methotrexate treatment, either in terms of dose or duration, to achieve therapeutic benefit. Although the exact mechanism of its beneficial effect in rheumatoid arthritis is not completely known, methotrexate appears to affect a variety of intracellular pathways that are of potential importance in the pathogenesis of not only rheumatoid arthritis but other related diseases of immune dysregulation. Methotrexate appears to provide initial improvement in most patients with rheumatoid arthritis within a few weeks and maximal benefit is noted at 6 months. When methotrexate was initially approved by the Food and Drug Administration for treatment of rheumatoid arthritis, the dosages used in the initial trials were 7.5 to 15 mg/wk. As experience has been gained with long-term use of the drug, current recommended dosages have nearly doubled to 15 to 25 mg/wk.

The appropriateness of the 20 mg dosage is affirmed by recent trials of new agents for rheumatoid arthritis (entanercept), in which the methotrexate regimen, viewed as standard therapy, is 20 mg/wk.

In our study, the choice of 20 mg/wk should have been sufficient to achieve a treatment effect as suggested by companion data in other autoimmune states. The methotrexate dose was escalated rapidly while participants were maintained when receiving high-dose prednisone, keeping mindful of the fact that the safety of this drug had not been established in AIED. Participants received at least 15 mg/wk of methotrexate with a goal of 20 mg/wk if adverse effects did not develop. The most common dose of methotrexate was 15 mg/wk. Furthermore, to determine if reaching end point was a consequence of inadequate methotrexate dosage, our study reviewed the future status of participants who were end point free at the time they reached their full methotrexate dose and compared this with the future status of participants in the placebo group who were end point free at comparable times. The rates of future end point were very similar between the 2 groups: 7 (78%) of 9 participants in the methotrexate group and 7 (70%) of 10 participants in the placebo group. The failure to detect a positive methotrexate effect does not appear to be because of failure in reaching full methotrexate dose.

Another possible explanation is that the study end point definition was overly sensitive to minor changes in audiometric results, which required confirmation according to study protocol. To address the possibility that a treatment effect was not measured by the primary end point, secondary end points were defined that required more changes in clinical status. No difference was found between methotrexate and placebo with respect to more conservative criteria.

One of the potential benefits of methotrexate might have been stabilization of hearing levels with fewer fluctuations over time. Many patients with AIED experience large swings in their hearing thresholds or speech discrimination that greatly impacts their function. Unfortunately, our study was unable to assess this. It was clear, however, that methotrexate was not able to maintain the significant hearing improvements obtained by high-dose prednisone over time any better than placebo.

The participants enrolled in our trial showed very acceptable complication rates and anticipated adverse events. There were no deaths or severe morbidities. The adverse events associated with prednisone included glucosuria and elevated blood glucose levels. No participants were admitted for drug-induced diabetes, although 1 participant required an oral hypoglycemic on a temporary basis. One participant was discovered to have a mild developing cataract. No participant developed clinically evident avascular necrosis of the hip or symptomatic osteoporotic fractures. Given the dosages of corticosteroids used in the study, osteoporosis probably developed in many participants. For this reason, study personnel required every participant to be cared for by a primary care physician with full knowledge of the risks of the experimental treatment disclosed to that physician. Several participants required discontinuation of study medication (n=2 in the placebo group and n=2 in the methotrexate group) or open-label methotrexate (n=5) during treatment for abnormal blood data. All resolved without further intervention. Based on these results and with proper informed consent, the use of prolonged and high-dose corticosteroids in patients with AIED may be safe, despite the inherent risks.

The results of our study clearly underscore the need for more effective and less toxic therapy for AIED, and that randomized controlled trials are necessary to establish benefit. Methotrexate is not effective in maintaining hearing after patients are tapered down from high-dose prednisone treatment. Despite prolonged high-dose prednisone and a slow taper treatment, the patients once again began to lose their hearing.

**Author Contributions:** Study concept and design: Harris, Weisman, Espeland, Gantz, Gulya, Hanley, Hughes, Moscicki, Nelson, Rauch, Brokhouser. Acquisition of data: Harris, Derebery, Gantz, Hammerschlag, Hughes, Nelson, Niparko, Rauch, Telian. Analysis and interpretation of data: Harris, Weisman, Espeland, Gantz, Hanley, Moscicki, Rauch, Telian. Drafting of the manuscript: Harris, Weisman, Espeland, Gantz, Gulya, Nelson, Niparko.
Critical revision of the manuscript for important intellectual content: Harris, Weisman, Derebery, Espeland, Gantz, Gulya, Hammerschlag, Hannley, Hughes, Moscicki, Rauch, Tellan, Brookhouser.

Obtained funding: Harris, Weisman, Espeland, Gantz, Hannley, Brookhouser.

Administrative, technical, or material support: Harris, Weisman, Derebery, Espeland, Gantz, Gulya, Hannley, Hughes, Nelson, Niparko, Rauch, Brookhouser.

Study supervision: Harris, Weisman, Gantz, Gulya, Hammerschlag, Hannley, Moscicki, Nelson, Niparko, Rauch, Brookhouser.

AIED Investigators and Key Professional Staff: Central Administration: Boystown National Research Hospital, Omaha, Neb; Patrick E. Brookhouser, MD (principal investigator); University of Texas-Southwestern, Dallas: Peter S. Rychlik, MD, Frank Musiek, PhD, Lanie Friedman Ross, MD, Leonard P. Rybak, MD, Naj Younes, PhD.

Funding/Support: This study was supported by grant 5 UD1 DC03209 from the National Institutes of Health/ National Institute on Deafness and Other Communication Disorders and the American Academy of Otolaryngology-Head and Neck Surgery Foundation Inc.

Wyeth Laboratories (Philadelphia, Pa) donated the methotrexate and placebo.

Acknowledgment: We thank Miriam Seva for editorial assistance with the manuscript.

REFERENCES


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(Reprinted) JAMA, October 8, 2003—Vol 290, No. 14