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Review Article

Clinical trials for inner ear drugs: Design and execution challenges

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ABSTRACT

The development of therapies for the inner ear presents unique opportunities and challenges. On the one hand, the ear presents an opportunity for localized drug delivery to avoid systemic side effects. However, we do not understand the pathobiology of many common ear disorders clearly enough to develop rational therapeutic solutions. Further, identification of biomarkers beyond conventional audiometry and balance testing to track disease progress and recovery remain elusive. Because of the comparatively low incidence and prevalence of many inner ear disorders, as well as issues with respect to timing of drug delivery for certain diseases, multi-center, multi-investigator collaborative networks are required to promote effective clinical trial design.

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One cannot help but be curious about the fact that, in contrast to most organ systems that have numerous drug treatments, in the United States there are no FDA approved drugs with primary action to treat inner ear disease. Otologists frequently use corticosteroids as a treatment for presumed inflammatory or immune-mediated disorders, particularly for idiopathic sudden sensorineural hearing loss and Ménière's disease, though in most instances there are no convincing lines of research confirming such underlying pathophysiologic mechanisms. The other drugs for inner ear disease routinely prescribed by otologists include pain medication, antiemetics and vestibular suppressants, and antidepressant and minor tranquilizer drugs. These medications are intended to provide symptomatic relief, but none has a primary mechanism of action targeting pathology in the inner ear. In this respect at least, otolaryngologists lag behind most other medical and surgical specialties. The inner ear does not lend itself to *in vivo* investigation. It is tiny and buried 2–3 cm deep in the bone of the skull base. However, we have now begun to identify and characterize primary pathophysiologic mechanisms of some common (and less common) ear diseases. As a result, we are on the verge of a new era of inner ear-specific drug therapies. In this paper we will describe some of the steps and barriers to acquiring new and effective medical treatments for patients with ear disease.

1. Mechanisms of inner ear disease and treatment

To bring a candidate drug to clinical trials, we must have a target disease/mechanism of action, a candidate drug, and a method of delivery. Each of these elements involves independent, converging lines of investigation. In this regard, there are several clinical entities that comprise the “low hanging fruit” for inner ear drug treatment. These include ototoxicity from platinum-based chemotherapy agents, acute noise injury, acute tinnitus, acute vestibular syndrome (vestibular neuritis), sudden sensorineural hearing loss, Ménière's disease, genetic sensorineural hearing loss, and age-related sensorineural hearing loss (presbycusis). These common conditions have clear and widely accepted diagnostic criteria. Presbycusis affects approximately two-thirds of the

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population by age 70 years (Lin et al., 2011). Tinnitus, the perception of sound in the absence of an external stimulus, affects upward of 50 million adults in the United States (Shargorodsky et al., 2010). The prevalence of SNHL at birth is about 1.9/1000 and rises to 3.5/1000 by adolescence due to progressive loss. It is estimated that 50–60% of such cases have a genetic basis (Morton and Nance, 2006). Ménière's disease is estimated to have a prevalence of 190/100,000 population, about 650,000 US adults (Alexander and Harris, 2010). Cisplatin ototoxicity is estimated to occur in 50% of treated adults and >90% of treated children (Rybak et al., 2009). For emergency conditions, sudden sensorineural hearing loss has an incidence of around 20/100,000/year (Alexander and Harris, 2013) and acute vestibular syndrome is cited at 3.5/100,000/year (Strupp and Brandt, 2009).

In some of these conditions, we understand the primary mechanisms of disease. In others, the story is only partially revealed. Pathways of inflammation, excitotoxicity, and apoptosis are often thought to play a role (Ryan et al., 2016). Drugs that mediate these pathways therefore may hold promise for mitigating these conditions. Likewise, pathways of damage in acute acoustic trauma and ototoxicity have been studied in animal models (Jiang et al., 2017; Ryan et al., 2016; Sheth et al., 2017). However, in many instances clinical "phenotypes" such as presbycusis and Ménière's disease may arise from a variety of underlying pathologies or may progress beyond the initial insult to involve multiple structures and cell types. When that is the case, treatment of one aspect of the problem cannot resolve the clinical illness. For example, if a patient has hearing loss due to loss of hair cells, supporting cells and other structures of the organ of Corti, a method of hair cell regeneration by itself will not restore hearing. Imagine rebuilding a house after it is damaged by a fire: installing new light bulbs is necessary but not sufficient to light the rooms. One also needs the wiring, the sockets, the outlets, the switches, and the circuit breakers. Now consider new experimental light bulbs: how could one know whether or not they were working if the rest of the electrical system was also damaged? Thus, in many cases of SNHL, it is not only necessary to target a specific pathologic mechanism, but also to have precise staging of disease or timing of treatment when the drug mechanism of action (MOA) is going to offer measureable and clinically relevant benefit. Aside from patient symptoms, physical examination, audiometry and vestibular function testing, we have few biomarkers to characterize many of these conditions and their stage of progression. The lack of good biomarkers further hinders the creation of animal models that accurately replicate the features and progression of many inner ear disorders.

Inner ear drug delivery is another field under similarly intense investigation (Nguyen et al., 2017). Oral and intravenous routes of administration present issues of drug dilution and/or systemic toxicities that can limit these approaches. Intratympanic drug injections have been in wide use for over 30 years, primarily for administration of aminoglycoside to treat Ménière's disease and corticosteroids to treat Ménière's disease and idiopathic sudden SNHL. The primary benefit of intratympanic drug injection is the ability to deliver a small amount of drug to the target organ and thereby reduce the risk of systemic side effects. The disadvantages of intratympanic treatment include the fact that only one ear is treated at a time, the risks of local side effects such as pain, caloric vertigo, persistent eardrum perforation, the inconvenience if multiple doses are required, and perhaps most important, the poor control of the actual dose of drug passing through the round and/or oval window to distribute to precise targets in the inner ear. Efforts to address these shortcomings are all underway. Extended release preparations of various compounds are reaching the market that enable good control of starting dose and duration of exposure to the active compound. However, these formulations do not solve the problem of inner ear diffusion and distribution. Direct inner ear delivery by microinjection, microfluidic pump, or drug-eluting implant is a goal that is being actively pursued but has not yet been achieved for clinical application.

2. Issues related to clincial trial design

Since we have, or soon will have, MOA targets and candidate drugs to act on them, what other considerations must be addressed to move forward with clinical trials? The first is subject selection. As noted earlier, many of our common ear "diseases" are actually syndromes or are progressive conditions in which a particular drug might only be applicable at an early stage of damage. We desperately need biomarkers for damage and dysfunction of the various cell types of the inner ear. Unfortunately, progress in this arena promises to be slow. The ability to refine study populations by use of appropriate biomarkers serves to enrich the study group for likely treatment responders. Until such biomarkers are available, study cohorts will have substantial heterogeneity. Cohort heterogeneity reduces apparent treatment effect of a candidate drug across that cohort, making it harder to identify a treatment "signal" and differentiate it from the natural variation of an untreated or placebo-treated comparison cohort.

A second critical detail of clinical study design is choice of outcome measure. In the case of hearing loss, the obvious choice is an audiogram. But even this choice is fraught with complexity. Should one look at pure tone threshold average over several frequencies or maximal response at a single frequency? It may depend on whether one is looking for modest response in many subjects or a dramatic response in only a few. What about a treatment that may improve speech perception, a measure of hearing clarity, but not alter threshold? Or vice versa? What about temporal aspects of the drug response or the durability and stability over time? The same issues apply in the study of vestibular disease and tinnitus and are further complicated by far fewer physiologic measures and greater dependence on questionnaires and other subjective, "patient-centered" outcomes. These issues around primary, secondary, and exploratory outcome measures are certainly not absolute barriers to clinical trials of inner ear drugs. However, they make it mandatory to expend considerable effort in careful and thoughtful and strategic planning of any such trial.

3. Issues related to clinical trial execution

Once the scientific decisions of a clinical trial are made – the target illness, candidate drug and its formulation, inclusion/exclusion criteria for subjects, and outcome measures and analytic/statistical methods – there remain many important logistical challenges to execution. Clinical research is ultimately a collaborative effort by many people, all of whom must have expertise in their respective parts of the project. It is not sufficient to read a book about clinical research or attend a workshop – there is an element of on-the-job training that must occur. In otolaryngology, there have been precious few multicenter clinical trials. Thus, there are few investigators with clinical trials experience. How are we to increase the number of qualified investigators? First, it is incumbent upon experienced investigators to train others. They can bring in junior faculty as co-investigators at their own sites. They can engage inexperienced faculty at other sites to join a multicenter trial as collaborators and then mentor and train them as the trial is conducted, perhaps best characterized as a "build a plane as you fly it" approach. In the case of industry-sponsored research, a great deal of the study administration is delegated to Contract Research Organizations (CROs). CROs are responsible for training and

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