



REVIEW ARTICLE

## Review of the Biological Agents Used for Immune-Mediated Inner Ear Disease<sup>☆</sup>

David Lobo,<sup>a,\*</sup> José R. García-Berrocal,<sup>b</sup> Almudena Trinidad,<sup>b</sup> José M. Verdaguer,<sup>a</sup> Rafael Ramírez-Camacho<sup>b</sup>

<sup>a</sup> Servicio de Otorrinolaringología, Hospital El Escorial, Universidad Francisco de Vitoria, San Lorenzo de El Escorial, Madrid, Spain

<sup>b</sup> Servicio de Otorrinolaringología, Hospital Puerta de Hierro, Universidad Autónoma de Madrid, Madrid, Spain

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### KEYWORDS

Immune-mediated inner ear disease; Biological agents; Etanercept; Tumour necrosis factor  $\alpha$ ; Anakinra; Rituximab

### Abstract

*Introduction and objectives:* Immune-mediated inner ear disease (IMIED) is one of the few reversible forms of sensorineural hearing loss. Treatment is based on high-dose corticosteroids, although long-term therapy is associated with serious adverse effects; this has led to the use of other agents or different routes of administration such as transtympanic delivery. This study analyses the role of biological agents in IMIED management.

*Material and methods:* We searched PUBMED for studies that examined the response to treatment with different biological agents in patients with IMIED. The following data were extracted from the selected studies and entered into a standardised database: exclusion and inclusion criteria, characteristics of the patients studied, treatment, outcome measures and response rates achieved.

*Results:* Thirteen studies were included in this review. A TNF alpha inhibitor (etanercept, infliximab, adalimumab) was used in 8 studies, an IL-1 antagonist (anakinra) was used in 3 studies and rituximab, and an antibody directed against the CD20 surface antigen on B lymphocytes was evaluated in 2 studies. Most studies achieved a hearing improvement or stabilisation in more than 70% of treated patients.

*Conclusions:* Biological agents can play a role in the management of patients with IMIED, at least in those patients who do not respond to conventional therapy or whose hearing is not stabilised. However, specially designed randomised controlled clinical trials are needed to assess their effectiveness.

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\* Corresponding author.

E-mail address: [dlobo28@gmail.com](mailto:dlobo28@gmail.com) (D. Lobo).

**PALABRAS CLAVE**

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Factor de necrosis  
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Anakinra;  
Rituximab

**Revisión de las terapias biológicas en la enfermedad inmunomediada del oído interno****Resumen**

*Introducción y objetivos:* La enfermedad inmunomediada del oído interno (EIOI) es una de las escasas afecciones del oído interno que pueden revertirse con tratamiento médico. Este se basa en los corticoides, si bien el tratamiento prolongado con los mismos se asocia a serios efectos adversos, lo que ha propiciado el uso de otros fármacos o vías de administración como la intratimpánica. En este estudio se analiza el papel de las terapias biológicas en el tratamiento de la EIOI.

*Material y métodos:* Se ha realizado una búsqueda sistemática en PUBMED de aquellos estudios que examinan la respuesta al tratamiento con distintos agentes biológicos en pacientes con EIOI. Se ha analizado los criterios de inclusión y exclusión de cada estudio, así como las características de la población estudiada, el tratamiento utilizado y, los criterios de respuesta y tasa de respuesta alcanzada.

*Resultados:* Se identificaron 13 estudios relevantes. En 8 estudios se utilizó un inhibidor del TNF $\alpha$  (etanercept, infliximab, adalimumab), en 3 un antagonista de la IL-1 (anakinra) y en el resto se empleó el rituximab, un antagonista del receptor CD20 de los linfocitos B. En la mayoría de los estudios se logró una mejoría o estabilización de la audición en más del 70% de los pacientes tratados.

*Conclusiones:* Las terapias biológicas pueden tener un papel en el tratamiento de los pacientes con EIOI, al menos en aquellos que responden mal a los corticoides o no se consigue su estabilización. Sin embargo, son necesarios más estudios controlados y aleatorizados para conocer su eficacia.

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**Introduction**

Current knowledge of immune-mediated inner ear disease (IMIED)<sup>1</sup> assumes the possibility of interfering in its evolution by stopping its progression and even improving the function of the affected organ through the use of anti-inflammatory or immunomodulatory drugs, such as steroids, which are the gold standard for such treatment.<sup>2</sup> However, IMIED remains a diagnostic challenge, since there are no fully specific markers. Nonetheless, there are therapeutic risk profiles<sup>3,4</sup> because a significant percentage of patients do not respond adequately to treatment. These circumstances are closely related since the lack of a well-defined diagnosis may lead to the treatment of patients exhibiting no IMIED and, therefore, a lack of response to corticosteroids, as is the case with autoinflammatory diseases. Furthermore, the use of high doses of corticosteroids for long periods of time is associated with unacceptable adverse effects.<sup>5</sup> Other treatments have also been used. However, despite being promising initially, they have not demonstrated efficacy in rigorous studies, as in the case of methotrexate,<sup>6</sup> or have shown an inadequate adverse effect profile, as in the case of cyclophosphamide or leflunomide. All these factors have redirected research towards the search for new drugs or safer routes of administration, such as the intratympanic approach.<sup>7,8</sup>

The present study analyses the role of biological therapies in the treatment of IMIED. Biological agents are fusion proteins or monoclonal antibodies created to block specific components of the inflammatory cascade. Despite an increasing experience with the use of these drugs for other autoimmune diseases, such as rheumatoid arthritis, there is not much experience in the treatment of IMIED.<sup>9</sup>

Specifically, we have studied the role of some tumour necrosis factor (TNF) inhibitors, such as etanercept, infliximab or adalimumab, antagonists of the interleukin-1 (IL-1) receptor, such as anakinra, and other treatments such as rituximab. We highlight the use of TNF inhibitors, which act by blocking TNF, a proinflammatory cytokine especially produced by macrophages which is expressed in the inner ear during the early stages of the inflammatory response.<sup>10</sup>

We have reviewed the literature seeking publications which presented the results of the clinical use of these therapies in the treatment of IMIED.

Moreover, we have also studied the effectiveness of these treatments in addressing sensorineural hearing loss occurring in the context of autoinflammatory diseases, such as Muckle–Wells syndrome or CINCA (chronic, infantile, neurological, cutaneous, and articular) syndrome. They present clinical symptoms similar to those of some systemic autoimmune diseases; however, they do not respond to corticosteroids and probably have a genetic origin.<sup>11</sup>

**Material and Methods**

We conducted a systematic search of PUBMED for studies examining the response to treatment with different biological therapies in patients with IMIED. Secondly, we included those studies which analysed the response to biological therapies in patients with sensorineural hearing loss secondary to other autoimmune or autoinflammatory diseases.

Specifically, we used the following search strategy: (“Hearing loss, Sensorineural” [Mesh]) AND (“TNFR-Fc fusion protein” [supplementary concept]) OR (“Hearing loss, Sensorineural” [Mesh] AND “Interleukin 1 Receptor

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