Azathioprine Reduces the Risk of Audiometric Relapse in Immune-mediated Hearing Loss

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KEYWORDS
Autoimmune disease;
Sensorineural hearing loss;
Recurrence;
Survival analysis

Abstract

Introduction: Current schemes for treatment of immune-mediated hearing loss with sporadic short-course, low-dose corticosteroids, are insufficient.

Methods: To determine the role of azathioprine in the control of auditory impairment, a longitudinal, observational, descriptive study was performed with 20 patients treated with azathioprine (1.5–2.5 mg/kg/day into two doses) for 1 year. The loss of 10 dB on two consecutive frequencies or 15 dB on an isolated frequency was considered as relapse.

Results: The mean age of the patients was 52.50 years (95% CI: 46.91–58.17), half were women. Bilateral affection was 65%. 75% had organ specific disease and 25% had systemic autoimmune disease. The difference between baseline PTA (46.49 dB; DS 18.90) and PTA at 12 months (45.47 dB; DS 18.88) did not reach statistical significance (P=.799). There was a moderate positive correlation between female sex and the presence of systemic disease (R=.577). By applying Student’s t for paired data, a significant difference (P=.042) was obtained between the PTA in frequencies up to 1000 Hz (PTA 125–1000 Hz). The relative incidence rate of relapse per year was .52 relapses/year (95% CI: .19–1.14]. The median time to audiometric relapse-free was 9.70 months (DS 1.03).

Conclusions: Azathioprine maintains the hearing threshold, decreases the risk of relapse, and slows down the rate at which patients relapse, altering the course of immune-mediated inner ear disease.

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Azathioprine Reduces the Risk of Audiometric Relapse in Immune-mediated Hearing Loss

La azatioprina reduce el riesgo de recaída audiométrica en hipoacusia inmunmediada

Resumen
Introduction: Los esquemas actuales de tratamiento de la hipoacusia inmunomediada con corticoides, a dosis baja y pauta corta, son insuficientes. Métodos: Para determinar el papel de la azatioprina en el control del deterioro auditivo se ha llevado a cabo un estudio observacional descriptivo longitudinal con 20 pacientes tratados con azatioprina por vía oral (1,5-2,5 mg/kg/día en dos dosis) durante 1 año. Se consideró recaída la pérdida de 10 dB en dos frecuencias consecutivas o de 15 dB en una frecuencia aislada. Resultados: La edad media de los pacientes fue de 5250 años (IC 95%: 46,91-58,17), y la mitad fueron mujeres. La afectación bilateral fue del 65%. Un 75% presentaban enfermedad orgañospecifica y un 25%, enfermedad autoimmune sistémica. La diferencia entre la PTA basal (46,49 dB; DE 18,90) y la PTA a los 12 meses (45,47 dB; DE 18,88) no alcanzó significación estadística (p=0,799). Existía una correlación positiva moderada entre sexo femenino y presencia de enfermedad sistémica (R=0,577). Aplicando t de Student para datos apareados se obtuvo una diferencia significativa (p=0,042) entre el descenso de la PTA en frecuencias hasta 1.000 Hz (PTA 125-1.000 Hz). La tasa relativa de incidencia de recaída por año fue de 0,52 recaídas/año (IC 95%: 0,19-1,14). El tiempo medio de supervivencia libre de recaída audiométrica fue de 9,70 meses (DE 1,03). Conclusiones: La azatioprina mantiene el umbral de audición, disminuye el riesgo de recaída y frena la velocidad con la que los pacientes recaen, alterando el curso de la enfermedad inmunomediada del oído interno.

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Introduction
The treatment of immune-mediated hearing loss is a race against time with the unique aim of changing the course of the disease. Without treatment, every patient with immune-mediated hearing loss is destined to become deaf in one or both ears.1

As occurs in other auto-immune diseases, the earlier treatment is started, the greater the likelihood of controlling the inflammatory process and reducing structural damage. Therefore, progressive sensorineural hearing loss of recent onset must be considered a diagnostic priority. Hearing response to corticosteroids is the fundamental clinical criterion for diagnosis. This response, although usually transient, reinforces the suspected diagnosis. Follow-up of these patients is also incomplete, since audiometric monitoring is reserved for acute hearing loss.

This deterioration, which is clinically evident, has not been sufficiently parameterised, despite the recommendations of some authors.2 At the moment, the response and relapse criteria are not sufficiently widespread and are not common, which makes it impossible to compare results. The current treatment schemes with sporadic corticosteroids, at low doses and with short courses, do not fit the chronic nature of the disease. Early use of effective doses for the appropriate time makes hearing recovery more likely, since there is a therapeutic window of opportunity. More than prompt treatment, the hearing response to corticosteroids should be considered an opportunity for these patients since it opens the door to immunosuppressive treatment.

Methods
This study is based on the data gathered in a single centre within the EMHA Project: azathioprine for the treatment of autoimmune hearing loss with response to oral corticosteroids: a multicentre study (Protocol code: INV-AZA-2014-01, dated 15 April, 2013), classified by the Department of Medicinal Products for Human Use of the Spanish Agency of Medicines and Medical Devices as a post-approval, prospective follow-up study, (PAS) authorised by the Office of Pharmaceutical and Health Product Control - Area of Clinical Investigation and PAS of the Community of Madrid and by the Clinical Research Ethics Committee of the Referral Hospital.

Design
Longitudinal, observational descriptive study.

Population
Patients with immune-mediated hearing loss selected consecutively in the outpatient clinic from June 2013 to June 2016, data was collected up until April 2017.

Inclusion Criteria
Patients with sensorineural hearing loss with response to oral prednisone at a dose of 1 mg/kg/day for 15 days. Response
was defined as an improvement on the baseline PTA, in at least one ear, of 15 decibels (dB) or more in the hearing threshold at any of the frequencies, or 10 dB at two consecutive frequencies.

Each patient’s hearing loss type was specified:

- Progressive, if the deterioration in hearing threshold of 10 dB at two consecutive frequencies or 15 dB at a single frequency occurred in less than 3 months.
- Fluctuating, if fluctuation was noted on 2 audiometries in less than 12 months.
- Repeated sudden hearing loss, if the patient presented more than 3 episodes.

For safety in the use of the drugs, the age of 18 was set as the lower age limit for inclusion in the study. All the patients underwent magnetic resonance imaging to discount retrocochlear disease.

Exclusion Criteria

- Having taken glucocorticosteroids at therapeutic doses (1 mg/kg/day) in the 3 months prior to the start of the study.
- Serious psychiatric illness that would compromise compliance with the treatment.
- A history of psychiatric reaction to glucocorticosteroids.
- Medical contraindications to azathioprine and/or corticosteroids.
- Liver disease.
- Acute of chronic pancreatitis.
- Retrocochlear disease demonstrated by imaging tests.
- Cochlear otosclerosis suspected by pure-tone audiometry.
- Family history of genetic hearing loss.
- Hearing loss within a malformation syndrome.
- Pregnant or breast-feeding mothers.
- Failure to give informed consent.

All the patients were treated with oral azathioprine (1.5–2.5 mg/kg/day in two doses) for 12 months. Audiometry was performed using AD33 interacoustics equipment before starting treatment at 3, 6, 9 and 12 months. Control analysis was performed (haemogram, liver and kidney profile) at 3 weeks of treatment and subsequently every 4–6 weeks, and according to the judgement of the rheumatologist in their routine clinical practice.

Data Analysis

The mean hearing threshold (pure tone average [PTA]) was calculated at each hearing check. The day of relapse (difference in days between the date of onset and the date of relapse), the number of relapses on this day of relapse and the product between both values were taken to calculate this relative incidence rate of relapse. To estimate the likelihood of audiometric relapse, a survival analysis was performed using the Kaplan–Meyer method. The Cox regression model and the logistic regression model were used to analyse the relationship between sex, type of hearing loss and presence of systemic disease and the likelihood of relapse.

Results

The data gathered from 20 patients treated with azathioprine (Table 1) and the audiometries from 31 affected ears were analysed. Half of the patients were women and the other half men. The mean age of the patients was 52.50 years (95% confidence interval [IC]: 46.91–58.17; range: 20.8–70.5 years). There was 65% bilateral involvement. Seventy-five percent had organ-specific disease and 25%, systemic autoimmune disease. Forty percent of the patients had fluctuating hearing loss (8), 10% progressive hearing loss (2), and 50% more than 3 episodes of sudden hearing loss (10). Two patients with systemic autoimmune disease had fluctuating hearing loss (40%), two patients had progressive hearing loss (40%), and one patient had repeated sudden hearing loss. On clinical history taking, the patients reported hearing loss of a median of 7 months (range: 2 weeks and 480 months). Once the clinical history had been opened, considering the follow-up time before starting treatment with azathioprine, the median was 15.67 months. Each ear with hearing loss was considered separately for the mean hearing threshold study. Two cophotic ears were discounted (PTA<sub>125-8000Hz</sub> = 120 dB).

Two patients discontinued the treatment voluntarily after 1.77 and 10.77 months of treatment. Four patients discontinued the treatment due to general malaise or gastrointestinal upset. One patient stopped the treatment due to an attack of vertigo in their cochleovestibular disease, and another patient due to mild hypertransaminasaemia (values less than double their baseline levels).

The mean baseline PTA before administration of azathioprine was 46.49 dB, standard deviation (SD) 18.90. The final PTA of the 20 ears with evolutive data at 12 months was 45.47 dB, SD 18.88. The difference between both mean thresholds did not achieve statistical significance (P=.799). There was a moderate positive correlation between the female sex and the presence of systemic disease (R=.577). There was also a correlation, albeit weak, between bilateral involvement and progression time of hearing loss greater or equal to 1 year (R=.453), and between the baseline PTAs greater than 60 dB and progression time of hearing loss greater than 1 year (R=.506). There was no correlation between bilateral involvement and systemic disease (R=.182). Performing the same study with the baseline and final PTA, calculating only 500–1000–3000 Hz, similar data were encountered with no significant difference (P=.219).

Analysing PTA at each of the frequencies and at each of the cut-off periods (3, 6, 9 and 12 months) a significant improvement was observed at low frequencies, and non-significant worsening at high frequencies (Fig. 1). Fig. 2 shows the mean PTA at each baseline frequency and at 12 months of treatment. The difference between the PTAs is more evident at low frequencies in the first three months (Fig. 3).

Using the Student’s t-test for paired data, we obtained a significant difference between the decrease of PTA from 125 to 10000 Hz (P=.042), whereas if the high frequencies were also considered (PTA<sub>500-8000Hz</sub>) no significant differences were obtained (P=.139).
Table 1  Demographic Data of the 20 Patients With Immune-mediated Hearing Loss Treated With Azathioprine Over 12 Months.

<table>
<thead>
<tr>
<th>No.</th>
<th>A</th>
<th>S</th>
<th>Type of hearing loss</th>
<th>Progression (months)</th>
<th>Involvement</th>
<th>Systemic dis.</th>
<th>Time until aza (months)</th>
<th>Aza maint. dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>M</td>
<td>Fluctuating hearing loss</td>
<td>60</td>
<td>Bilateral</td>
<td>No</td>
<td>1.20</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>M</td>
<td>Repeated sudden hearing loss</td>
<td>1</td>
<td>Unilateral</td>
<td>No</td>
<td>18.00</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>M</td>
<td>Repeated sudden hearing loss</td>
<td>480</td>
<td>Bilateral</td>
<td>No</td>
<td>.13</td>
<td>175</td>
</tr>
<tr>
<td>4</td>
<td>51</td>
<td>M</td>
<td>Repeated sudden hearing loss</td>
<td>36</td>
<td>Bilateral</td>
<td>No</td>
<td>.23</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>M</td>
<td>Repeated sudden hearing loss</td>
<td>36</td>
<td>Bilateral</td>
<td>No</td>
<td>13.33</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>67</td>
<td>M</td>
<td>Repeated sudden hearing loss</td>
<td>.3</td>
<td>Bilateral</td>
<td>No</td>
<td>1.77</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>44</td>
<td>F</td>
<td>Fluctuating hearing loss</td>
<td>7</td>
<td>Unilateral</td>
<td>No</td>
<td>28.50</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>71</td>
<td>M</td>
<td>Fluctuating hearing loss</td>
<td>1.5</td>
<td>Unilateral</td>
<td>No</td>
<td>27.47</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>52</td>
<td>M</td>
<td>Repeated sudden hearing loss</td>
<td>.75</td>
<td>Unilateral</td>
<td>No</td>
<td>8.60</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>F</td>
<td>Progressive hearing loss</td>
<td>24</td>
<td>Bilateral</td>
<td>SLE</td>
<td>123.13</td>
<td>50</td>
</tr>
<tr>
<td>11</td>
<td>54</td>
<td>F</td>
<td>Repeated sudden hearing loss</td>
<td>144</td>
<td>Bilateral</td>
<td>No</td>
<td>5.90</td>
<td>150</td>
</tr>
<tr>
<td>12</td>
<td>45</td>
<td>F</td>
<td>Fluctuating hearing loss</td>
<td>.5</td>
<td>Bilateral</td>
<td>No</td>
<td>4.77</td>
<td>100</td>
</tr>
<tr>
<td>13</td>
<td>43</td>
<td>F</td>
<td>Progressive hearing loss</td>
<td>12</td>
<td>Bilateral</td>
<td>Autoimmune hypothyroidism</td>
<td>45.00</td>
<td>100</td>
</tr>
<tr>
<td>14</td>
<td>65</td>
<td>M</td>
<td>Repeated sudden hearing loss</td>
<td>.25</td>
<td>Unilateral</td>
<td>No</td>
<td>24.70</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>61</td>
<td>F</td>
<td>Fluctuating hearing loss</td>
<td>1</td>
<td>Bilateral</td>
<td>Sjogren</td>
<td>6.43</td>
<td>100</td>
</tr>
<tr>
<td>16</td>
<td>64</td>
<td>F</td>
<td>Fluctuating hearing loss</td>
<td>7</td>
<td>Unilateral</td>
<td>Hashimoto</td>
<td>31.87</td>
<td>100</td>
</tr>
<tr>
<td>17</td>
<td>56</td>
<td>F</td>
<td>Repeated sudden hearing loss</td>
<td>312</td>
<td>Bilateral</td>
<td>No</td>
<td>40.10</td>
<td>50</td>
</tr>
<tr>
<td>18</td>
<td>67</td>
<td>F</td>
<td>Repeated sudden hearing loss</td>
<td>.5</td>
<td>Bilateral</td>
<td>Graves</td>
<td>5.13</td>
<td>100</td>
</tr>
<tr>
<td>19</td>
<td>59</td>
<td>F</td>
<td>Fluctuating hearing loss</td>
<td>1</td>
<td>Bilateral</td>
<td>No</td>
<td>47.37</td>
<td>150</td>
</tr>
<tr>
<td>20</td>
<td>41</td>
<td>M</td>
<td>Fluctuating hearing loss</td>
<td>120</td>
<td>Unilateral</td>
<td>No</td>
<td>38.33</td>
<td>100</td>
</tr>
</tbody>
</table>

Aza: azathioprine; A: age; dis.: disease; SLE: systemic lupus erythematosus; F: female; maint.: maintenance; No.: number; S: sex; M: male.

Figure 1  Progression of mean PTA over the first year: analysis by frequency (Hz).
Graphic representation by mean PTA frequencies in each cut off period. Mean PTA in decibels (ordinate axis): baseline, at 3 months (3m), at 6 months (6m), at 9 months (9m) and at 12 months (12m) with their corresponding standard deviations, in 125–250–500–1000–2000–4000–8000 Hz (abscissa axis).

Figure 2  Progression of mean PTA at 12 months: analysis by frequency (Hz).
Graphic representation by mean PTA frequencies in decibels (ordinate axis): error bars of baseline audiometry (blue) and at 12 months (green) with their corresponding standard deviations, in 125–250–500–1000–2000–4000–8000 Hz (abscissa axis).
Discussion

Since this is a rare and probably under-diagnosed disease due to the lack of specific markers, studies are enormously complex. In order to limit the inclusion of patients with progressive idiopathic bilateral hearing loss we used the inclusion and exclusion criteria of the study by Harris et al.\(^3\) In our paper, like those of other authors,\(^1,4\) we used high doses of long-course corticosteroids. The audiometric response was parameterised following the recommendations of Niparko et al.\(^2\) to make the studies comparable. Speech discrimination tests were not performed before and after treatment, therefore it was not possible to demonstrate an increase in speech discrimination score (SDS) in the patients treated with immunosuppressive drugs, as suggested by other authors.\(^4\)

The dose of azathioprine was calculated by weight in order to avoid a lack of response due to under treatment, and was adjusted according to thiopurine methyltransferase levels in order to reduce side effects to a minimum. There were no high frequency audiometers to detect subclinical disease as described by Lasso et al., in their studies on patients with systemic lupus erythematosus\(^7,8\) and rheumatoid arthritis,\(^7\) and by Zlavra et al. in Sjögren’s disease.\(^8\)

Recruitment Rate and Adverse Effects

Our study recruited a similar number of patients/year to that of Salley et al.\(^9\)

The number of patients recruited per year described in the literature (Table 3) varies between the maximum achieved in the prospective study by Harris et al.,\(^3\) with 22.33 patients recruited per year, and the minimum of 1.29 patients/year again by Harris et al.\(^10\) Broughton et al.\(^4\) managed to recruit 4.67 patients per year and Loveman et al.\(^11\) recruited 10 patients per year.

The discontinuation rate of treatment with azathioprine was high, perhaps due to the information that the patients were given on using the drug outside the datasheet and the lack of immediate improvement, in contrast to the immediacy of response achieved with corticosteroids.

All the adverse effects were minor: most involved gastric intolerance and general malaise. The data sheet describes hypersensitivity reactions in 2% of cases, bone marrow suppression in 2% (reversible, dose-dependent and usually expressed as leukopenia), susceptibility to viral, bacteria and mycotic infections (7.4%), affecting the skin and other systems, severe diarrhoea, recurrent with reintroduction, pancreatitis (3.3%), cholestasis, and reversible deteriorating liver function, reversible pneumonitis, and self-limiting hair loss.

There were no cases of leukopenia or medullary aplasia in our studies that led to discontinuation of medication, which confirms the safety of azathioprine as an immunosuppressive drug. More detailed information on the initial symptoms might result in fewer discontinuations for this reason.

Azathioprine as Maintenance Treatment

The first study on immune-mediated hearing loss where azathioprine was used\(^12\) was in 1993. Twelve patients were
Azathioprine reduces the risk of audiometric relapse in immune-mediated hearing loss.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Mean Audiometric Relapse-free Survival (in Months) of the Patients With Immune-mediated Hearing Loss Treated With Azathioprine.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean survival time (first year)</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>9.70</td>
<td>1.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Recruitment of Patients per Year in Immune-mediated Hearing Loss Studies.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
<td>Year of pub.</td>
</tr>
<tr>
<td>Harris</td>
<td>2003</td>
</tr>
<tr>
<td>Broughton</td>
<td>2004</td>
</tr>
<tr>
<td>Loveman</td>
<td>2004</td>
</tr>
<tr>
<td>Harris</td>
<td>2013</td>
</tr>
<tr>
<td>Mata</td>
<td>2017</td>
</tr>
</tbody>
</table>

End year: year the study ended; start year: the year the study started; No.: number of patients; pub.: publication.

treated with prednisone 30 mg/day for 4 weeks and azathioprine 1 mg/kg/day, with a response in 10 of the patients. A long course of prednisone at medium doses was used in this study combined with low doses of azathioprine over a short period. Because the immunosuppressive effect of azathioprine starts at 3 weeks of treatment, it is possible that the response was due to the effect of the corticosteroid. Other subsequent studies\(^{13,14}\) combine prednisone and azathioprine with an initial response and relapse on discontinuing the corticosteroids. Broughton et al.\(^{4}\) refer to one patient, of five treated with azathioprine, who achieved stabilisation of disease without fluctuations over 30 months of treatment.

Azathioprine has also been used in sensorineural hearing loss associated with some systemic auto-immune diseases: systemic lupus erythematosus,\(^{14}\) polyarteritis nodosa,\(^{15}\) Cogan’s syndrome,\(^{16-18}\) and granulomatosis with polyangiitis, once the severe systemic disease has been controlled with prednisone and cyclophosphamide.

In our study, the percentage of patients with systemic disease treated with azathioprine (25%) is in line with the literature (15%–30% of cases).\(^{19}\)

No correlation was found between hearing loss and sex or age, and the relapses did not coincide with outbreaks of associated systemic disease. The study by Bowman et al.\(^{20}\) with 30 patients with hearing loss and systemic lupus erythematosus, found no correlation with age, sex or disease activity either. In contrast, Roverano et al.,\(^{21}\) with a similar sample, and Abbasi et al.,\(^{22}\) with 45 patients, did find a correlation with the duration of symptoms and disease activity. No relationship between hearing loss and age was found in Sjögren’s disease, although a relationship was found with the duration of the disease.\(^{8}\) In rheumatoid arthritis, no relationship was found with sex, age or duration of the disease either.\(^{23}\) There might be a correlation between hearing loss in rheumatoid arthritis and erythrocyte sedimentation rate, interleukin levels and disease activity.\(^{24}\) However, no correlation was found between bilateral involvement and systemic disease (R=.182), which could support the asynchronous nature of bilateral involvement.

A moderate positive correlation was found between the sex variable (female) and the systemic involvement present variable (R=.577). This correlation was also found in the author’s study for the group of patients treated exclusively with corticosteroids (R=.356). A predomination of females is also described in other autoimmune diseases. Females respond with a higher production of antibodies and T2 helper cells (Th2), whereas Th1 predominate in males. The autoimmune diseases that are most common in men manifest clinically before the age of 50 and are characterised by acute inflammation and a predominance of Th1 cell response. The autoimmune diseases that are most common in women (Graves disease and systemic lupus erythematosus) are antibody-mediated diseases. The autoimmune diseases with a higher incidence in females over the age of 50 are associated with chronic Th2-mediated fibrosis.\(^{25}\)

Response to treatment of hearing loss is not similar over the entire spectrum of systemic diseases. Hearing loss from granulomatosis with polyangiitis usually responds to treatment, while that from Susac’s or Cogan’s syndrome is characterised by a poor response. Similarly, immunemediated disease of the inner ear can include a spectrum of diseases with a different pathogenic mechanism that respond to different types of treatment, and not all of them in the same way.

We also analysed the response at each frequency explored audiometrically and each cut-off period (3, 6, 9 and 12 months) and we observed that in the group treated with azathioprine improvement was greater at 3 weeks of treatment and at the low frequencies. Bearing in mind that most of the hearing losses in systemic disease affect the high frequencies, from 4000 Hz, it might be necessary to look for a frequency-specific immunosuppressant.

With regard to systemic involvement and onset of relapse, in our study there was a clear tendency between the absence of systemic disease and the speed of onset of relapse. The results suggested that azathioprine delayed the progression of the disease in patients without systemic disease, since they took longer to relapse, although in the end they relapsed in the same proportion as the patients with systemic disease.
Table 4 Cox’s Model of Proportional Risk to Analyse the Effect of the Age, Sex and Absence of Systemic Disease Variables on the Likelihood of Relapse.

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>Df</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95% CI for Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.018</td>
<td>.035</td>
<td>.251</td>
<td>1</td>
<td>.616</td>
<td>1.018</td>
<td>.950 – 1.090</td>
</tr>
<tr>
<td>Absence of systemic disease</td>
<td>2.307</td>
<td>1.341</td>
<td>2.958</td>
<td>1</td>
<td>.085</td>
<td>10.039</td>
<td>.725 – 139.093</td>
</tr>
</tbody>
</table>

The initial transitory response (the first three months) might be due to the added effect of the descending course of corticosteroids overlapped at the start of treatment in some patients. This transitory effect is also in line with studies that refer to a loss of immunosuppressant effect over time, even for corticosteroids. The loss of effect over time might suggest longer term baseline treatment combined with oral corticosteroids at low doses and azathioprine, or with two immunosuppressive drugs.

The combination with immunosuppressive drugs has been extensively described in the literature, always in relation to the severity of the disease (granulomatosis with polyangiitis, Cogan, Susac), reserving cochlear implant for those who have not responded to medical treatment.

Khalidi et al.14 have already suggested the combination of prednisone and azathioprine at high doses for the treatment of patients with systemic lupus erythematosus and hearing loss.

According to our results, azathioprine could be recommended for hearing losses that preferentially compromise the low frequencies, combined with oral corticosteroids, with slower decreasing course over a year as suggested by Noguchi et al.,26 to treat patients with hearing loss and Behçet’s disease. Intratympanic corticotherapy would be reserved for relapses with low and middle frequency involvement (250, 500, 1000 Hz), and oral corticosteroids for bilateral and high frequency relapses (4000–8000 Hz).27

In relation to systematic diseases and subclinical hearing loss, we support the proposal to use hearing loss to monitor serious diseases such as Susac’s syndrome,28 and the recommendations to use audiometry to screen for common diseases, such as systemic lupus erythematosus or rheumatoid arthritis, in which hearing loss can occur even years after developing the disease, as occurs with granulomatosis with polyangiitis29,30 or Sjögren’s syndrome,31 before discounting cranial nerve involvement.

The patients with a history of hearing loss over more than one year had more bilateral involvement and poorer hearing thresholds, which supports the indication to act before the disease progresses to affect both ears.

The rate of relapse of the patients treated with azathioprine was 52 relapses/year. In a study by the author with a group of patients treated exclusively with corticosteroids, the relative incidence rate of relapse per year was higher, 2.01 relapses/year, to be specific.32

These relapses have been described even after long periods of treatment, on discontinuing medication that achieved a response when it was reintroduced.33,34 Relapses can be salvaged with intratympanic infliximab.35 In a clinical study by Vambutas et al. on patients with immune-mediated, corticosteroid-resistant hearing loss, subcutaneous anakinra36 was used at doses of 100 mg, over a period of 84 days. Seven of 10 patients showed audiometric improvement (PTA and SDS), then 3 of the 7 treated relapsed on discontinuing treatment.

In our study, 50% of the patients relapsed at 9.70 months; SD 1.03 (Table 4). This mean audiometric relapse-free survival time is greater than that found by the author in a group of patients treated exclusively with corticosteroids (5.25 months; SD .76).32

Conclusions

The patients with immune-mediated hearing loss treated with azathioprine maintained their hearing thresholds. Azathioprine reduces the risk of relapse and slows down the rate at which patients relapse, altering the course of immune-mediated disease of the inner ear. Our study supports starting immunosuppressant treatment earlier, and maintaining it long term. Specific referral units are required with multidisciplinary assessment to treat these types of patients, as well as multicentre studies that group patients with different clinical courses who require different treatments, and compare the effectiveness of the treatments given to preserve function, before definitive structural damage occurs.

Conflict of Interests

The authors have no conflict of interest to declare.

References

Azathioprine Reduces the Risk of Audiometric Relapse in Immune-mediated Hearing Loss


