The Journal of Laryngology & Otology (2013), ***127***, *1145–1147.*

doi:10.1017/S002221511300217X

CLINICAL RECORD

Infliximab for autoimmune inner ear disease: case report and literature review

R L HEYWOOD[1], S HADAVI[2], S DONNELLY[2], N PATEL[1]

Departments of [1]Otorhinolaryngology and [2]Rheumatology, Whipps Cross University Hospital, London, UK

Abstract

Objectives: This study aimed (1) to report the long-term effects of infliximab, a murine monoclonal antibody directed against tumour necrosis factor-α, on autoimmune inner ear disease, and (2) to discuss dilemmas surrounding the long-term management of autoimmune inner ear disease.

Case report: A 49-year-old man presented with sudden-onset, left-sided, sensorineural hearing loss, tinnitus and vertigo. He was prescribed oral prednisolone, with benefit. Over several subsequent months, he experienced frequent relapses and progressive deterioration of high-frequency hearing bilaterally. Multiple agents failed to stabilise his condition. Following infliximab treatment, there was a documented and sustained improvement in his hearing and tinnitus. He stopped the treatment after 46 weeks, with rapid relapse of his condition. His hearing recovered quickly again after recommencing infliximab.

Conclusion: The benefits of prolonged infliximab use and potential side effects must be balanced against allowing the disease to take its course, with progressive deafness. Randomised controlled trials are required to assess infliximab's optimal duration of use, long-term efficacy and safety in the treatment of autoimmune inner ear disease.

Key words: Autoimmune Diseases; Tumor Necrosis Factor-Alpha; Antibodies, Monoclonal; Hearing Loss, Sensorineural

Introduction

Autoimmune sensorineural hearing loss was first described by McCabe in 1979.[1] 'Autoimmune inner ear disease' is now thought to be a more appropriate term for sudden or rapid onset of sensorineural hearing loss (SNHL) over weeks or months, often bilateral, and frequently accompanied by tinnitus, aural fullness and/or vestibular symptoms. Autoimmune inner ear disease is one of the few causes of SNHL amenable to medical treatment, but, if untreated, the sequelae include profound deafness and vestibular dysfunction. There is no consensus on the management of the condition, reflecting a paucity of knowledge on its pathogenesis, diagnosis and treatment.

There is now substantial evidence to confirm McCabe's theory of an autoimmune process. In 1990, Harris and Sharp identified circulating antibodies against an unknown 68-kDa inner ear antigen in patients with rapidly progressive SNHL.[2] The identity of this 68-kDa antigen has been proposed to be either heat shock protein-70 or a member of the inner ear choline transporter like protein family.[3] Subsequently, other antibodies and possible inner ear antigens have been reported. However, no single autoantibody has been found to be universal, and the trigger for autoantibody production remains unclear.

The diagnosis of autoimmune inner ear disease is primarily based on the clinical syndrome and on steroid responsiveness, as there is no specific diagnostic test and no universally accepted diagnostic criteria.

Similarly, there is no standard management. Models of cochlear damage have shown that tumour necrosis factor-α (TNFα) is a key mediator, and recent developments in the treatment of autoimmune inner ear disease have included TNFα-targeted therapies.

Here, we report one patient's response to the use of infliximab, a murine monoclonal antibody directed against TNFα, and we discuss the management dilemmas surrounding its use.

Case report

A 49-year-old man presented with sudden-onset, left-sided, sensorineural hearing loss, tinnitus and a brief episode of vertigo. Otoneurological examination was normal.

Serum cholesterol was slightly elevated at 5.6 mmol/l (normal range, <5.0 mmol/l), but glucose levels, erythrocyte sedimentation rate and thyroid function tests results were normal. Tests for autoantibodies, viral titres and syphilis serology were all negative.

Magnetic resonance imaging of the cerebellopontine angles and internal auditory meati was normal.

The patient was prescribed prednisolone (reducing in dose from 60 mg/day to 0 mg over 8 days) and acyclovir (800 mg 5 times per day for 7 days), with hearing improvement.

Over the following months, the patient suffered multiple similar episodes. During each, his hearing would deteriorate predominantly in the low frequencies, with a mild but persistent deficit at 6 and 8 kHz (see Figure 1). He was treated

Accepted for publication 25 March 2013 First published online 15 October 2013

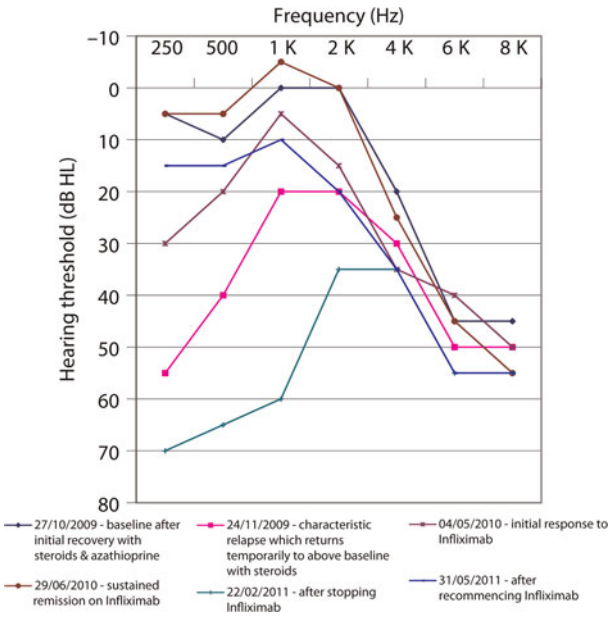

FIG. 1
Left ear pure tone audiograms.

as a case of 'definite' Ménière's disease (based on the American Academy of Otolaryngology criteria), with dietary salt and caffeine restriction and betahistine (16 mg 3 times daily), but gained little benefit. He received several intratympanic injections of methylprednisolone 28 mg, with good but short-lived hearing improvement. This had no effect on the course of his disease, which continued with persistently fluctuating symptoms and new high-frequency loss in his right ear.

Further investigations were undertaken, including electrocochleography and testing of auditory brainstem responses and intracochlear pressure, all of which were normal. However, the patient's immunoglobulin (Ig) M concentration was elevated, at 4.72 g/l (normal range, 0.4–2.3 g/l). Otoblot testing was negative.

The patient was started on azathioprine 100 mg daily, with some initial benefit, but the dose had to be reduced due to steatorrhoea. A diagnosis of autoimmune inner ear disease was made based on response to steroid therapy, raised IgM level, initial response to azathioprine, and a family history of autoimmune disease (the patient's mother had pernicious anaemia, and two other relatives had conditions with an autoimmune basis). Methotrexate was tried but stopped due to derangement of liver function.

The patient continued to have episodes of fluctuating hearing loss, tinnitus and aural fullness, together with progressive deterioration of his high-frequency sensorineural thresholds bilaterally.

Sixteen months after his symptoms began, he started a course of etanercept, but had no response at six weeks.

The patient was switched to infliximab, initially 400 mg intravenously over 2 hours. After the second infusion, he experienced hearing loss and tinnitus for several days, and the dose was reduced. He was treated with intravenous infliximab 100 mg every 2 weeks for 10 months. There was considerable improvement in his tinnitus and low-frequency hearing. Furthermore, his condition stabilised, with fewer acute episodes. Due to his desire to start a family, he stopped the treatment after 46 weeks and his hearing deteriorated markedly. After recommencing infliximab, his hearing recovered again, as shown in Figure 1.

Discussion

A literature search was carried out using the Medline and Embase databases, searching from 1996 to 2011 and using the search terms 'autoimmune inner ear disease' and 'tumour necrosis factor'.

Steroids have become a widely accepted therapy for autoimmune inner ear disease, but they have significant side effects and their benefits are not sustained in all patients. Accordingly, long-term management options employed include the use of immune-modulating drugs or cochlear implantation if hearing becomes unserviceable. Immune-modulating drugs, however, have a myriad of potential adverse effects.

Over the last decade, tumour necrosis factor-α (TNFα) has been identified as a key mediator in the recruitment of inflammatory cells to the inner ear, using models of cochlear damage.[4,5] Although the inflammatory response is triggered in order to reduce the deleterious effects of antigenic challenge, it can in itself cause irreversible damage to the structure and function of normal cells, particularly to the delicate cochlear hair cells, which have no regenerative capacity. The degree of hearing loss is related to the amount of infiltrated inflammatory cells.[6] It is therefore logical that modulation of TNFα receptor levels or functionality may prevent amplification of the inflammatory pathway.

Two types of agent capable of modulating TNFα function have emerged: TNFα-receptor antagonists, such as etanercept, and anti-TNFα antibodies. Infliximab is a murine monoclonal antibody directed against TNFα. Significant reductions in cochlear inflammation and hearing loss have been demonstrated following etanercept administration in animal models of immune-mediated labyrinthitis.[5–8] Anti-TNFα therapy has been used successfully, in a clinical setting, for systemic autoimmune diseases such as rheumatoid arthritis and Crohn's disease. It would seem to be beneficial in patients with systemic autoimmune disease and associated hearing loss.[9–11]

The role of anti-TNFα therapy in organ-specific autoimmune disease remains undetermined. There are variable reports of its benefit in autoimmune inner ear disease, none of which address long-term management. Van Wijk *et al.* administered intratympanic infliximab to nine patients for four weeks; hearing improved in seven patients.[12] Rahman *et al.* reported a retrospective case series of 12 patients treated with etanercept; 7 patients improved, 4 stabilised and 1 improved but relapsed again after 5 months.[13] The only other published study did not demonstrate any benefit from anti-TNFα therapy.[14,15] Liu *et al.* report eight patients treated with infliximab.[16] No patient exhibited a positive response, by objective measurements. However, none of the eight patients responded to steroid therapy or other immunosuppressive drugs, in our practice an essential criterion for the diagnosis of autoimmune inner ear disease; thus, the authors may have been dealing with a different subset of patients to the patient presented here.

The published literature reports treatment of very diverse groups of patients, which may partly explain most studies' poor results, compared with the beneficial outcome reported here. Our patient was in the acute phase of autoimmune inner ear disease, which is likely to respond better than long-term,

https://doi.org/10.1017/S002221511300217X Published online by Cambridge University Press

'burned-out' disease. He responded well to steroids and had a raised IgM and a family history of autoimmune disorders, implicating an autoimmune basis for his condition. He was treated with infliximab every 2 weeks over a 10-month period initially. Although both etanercept and infliximab are able to reduce TNFα availability, only infliximab is able to bind to and induce apoptosis of activated lymphocytes.[17] Our patient seemed to benefit from oral steroids, intratympanic steroids, azathioprine and acyclovir at different times throughout his clinical course. Infliximab was the only agent that prevented further deterioration over a prolonged period, and, indeed, the patient's symptoms relapsed when it was stopped briefly after 10 months.

The long-term safety of anti-TNFα therapy has not been determined. Etanercept itself has not been found to have a cochleotoxic effect, and no side effects have been noted as a result of intratympanic infliximab administration.[6,12] As regards non-otological side effects, the short-term effects of systemic agents mainly relate to injection site reactions. Systemic anti-TNFα agents seem to be safe in the long term in the majority of patients with other autoimmune disease, but it must be borne in mind that bacterial infections, tuberculosis, opportunistic infections, demyelinating conditions and a possible relationship to lymphoma have all been reported. This poses a management dilemma which must be discussed frankly with patients. Despite the dramatic effect of infliximab on the disease course, the long-term effects of therapy are unknown. Some may argue that autoimmune inner ear disease should be left to run its course if there is any risk of life-threatening disease associated with infliximab treatment, with the option of cochlear implantation available for burned-out disease.

- **Infliximab has initial beneficial effects on autoimmune inner ear disease, which are maintained with prolonged administration**
- **Its long-term side effects are unknown**
- **Benefits and potential side effects of prolonged use must be balanced against the untreated outcome (progressive deafness)**

Many questions remain over the use of anti-TNFα therapy in autoimmune inner ear disease, in particular regarding: the subpopulation of patients with cochleovestibular symptoms in whom it is effective; long-term efficacy; side effect profile; and route of administration. Our case suggests that anti-TNFα agents may be useful in carefully selected patients. A large randomised, controlled trial is required to further assess the use of these agents.

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Address for correspondence:
Miss Rebecca L Heywood,
Department of Otorhinolaryngology,
Whipps Cross University Hospital,
Whipps Cross Road,
London E11 1NR, UK

E-mail: rebecca_heywood@yahoo.com

Miss R L Heywood takes responsibility for the integrity of the content of the paper
Competing interests: None declared

https://doi.org/10.1017/S002221511300217X Published online by Cambridge University Press