Eur Arch Otorhinolaryngol (2006) 263:977–982
DOI 10.1007/s00405-006-0096-9

OTOLOGY

Alternatives to systemic steroid therapy for refractory immune-mediated inner ear disease: a physiopathologic approach

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Received: 12 February 2006 / Accepted: 20 May 2006 / Published online: 27 June 2006

Abstract Immune-mediated inner ear disease (IMIED) is one of the few forms of reversible sensorineural hearing loss. Corticosteroids-responsive patients are usually associated with hearing improvement. Due to the long clinical course of IMIED that frequently present recurrences (hearing loss and vertigo), alternatives to corticosteroids such as methotrexate and recently TNF-α blockers have been proposed. Likewise new procedures for delivering corticosteroids to the inner ear have been developed. The aim of this article is to assess the efficacy of methotrexate and transtympanic 6-methylprednisolone in refractory IMIED. From a database of 200 patients affected by IMIED, 16 selected patients with refractory disease were included in the present study. Five patients were treated with methotrexate and 11 by means of transtympanic injection of 6-methylprednisolone. All patients treated with methotrexate had an improvement in their vestibular symptoms. However, hearing loss did not improve. Most patients treated with local 6-methylprednisolone (68.75%) showed an improvement in hearing loss and vestibular symptoms. Methotrexate has been shown to be ineffective in maintaining long-term remissions of hearing relapses although patients presented an improvement in vestibular symptoms. However, transtympanic 6-methylprednisolone has been shown to be a safe, easy and useful therapy in refractory IMIED and it may actually become the first-line treatment for these patients based on the existence of glucocorticoid receptors and the possible targets of immune-mediated damage within the inner ear.

Keywords Methotrexate · 6-Methylprednisolone · Transtympanic therapy · Immune-mediated inner ear disease

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Introduction

Immune-mediated inner ear disease (IMIED) is one of the few forms of sensorineural hearing loss amenable to medical treatment. Traditionally, corticosteroids are usually associated with positive responses and suggest an autoimmune insult as the cause of the hearing loss. However, prolonged administration of these drugs has been associated with serious adverse reactions. In order to minimize the adverse effects and due to the long clinical course of IMIED that frequently presents recurrences of the disease (hearing loss and vertigo), corticosteroids have been associated and/or replaced with other immunomodulating drugs, such as methotrexate [15, 27] and recently TNF-α blockers [13, 28]. Likewise new procedures for delivering corticosteroids directly to the inner ear have been developed, achieving higher concentrations and avoiding the systemic side effects [8, 25].

We report a retrospective study of 16 patients with treatment-refractory IMIED to assess the efficacy of

low-dose methotrexate given long-term and/or transtympanic administration of steroids. A physiopathologic approach based on the existence of glucocorticoid receptors within the inner ear, the corticosteroid pharmacokinetics in the inner ear fluids and the possible targets of immune-mediated damage is presented.

Patients and methods

A retrospective case series study was performed. From 200 patients affected with IMIED included in our database, 16 patients with poor response to corticosteroid therapy (6-methylprednisolone at a starting dose of 1 mg/kg of body weight per day during 21 days) and/or recurrences were included in the present study [5].

The clinical evaluation included a routine history and physical examination, a pure-tone audiogram, syphilis tests and a limited immunologic work-up study: antinuclear autoantibodies (ANA) and phenotype of peripheral blood lymphocytes (PBL). An imaging study (MRI) was performed to rule out abnormalities of the eighth cranial nerve. The following criteria were applied to support a high suspicion of IMIED [1, 3, 6]:

- Bilateral or recurrent disease
- Young adults
- Presence of systemic autoimmune disease
- ANA titer > 1:80
- Reduced number of naive T cells (CD4CD45 RA)
- Positive response to steroid treatment

A positive response was defined as (1) an improvement in pure-tone average at 250, 500, 1,000, 2,000 and 4,000 Hz of more than 10 dB and/or (2) the elimination or marked alleviation of vertiginous symptoms.

The main age of the selected patients was 39 years (age range 17–64), 7 males (43.75%) and 9 females (56.25%). Four patients displayed right side hearing loss, two left side and ten bilateral hearing loss. Vertigo was present in 13 patients.

After the initial steroid trial, cytotoxic treatment was offered to those patients who did not improve and/or those with recurrent disease. Oral methotrexate was administered at an initial dose of 7.5 mg/week, increasing to 15 mg/week over the ensuing 4–8 weeks for at least 12 months unless toxicity or a lack of response required an earlier termination of treatment. A complete blood count and liver enzyme testing are performed every 4–8 weeks to assess for methotrexate toxicity. Folic acid at a dose of 1 mg/day is prescribed to minimize potential toxicity.

Those patients who did not respond to methotrexate or who relapsed during therapy or who rejected this drug were offered a local therapy by means of a steroid perfusion of 6-methylprednisolone (0.3–0.5 ml of the standard 6-methylprednisolone solution, 40 mg/ml, weekly during at least 2 months) to the round window [4]. We used a modified intratympanic steroids technique reported by Silverstein et al. [26]: topical anesthesia with lidocaine 5% before the injection is administered. A tuberculin syringe (27 gauge needle, 1.5 in. long) was used to inject 0.3–0.5 ml of the standard 6-methylprednisolone solution, 40 mg/ml, into the middle ear through an intact tympanic membrane just posterior to the umbo of the malleus, over the round window niche area. Patients were asked to remain in the supine position with their head turned to the side for 20–30 min and asked not to swallow in order to avoid the clearance of the drug from the middle ear towards the eustachian tube.

Results

Of the 16 patients studied, 8 were treated with local steroid perfusion of 6-methylprednisolone (53.3%), 5 with oral methotrexate (33.3%) and 3 patients received both treatments.

Methotrexate therapy (Table 1)

The mean duration of symptoms prior to the initiation of treatment was 70.8 months (range 6–108 months). The mean duration of methotrexate treatment was 21.2 months (range 13–40 months), and the mean follow-up was 109 months (range 43–214 months). No major side effects were presented by patients treated with methotrexate. Although four patients experienced a subjective improvement of their hearing, after exhaustive application of our criteria of positive response, hearing remained stable in five ears, worse in four ears and improved in one ear. Recurrences did not diminish (mean: 3.6 before treatment vs. 3.8 along the methotrexate therapy). All patients showed an improvement in their vestibular symptoms. Only one patient showed elevated liver enzymes and nausea.

Local therapy (Table 2)

The mean duration of symptoms prior to the initiation of treatment was 30.6 months (range 1–96 months). The mean follow-up was 31.7 months (range 2–115 months). Six patients (68.75%) showed an improvement of their hearing, three unchanged and only two presented

Table 1 Patients treated with methotrexate

Patient	Age	Gender	Side	Time elapsed before treatment	Vertigo	Hearing	Follow-up (months)	Therapy (months)
1	53	Male	Bilateral	8 years	Improved	W RE U LE	94	40
2	35	Male	Bilateral	4 years	Improved	U RE W LE	94	17
3	45	Female	Bilateral	9 years	Improved	U RE U LE	43	16
4	53	Male	Bilateral	8 years	Improved	U RE W LE	214	20
5	30	Female	Bilateral	6 months	Improved	I RE W LE	100	13

I improved, *U* unchanged, *W* worse, *RE* right ear, *LE* left ear

Table 2 Patients treated by means of transtympanic injection of 6-methylprednisolone

Patient	Age	Gender	Side	Time elapsed before treatment	Vertigo	Hearing	Follow-up (months)
1	21	Female	Left ear	4 months	Improved	Improved	16
2	26	Female	Left ear	2 months	Improved	Improved	6
3	17	Male	Bilateral	3 months	Improved	Improved	70
4	43	Male	Right ear	1 month	Improved	Improved	73
5	21	Female	Bilateral	3 years	NA	Improved	8
6	64	Male	Bilateral	3 years	Improved	Unchanged	33
7	50	Female	Right ear	2 years	Improved	Worse	6
8	45	Female	Right ear	6 years	Improved	Worse	115
9[a]	53	Male	Bilateral	8 years	NA	Unchanged	3
10[a]	37	Female	Bilateral	5 years	NA	Improved	17
11[a]	43	Female	Right ear	3 months	Improved	Unchanged	2

NA not applicable

[a] Patients that had previously been treated with methotrexate

worse hearing. All patients affected by vestibular symptoms improved. We have not observed major side effects; only two patients presented one episode of vertigo after one of the transtympanic injection. No perforations of the tympanic membrane were observed. Recurrences stopped at the end of the schedule therapy.

Discussion

The diagnosis of IMIED is ascertained by the history, clinical findings and response to immunosuppressive medication. As spontaneous improvement or resolution of untreated sensorineural hearing loss does not occur often, patients with suspected IMIED would be promptly treated in order to stop the steady deterioration of hearing. McCabe first reported the benefits of using prednisolone and cyclophosphamide in 1979 [17] although he believed that cyclophosphamide was the cornerstone of treatment [16].

High doses of corticosteroids may be useful in the initial management of IMIED. Treatment with 60 mg prednisone daily for 4 weeks is widely used. Shorter-term or lower-dose long-term therapy has been ineffective and increases the risk of relapse [23]. Patients with recurrent disease are placed on a repeat course of steroids but when the improvement in hearing is not sustained and side effects from the corticosteroids appear, the use of cytotoxic drugs has been proposed. This therapeutic alternative could serve as steroid-sparing drug and maintain long-term remissions. The patients in the present study were first treated with a steroid. Those who were unresponsive and those who did respond but whose hearing deteriorated as the steroid was tapered and discontinued were switched to the cytotoxic drug methotrexate.

Methotrexate is the drug most widely used. It is less toxic and has fewer long-term risks such as the development of neoplasia than cyclophosphamide. Oral methotrexate was administered at an initial dose of 7.5 mg/week, increasing to 15 mg/week over the ensu-

ing 4–8 weeks for at least 12 months. Methotrexate is given with folic acid and patients are monitored for toxicity by means of complete blood count, platelet count, blood urea nitrogen and creatinine levels, liver function determination and urinalysis. No major side effects were presented by patients treated with methotrexate. Hearing remained stable in five ears, worse in four ears and improved in one ear. The lack of hearing recovery may result from the long time elapsed from the initial insult to the inner ear (mean 70.8 months) in this group of patients. However, improvement in disequilibrium or vertigo was noted by all patients. Three patients whose relapses could not be controlled were offered to be treated with local steroids.

A recent multi-institutional clinical trial has concluded that methotrexate does not appear to be effective in maintaining the hearing improvement achieved with prednisone therapy in patients with autoimmune inner ear disease (AIED) [7]. However, some authors [9, 14, 15] have considered methotrexate for patients with immune-mediated bilateral Meniere's disease, Cogan's syndrome and progressive sensorineural hearing loss responsive to prednisone, when long-term treatment is required or when a steroid or cyclophosphamide is contraindicated. These controversial results question the utility of methotrexate as a therapy for IMIED in those cases in which high-dose prednisone has not been effective in restoring hearing although this drug could be useful for the control of vestibular symptoms as shown by our patients.

For patients with non-responsiveness to steroid and/or methotrexate therapy and for those who rejected these alternatives, local therapy can be considered. Local immunosuppression produces fewer systemic effects with reduced systemic toxicity. Inner ear perfusion therapy is designed to increase the concentration of medication delivered to labyrinth by infusing the drugs into spaces in proximity to the labyrinth. Transtympanic application can be achieved through different routes including direct injection and infusion through a myringotomy, wick, minipumps or a tympanostomy tube [8, 10, 25]. These indirect approaches could help the drugs permeate through the round window membrane into the inner ear fluids with a higher and more sustained perilymph levels than systemic treatment.

In an animal study Parnes et al. [19] have established cochlear fluid pharmacokinetics profiles of hydrocortisone, methylprednisolone and dexamethasone, following oral, intravenous and topical (intratympanic) administration. All three corticosteroids successfully penetrated the blood–labyrinthine barrier and the round window membrane into the inner fluids. High systemic doses produced higher inner ear drug levels but intratympanic administration resulted in a significantly higher inner ear drug level compared with systemic administration. Plasma drug levels were higher than cerebrospinal fluid (CSF) and perilymph levels after systemic administration, with no significant differences between the perilymph and CSF drug levels, reflecting either a similar source of production or the potential communication through the cochlear aqueduct. Similar drug concentrations were observed in scala vestibuli and scala tympani perilymph for all drugs following intratympanic administration, suggesting free communication between these compartments. Active transport through the membranous labyrinth to become concentrated within the endolymph led to higher endolymph drug levels. Of the three drugs, methylprednisolone displayed both highest concentration and longest duration in perilymph and endolymph. Thus, intratympanic methylprednisolone appears to have the greatest potential for clinical application in treating inflammatory and immune-mediated inner ear disorders and avoids the potential risks of systemic corticosteroids.

The absorption of the glucocorticoid (GC) through the round window membrane depends on the permeability of the membrane, the amount of time the solution remains in contact with the membrane and the concentration of the solution. Steroids may also cause vasodilatation with increased microvascular blood flow in the cochlea.

Likewise, the presence of type II glucocorticoid receptors (GR) in the lateral wall of the cochlea and ampullae of the vestibule has been demonstrated [20]. The effect of GC on the heterologous inner ear tissues is directly proportional to the number of GRs. Shimazaki et al. [24] demonstrated the strongest GR expression in the type III fibrocytes of the spiral ligament. Spiral ligament fibrocytes play a role in cochlear fluid and ion homeostasis; the localization of Na-K-ATPase in the fibrocytes suggests that K^+ ions are taken up from root cells into the fibrocytes through the gap junctions among the fibrocytes and moved down the concentration gradient into the stria vascularis basal or intermediate cells. Strial marginal cells pump the K^+ ions into the cells and the K^+ ions then flow down a concentration gradient into endolymph.

Glucocorticoid receptors' expression is not prominent in the cochlear hair cells, although supporting cells in the organ of Corti were positive for GR, suggesting that GC treatment does not directly affect the hair cells. The affectation of the stria vascularis and spiral ligament could represent the first step in the immune damage to the inner ear. Metabolic changes induced by the immune system on the lateral wall

structures (endothelial cells and fibrocyte II dysfunction leading to impaired diffusion of K^+ through marginal cells to the endolymph fluid) could affect the supporting cells of the organ of Corti preceding the late effect of the hair cells [21]. This new theory has been raised by the presence of Cogan's peptide and the KHRI-3 cochlear protein (68 kDa) in the supporting cells [12, 18], making vulnerable to the immune attack. Thus, the existence of a great number of glucocorticoid receptors in the stria vascularis and the supporting cells suggest their role as immune targets of the inner ear.

Six patients (68.75%) from the present study showed improvement in their hearing, three unchanged and only two presented a worse hearing. A possible explanation for the hearing recovery could be a shorter clinical course presented by this group of patients. Likewise, all patients affected by vestibular symptoms improved. Using transtympanic injections we have not observed significant side effects (two vertiginous episodes). In a previous study we used tympanostomy tubes, and perforations of the tympanic membrane were reported [2]. The safety of inner ear perfusion has been established. However, research continues on improving the success of current treatment schedules as well as developing new systems for drug delivery to the inner ear.

Despite initial optimistic report suggestive of a therapeutic effect of the immunosuppressive agent etanercept, a recent pilot study data do not suggest substantial efficacy in improving hearing loss [13] and an animal model of autoimmune labyrinthitis showed that etanercept was not more effective than GC in preserving the hearing [11]. Likewise, with the advent of cochlear implants, the administration of toxic medications to preserve hearing at all costs is not a desirable option [22].

As refractory IMIED may require the administration of cytotoxic agents with uncertain outcome and high risk for developing major side effects, local therapy may actually become the first-line treatment for these patients. Additional research into IMIED diagnostic, treatment strategies and new therapeutic agents that act on different arms of the immune system, minimizing adverse effects and preserving hearing and vestibular function, should be encouraged.

Conclusions

High doses of corticosteroids may be useful in the initial management of IMIED but when the improvement in hearing is not sustained and side effects from the corticosteroids appear, the use of cytotoxic drugs have been proposed. Although controversial outcomes regarding methotrexate have been reported, this drug has been shown to be ineffective in maintaining long-term remissions of hearing relapses even though patients presented an improvement of vestibular symptoms. However, transtympanic 6-methylprednisolone has been shown to be a safe, easy and useful therapy in refractory IMIED and it may actually become the first-line treatment for these patients.

Acknowledgment This study was partially supported by a grant of the Spanish FIS PI050673.

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