Perspective

Translating Drugs From Animals to Humans: Do We Need to Prove Efficacy?

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The goal of this journal is to publish multidisciplinary research that bridges the gap between basic research and clinical care. This “bridge” (or “translation”) requires making the decision to take potential therapies from preclinical studies to humans, so called “First-in-Human” studies. From a regulatory perspective, the sponsor of such studies is required to submit an application. In the United States, this application is called an Investigational New Drug Exemption (IND). Other countries have similar submissions (e.g., Clinical Trial Application in Canada). The First-in-Human studies are typically closely monitored and may be conducted in patients or healthy volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the safety issues associated with increasing doses, and, if possible, to gain early evidence on effectiveness (21CFR312.21). The total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80 (21CFR312.21). As an ophthalmic drug development consultant, I am frequently asked if regulatory agencies require that the sponsor prove efficacy of the drug in animals. The short answer is no.

The content and format of an IND is stated in 21CFR312.23. Preclinical information required in an

IND includes the investigator’s brochure (IB) and a section on pharmacology and toxicology (“Section 8” in the Food and Drug Administration [FDA] Form 1571 format [21CFR312.21], or Module 4 in the Common Technical Document [CTD] format). The IB must contain, among other items, a summary of the pharmacological and toxicological effects of the drug in animals, and of the pharmacokinetics and biological disposition of the drug in animals (21CFR312.21). The Pharmacology and Toxicology section must contain “...adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations” (21CFR312.21). There is a requirement that the overall plan for investigating the drug product include “the rationale for the drug or the research study” (21CFR312.21). However, a “rationale” is not the same as showing efficacy in animals.¹

Ideally, one would have an animal model of an ocular disease that is similar to the human condition in response to approved drugs as well as to drugs that were not effective in humans (i.e., no false negatives or false positives). Such an ideal model would also be similar to humans in the efficacy, potency, and duration of action of drugs. In such an ideal model, if a new agent was safer, more effective, or longer lasting than a benchmark molecule, one could assume such positive attributes would be seen in humans. Note that, in order for the ideal model to be validated, a compound that demonstrates clinical efficacy must already exist for evaluation in the ideal model. This implies that animal models are easier to validate for follow-on molecules in the same class of pharmacotherapy. For “first in class” molecules, by definition, there can be no “validated” animal model until clinical efficacy has been demonstrated.

Decades ago, one of my professors, the late Keith F. Killam, Jr, PhD, told me of the high predictability of blockade of induced emesis in dogs with subse-

quent clinical efficacy and potency of phenothiazines in treatment of psychosis. This model was used to select new molecules for development. At that time (1950's and 1960's), the rationale for this connection was unknown.² Subsequently, it turned out that both activities were related to blockade of D₂-dopamine receptors.³

So what does this mean for drug discovery in ophthalmology? Perhaps the animal models that approach this ideal are treatments for allergy and inflammation. Other good models include antibacterials (where in vitro efficacy predicts bacteriological eradication in humans, albeit not always clinical efficacy due to the self-resolving nature of bacterial conjunctivitis⁴), and topical β -adrenoceptor antagonists (where antagonism of isoproterenol-induced ocular hypotension in rabbits⁵ predicts ocular hypotensive efficacy in patients with elevated intraocular pressure [IOP]). As well, reduction of elevated IOP in subhuman primates with laser-induced ocular hypertension is also predictive of ocular hypotensive efficacy in humans, at least for most known drug classes.⁶ Some compounds showing prophylaxis of choroidal neovascularization in mice with ruptured Bruch's membranes show human efficacy, but others do not. There are species-dependent issues (e.g., molecules targeting primate genomes require transgenic mice), and the pharmacokinetics of an intravitreal injection in a murine eye are unlikely to predict the human experience.⁷⁻¹⁰

However, for other diseases and drug classes, the prediction is weaker. For example, memantine that showed functional and structural signs of neuroprotection in a subhuman primate model,^{11,12} was not more effective than a placebo in two controlled clinical trials. With respect to dry eye, cyclosporine shows efficacy in preclinical models.¹³ However, the efficacy of ocular cyclosporine was already known from clinical practice in dogs with keratoconjunctivitis,^{14,15} rather than from these preclinical models. Several molecules have shown efficacy in preclinical models of dry eye,¹⁶⁻¹⁸ although the clinical efficacy of these agents is variable, especially in both signs and symptoms, only in initial studies, or as yet only approved in limited markets.¹⁹ With respect to treatment of dry age-related macular degeneration, there are limited full papers on novel therapies in controlled clinical studies, and so little opportunity yet to validate animal models. While some retinal degenerative conditions share etiologies (and, one would hope, treatments), the myriad of diseases

challenges the efficiencies of disease-specific preclinical models.²⁰⁻²³

In 2010, DiMasi et al.²⁴ analyzed clinical approval success rates and clinical phase transition analyses for the investigational compounds that entered clinical testing between 1999 and 2004 with confidential data from the 50 largest pharmaceutical firms. They reported that the likelihood that a compound entering clinical testing (i.e., the filing of an IND) will eventually gain marketing approval was 16%. While the reasons for failure were not part of the report or perhaps even in the confidential data, in a related publication, Kaitin²⁵ posits that "... the growing time, cost, and risk related to drug development are stubborn obstacles to filling industry pipelines and boosting the output of new pharmaceutical and biological products."

For the most part, drug development is financially supported by the for-profit sector. Given the low success rate for molecules during clinical development, investors want to minimize risk in selecting molecules for expensive clinical development. So what does this mean for drug discovery in ophthalmology? It would be wonderful if we had preclinical models that, either pragmatically or mechanistically, had the same high predictability for eye disease as did the canine model for phenothiazines and psychoses. However, we do not, at least, not yet. One would think that today's scientific methods applied to drug discovery might improve the chance of success. However, Kaitin²⁵ states that such successes are lacking and that "...for many years, however, in the absence of appropriate validation tools that would allow researchers to identify molecules having the greatest likelihood of successful development, these discovery technologies merely added time and cost to the R&D process without providing any appreciable benefits."

So what do we do? Given the low chance of success of molecules in discovery (by definition, less than 16% of compounds in Phase I), and high cost of development, some would say that only drugs showing efficacy in animal models should be taken forward into development. If there are yet no validated models for some diseases, then so be it. That is, no molecule would be taken forward. Others would say that if there is some rationale for efficacy, pharmacokinetic evidence of a therapeutically relevant concentration in the target tissue and an adequate safety margin, then the molecule should be taken into development. These are complex decisions that involve issues of science and economics, and

indeed social policy as to "... who will develop tomorrow's medicines?"²⁵ Nonetheless, at present, regulatory agencies do not require novel drugs to show efficacy in animal models before they are evaluated in humans, only adequate safety and pharmaceuticals to support the intended clinical studies.

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