New Directions on the Drug Development Pathway

The development of therapies for orphan retinal diseases and genetic disorders differs from that of traditional treatments.

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The retina is a prime target for gene therapy research, given the large number of monogenic retinal disorders, the retina's accessibility to target cell delivery, the ability to noninvasively monitor for disease progression or therapeutic response, and the eye's relative immune-privileged status, which limits inflammatory response.[1] Unfortunately, however, the biotech industry has historically had little incentive to undertake the long-time commitment and incur the substantial costs associated with developing treatments for rare disorders such as inherited retinal diseases (IRDs) because the patient populations are small and there is limited commercial potential.

The US FDA's approval of the first gene therapy for a genetic disorder, in patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy may signal the beginning of a new cycle of innovation in retinal therapies. However, this approval also introduces new paradigms for clinicians, including functional vision endpoints, unfamiliar orphan disease treatment pathways, and precision medicine with novel genetic testing requirements. This article compares the traditional drug development pathway with that of new treatments, namely gene therapies, aimed at orphan diseases and genetic disorders.

TRADITIONAL DRUG DEVELOPMENT PATHWAY

The drug and biologics development process in the United States has traditionally been lengthy and expensive (Table 1).[2,3] One recent study analyzed the time and costs devoted to developing 10 cancer drugs, including nine that had received orphan drug designation. The authors noted a median development time of 7.3 years and a mean cost of development of approximately $720 million (in 2017 US dollars).[3] Another study of 106 randomly selected investigational products from 10 companies calculated the approximate mean length of time and cost for phase 1 studies at 33 months and $25 million, respectively; phase 2 studies at 38 months and $59 million, respectively; and phase 3 studies at 45 months and $255 million, respectively.[2] (See Table 2 for a refresher on the phases of clinical trials.) The mean pretax capitalized clinical cost per approval was $1.46 billion, including the total direct cost of development and the indirect cost of failures, using the estimated 12% overall likelihood of successful approval once a drug enters clinical testing.[2] When the opportunity cost of capital was factored in, the authors estimated a mean total preapproval cost of $2.6 billion (all costs in 2013 dollars).[2]

AT A GLANCE

- The rarity of some genetic diseases is an obstacle to the development of gene therapies for them.
- Gene therapies have the potential to address the underlying genetic cause of a disease and deliver long-term benefits to patients and the health care system by reducing the need for chronic therapy.
- To support ongoing innovation in retinal therapeutics, new reimbursement models are needed.

DEVELOPMENT PATHWAY OF TREATMENTS FOR ORPHAN DISEASES

Rare diseases have historically been neglected, or orphaned, in drug development because of the inherent challenges of lengthy and expensive clinical trial operations in small, often geographically dispersed patient populations. These small patient populations complicate clinical study, not only because they limit study recruitment, but also because there may be limited natural history data and suitable, validated study endpoints, as for IRDs that primarily affect rods and do not impact visual acuity until late stages.

Even with successful approval, commercialization potential is limited because of the small markets, as with IRDs. In recognition of these unique challenges and the unmet needs of patients with rare disorders, both the FDA and the European Medicines Agency (EMA) have incentivized development of therapies for these conditions. In the United States, the Orphan Drug Act of 1983 provided developers of treatments for orphan diseases with protocol assistance, tax credits to defray the cost of development, a waiver of FDA fees, and 7 years of market exclusivity.[4] (Orphan diseases are defined as diseases that affect fewer than 200,000 Americans or diseases that affect more than 200,000, but for which costs associated with developing and marketing a therapy are not expected to be recovered after commercialization.[5]) The EMA provided similar incentives in 2000, with orphan designation for products addressing life-threatening or debilitating disorders that affect five or fewer per 10,000 individuals.[6]

Another challenge in the development of treatments for orphan diseases is that these diseases often involve unique care pathways; the rarity of the disease often necessitates centralization of care with a multidisciplinary team of providers. In particular, centralized care helps to optimize safety and treatment because consistent patient and procedural volume drives a virtual cycle of expertise, positive outcomes, and continued referrals. In some cases, health authorities can mandate a centralized treatment center model as part of a risk management plan to maximize patient safety. Complex quaternary referral patterns result, with only a few treating specialists at multidisciplinary centers. The difficulties of navigating such a complex process or finding a treatment center may restrict access for some patients. In retina care, these referral patterns already exist to some extent for patients seeking treatment for choroidal melanoma or retinal detachment from retinopathy of prematurity. Centralization of care will likely exist, at least initially, for IRD gene therapy.

TABLE 1. DRUG AND BIOLOGIC DEVELOPMENT PROCESS IN THE UNITED STATES[8,9]

1. Preclinical laboratory testing, animal studies and formulation studies conducted in accordance with Good Laboratory Practices
2. Investigational New Drug submission to the US FDA prior to human clinical trials
3. Human clinical trials, conducted in accordance with Good Clinical Practice, to establish the efficacy and safety of investigational drugs and biologics
4. Approval by an institutional review board prior to initiation of each clinical trial
5. Submission to the FDA of a New Drug Application or Biologics License Application
6. Validation of manufacturing process
7. FDA inspection of manufacturing facilities to assess compliance with Good Manufacturing Practice to ensure that the facilities, methods, and controls are adequate to preserve the drug's identity, strength, quality, and purity
8. FDA review and approval

ROADBLOCKS

Gene therapy has the potential to address the underlying genetic cause of a disease and to deliver long-term benefits to patients and the health care system by reducing the need for chronic therapy. The Orphan Drug Act partially addressed some of the challenges inherent in developing treatments for rare diseases, but the business model for the development of gene therapy is even more complex and unique.

The current health care system may readily value chronically administered medications, but it may not properly value therapies that deliver long-lasting benefits in one dose or administration. Payers, including Medicare, have accepted the responsibility of paying for multiple doses over multiple years in common chronic disorders such as diabetes or macular degeneration. However, with the increasing feasibility and potential efficacy of gene therapies, the discord between this traditional system and a potentially one-time treatment for a rare disorder becomes apparent.

Current cost-effectiveness assessment is biased against one-time therapies due to the sequencing of current costs and future benefits: That is, costs are incurred in the short term, but benefits are distributed over the long term. In particular, the future benefits of one-time therapies are disproportionally

TABLE 2. CLINICAL TRIAL REFRESHER[9]

The four phases of clinical trials and what each encompasses.

PHASE 1

- After undergoing preclinical testing in animal models, investigational drugs move into phase 1 studies, which generally involve small groups of healthy volunteers to evaluate safety, dose ranges, absorption, metabolism, distribution, excretion, and adverse events.
- In situations in which investigational drugs designed to treat severe or life-threatening disease may be too toxic to ethically administer to healthy volunteers, phase 1 studies can be conducted in patients with the target disease.
- Phase 1 studies are exploratory, assessing initial safety.

PHASE 2

- Similar to phase 1 studies, phase 2 studies are exploratory, further assessing safety while gathering some initial efficacy evidence in the intended patient population.
- Phase 2 studies evaluate safety and preliminary efficacy in patients with the target disorder and may be controlled or uncontrolled.
- Dosing is often assessed in phase 2 studies. Dose response can provide critical insights into the biologic plausibility of a treatment effect and inform the design of larger later-phase trials.
- Positive results in phase 2 trials generally do not merit claims of efficacy, but instead can result in a call for confirmatory phase 3 randomized controlled trials (RCTs).
- Due to the limited patient population in rare diseases, and particularly for clinical trials of investigational gene therapy products, phases 1 and 2 are typically combined to assess safety, dosing, and initial efficacy in the target population.

PHASE 3

- Phase 3 studies are larger confirmatory RCTs to more thoroughly investigate the efficacy and safety of investigational drugs and biologics. Phase 3 studies establish the risk/benefit ratio and support approval by regulatory authorities (registration trials).
- These RCTs are often parallel group, randomized, double-masked, multicenter design and involve extensive statistical testing and modeling.
- Randomization and masking are employed to minimize bias in treatment allocation and to allow unbiased evaluations of patients in different treatment groups.
- Multiple trial sites are often employed, not only to enhance recruitment, but also to enhance generalizability of study results to a disease population, and also to minimize risk associated with single-center trials.

PHASE 4

- Phase 4 studies are larger postmarketing studies that often assess less common adverse events.

discounted when compared with their current costs.[7]

Couple this with the extreme rarity and orphan status of some genetic diseases, such as IRDs, which may be considered gene therapy targets, and the situation represents a large obstacle—perhaps even a disincentive—to the development of gene therapies.

New reimbursement models are therefore needed. There has already been some public discussion of health coverage approaches that would pay in installments or would tie payment to the real-world effectiveness of the treatment. With the potential for continued rapid therapeutic innovation, especially in gene therapy, the future looks quite promising for the field of retina. New health care financing and coverage systems will hopefully continue to evolve to support these ongoing innovations in retinal therapeutics. ■

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