REVIEW ARTICLE

FRONTIERS IN MEDICINE

Gene Therapy

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Gene therapy has provided treatment options for diseases that are beyond the reach of traditional approaches. Since 2016, between the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA), six gene therapy products have been approved: two chimeric antigen receptor T-cell products for B-cell cancers and four additional products for serious monogenic disorders, including β-thalassemia, a rare form of vision loss, spinal muscular atrophy, and a rare form of primary immunodeficiency. The first proofs of gene therapy are thus now market-approved pharmaceuticals. With more than 800 cell- and gene-therapy programs now in clinical development, including for previously untreatable diseases such as Duchenne's muscular dystrophy and Huntington's disease, it seems likely that more therapies will follow. Here, we review the field as it stands today, with a focus on monogenic diseases (see the interactive graphic, available at NEJM.org).

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This article was updated on August 1, 2019, at NEJM.org.

N Engl J Med 2019;381:455-64.
DOI: 10.1056/NEJMra1706910

An illustrated glossary and an interactive graphic on gene therapy are available at NEJM.org

BASIC PRINCIPLES

The goal of gene therapy for genetic diseases is to achieve durable expression of the therapeutic gene or "transgene" at a level sufficient to ameliorate or cure disease symptoms with minimal adverse events. There are two basic strategies: an integrating vector is introduced into a precursor or stem cell so that the gene is passed to every daughter cell (the vector is designed to integrate at one or more loci in the patient's chromosomes) or the gene is delivered in a nonintegrating vector to a long-lived postmitotic or slowly dividing cell, ensuring the expression of that gene for the life of the cell. In the latter case, integration of the therapeutic DNA into chromosomes of the patient's cells is not required; instead, the transferred DNA is stabilized extrachromosomally. Transduction of stem cells is generally an ex vivo process and requires an integrating vector, whereas delivery to long-lived postmitotic cells is usually achieved through in vivo gene delivery.

EX VIVO, IN VIVO

For ex vivo transduction, cells are extracted from the patient and transduced with the gene of interest, and then the cells are returned to the patient in procedures such as those used in hematopoietic stem-cell transplantation (although in this case, the transplant is made up of autologous genetically modified cells) (Fig. 1). This approach requires a gene-delivery vehicle (or vector), the DNA that makes up the gene itself, and a technically sophisticated facility for processing the cells. In contrast, in vivo gene delivery resembles the delivery of other types of pharmaceutical agents (Fig. 2). The vector–gene construct is stored frozen; it is then thawed and prepared by a pharmacist and is typically administered in an outpatient procedure.

Treating a genetic disease with gene therapy requires a great deal more than the identification of the etiologic gene. The transgene (or its protein product) must

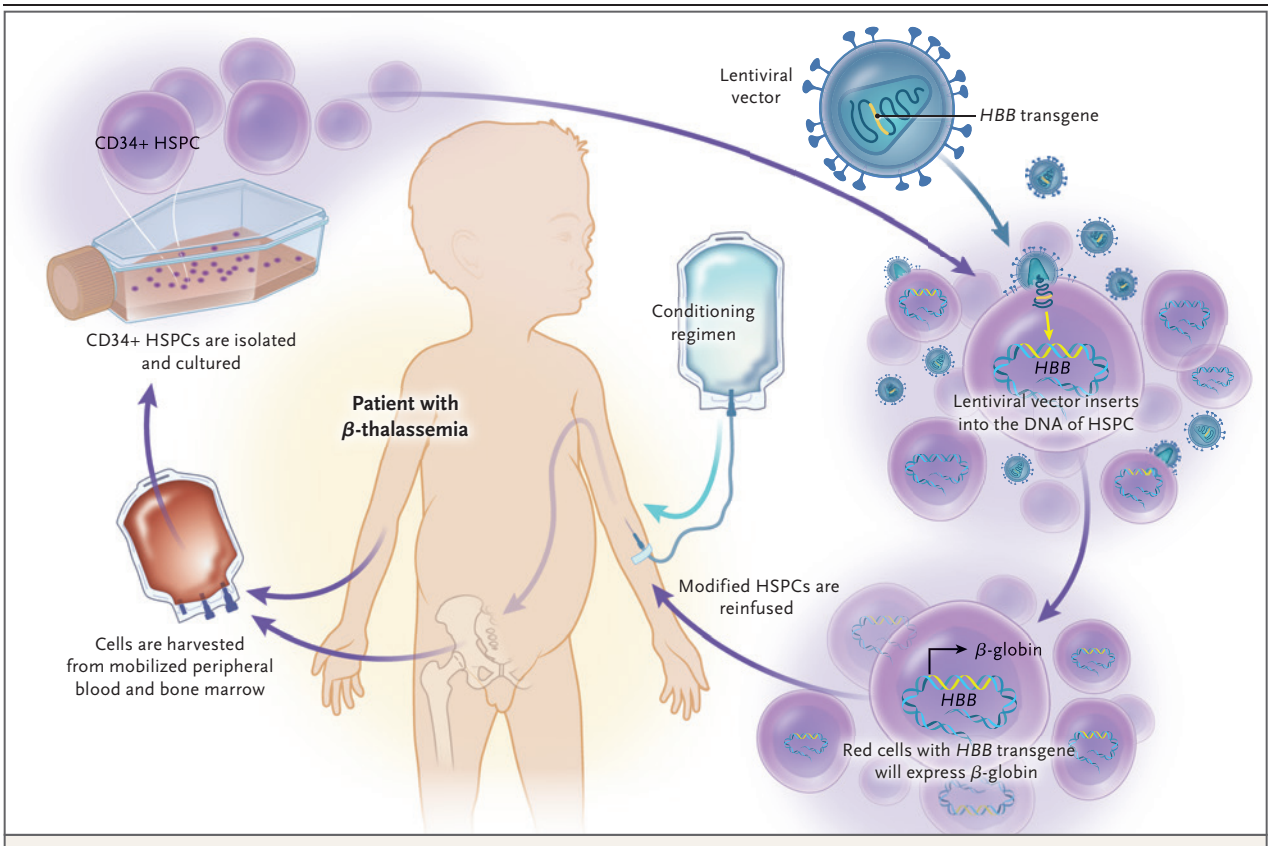

Figure 1. Ex Vivo Delivery of Gene Therapy.

An example of ex vivo delivery of gene therapy is the treatment of β-thalassemia, involving gene transfer to hematopoietic stem and progenitor cells (HSPCs). These cells are harvested from the bone marrow or from the mobilized peripheral blood of the patient, and CD34+ HSPCs are isolated with the use of affinity columns. The HSPCs are cultured ex vivo in the presence of growth factors, which allows the maintenance and expansion of self-renewing stem cells, and are then subjected to gene transfer with an integrating lentiviral vector encoding the β-globin complementary DNA under the control of an erythroid-specific promoter. The patient receives a conditioning regimen that depletes the endogenous HSPCs from the bone marrow and creates space in the bone marrow niches for the ex vivo–engineered cells to engraft. The gene-corrected HSPCs are then reinfused intravenously and engraft in the bone marrow, where they self-renew and differentiate into all hematopoietic lineages. However, thanks to the vector design, expression of the β-globin gene is restricted to the erythroid lineage.

be delivered to the physiologically relevant target tissue or tissues, must be stably expressed, and must not interfere with the functional integrity of those cells.

SAFETY

Before any clinical experience with gene therapy had been gained, investigators identified potential theoretical risks (Table 1). Clinical data have reshaped and reprioritized these risks, and it is now clear that the major risks of integrating vectors (e.g., retroviral vectors) arise from their potential for insertional mutagenesis, in which the vector inserts into the DNA of a cell and disrupts a functional element of that DNA, such as a gene.[1-4] For vectors administered in vivo, the major risks arise from immune responses to the vectors, as discussed below.[5-10,14,15] The risk of insertional mutagenesis has been reduced or circumvented by production of safer (lentiviral) vectors, and the risk of an immune response has been reduced through use of adjuvant immunomodulatory drugs.[16] These adjustments were driven by research guided by early failures or unexpected adverse events.[6,17,18]

Lentiviral and adeno-associated viral (AAV) vectors lack the capacity for ongoing replication. In theory, wild-type replication-competent virus could be reconstituted, or mobilized, if the vector and wild-type virus coinfect the same tissue or if replication-competent virus contaminates the vector preparation.[19] Assays for

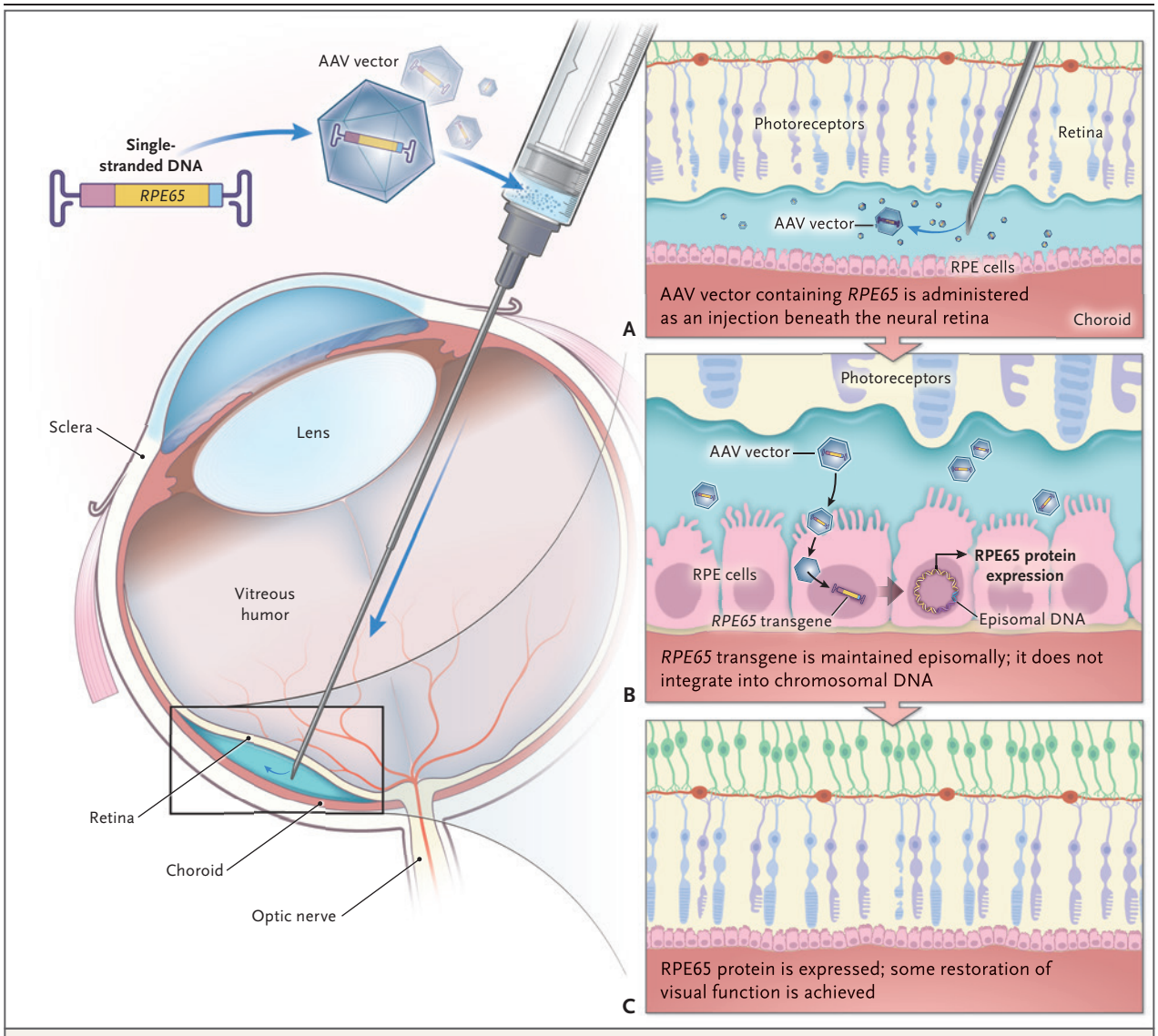

Figure 2. In Vivo Delivery of Gene Therapy.

An example of in vivo gene therapy is the treatment of vision loss caused by loss-of-function variants in *RPE65*, which encodes an enzyme that converts all-trans-retinyl ester to 11-cis-retinol, part of the visual cycle that takes place in the retinal pigment epithelium. The gene is delivered within an adeno-associated viral (AAV) vector by injection beneath the neural retina, through vitrectomy followed by direct injection in an operative procedure. A false space ("bleb") under the retina is created by injecting vector suspended in fluid, whereupon the vector transduces retinal pigment epithelial (RPE) cells. The transgene remains episomal; it does not integrate into the DNA of the cell.

replication-competent virus are therefore required for lot release.

EX VIVO GENE THERAPY

SEVERE COMBINED IMMUNODEFICIENCIES — LESSONS LEARNED

In 2016, ex vivo gene therapy with hematopoietic stem and progenitor cells (HSPCs) reached a milestone when the EMA approved an HSPC gene therapy, Strimvelis (Orchard Therapeutics), for the treatment of adenosine deaminase (ADA)–deficient severe combined immunodeficiency (SCID), a disease that is usually fatal in early childhood. The therapy consists of an infusion of autologous HSPCs that are genetically modified with the use of a γ-retroviral vector to insert a functional copy of the gene *ADA*.[20-22]

Table 1. Potential and Observed Complications of Gene Therapy.*

Complication	Clinical Presentation	Vector	Evidence
Gene silencing	Gradual loss of gene expression without evidence of immune response	—	Theoretical; not reliably described clinically
Genotoxicity: integration events and insertional mutagenesis	Development of leukemia or solid tumors	Retroviral	Documented in studies of gene therapy for X-linked SCID,[1,2] Wiskott–Aldrich syndrome,[3] and chronic granulomatous disease[4]
Phenotoxicity: overexpression or ectopic or dysregulated expression of the transgene	Dependent on transgene, tissue in which transgene is expressed, or both	—	Theoretical
Immunotoxicity	Dependent on tissue transduced — for example, elevated aminotransferase levels when liver is transduced or elevated creatine kinase levels when muscle is transduced	More likely with AAV (in vivo delivery)	Documented in experiments involving muscle[5] and trials of treatment for hemophilia,[6,7] spinal muscular atrophy,[8] Leber's hereditary optic neuropathy,[9] and retinal dystrophy caused by mutations in *RPE65*[10]
Horizontal transmission	Household contacts seropositive	AAV	Not documented; vector not infectious after 72 hr[11]
Vertical transmission	Offspring positive for vector transgene	More likely with AAV (in vivo delivery)	No documented cases; vector has been detected in semen transiently[7,12,13]

* AAV denotes adeno-associated virus, and SCID severe combined immunodeficiency.

More than 20 years ago, the first ex vivo gene-therapy studies of γ-retroviral vectors in children with ADA-deficient SCID were unsuccessful because of the low numbers of gene-corrected HSPCs.[23,24] The success of the trial in which sustained long-term ADA production and therapeutic benefit were achieved rested on pretransplantation cytoreductive conditioning with low-dose busulfan (allowing a higher level of engrafted gene-corrected stem cells) and the withholding of enzyme-replacement therapy, in order to favor expansion of the gene-corrected cells.[20,21] This trial also showed long-term safety.[22] Over the past decade, it has become clear that opening the bone marrow niches and creating spaces for the autologous genetically modified stem cells is necessary in order to achieve long-term therapeutic benefits. Unfortunately, the chemotherapy needed for bone marrow myeloablation has toxicity and increases the risk of secondary tumor development or bone marrow failure. Alternative strategies, such as antibody-based conditioning, are currently under investigation.[25,26]

Another early approach to treating a different form of SCID[27-29] involved the use of a γ-retroviral vector to force the expression of *IL2RG* (encoding the common gamma chain) in autologous HSPCs ex vivo, which, after transplantation back into the patients, resulted in the restoration of immune function, a clear demonstration of clinical efficacy in gene therapy. Unfortunately, T-cell leukemia developed in some of the trial participants, which led to treatment with high-dose chemotherapy and bone marrow transplantation,[1,2] thus prompting the search for safer vectors.[30-33]

Lentiviral vectors transduce hematopoietic cells in the quiescent G_0 or G_1 phase of the cell cycle at high efficiencies[34] and have a safer integration pattern in the human genome than do the γ-retroviral vectors.[35] However, clinical-scale production of lentiviral vectors remains a challenge. Despite this difficulty, lentivirus-based ex vivo trials are ongoing for the treatment of primary immunodeficiencies, metabolic diseases, and genetic blood disorders.[36-41]

Thanks to the higher transduction efficiency of lentiviral vectors, gene-corrected HSPCs have been used in the treatment of adrenoleukodystrophy and metachromatic leukodystrophy. In these autosomal recessive lysosomal-storage diseases, the gene-corrected cells migrate to the brain and "cross-correct" the cells containing

the mutated gene: the gene-corrected cells synthesize and secrete the critical protein, which is then taken up and used by the genetically uncorrected cells. However, to reach therapeutic levels of gene transfer in the repopulating stem cells, full myeloablation, high viral copy number, or supraphysiologic expression of the transgene is required.[38,39,42]

THALASSEMIA AND SICKLE CELL ANEMIA

Gene therapy for the treatment of thalassemia and sickle cell anemia has been an elusive goal for more than three decades because of the complex regulation of globin gene expression.[43] Initial gene-transfer trials involving patients with severe β-thalassemia showed feasibility but no durable clinical benefit, because sufficient engraftment of gene-corrected stem cells did not occur in most of the patients, with the exception of one who had a dominant, myeloid-biased cell clone that led to transfusion independence.[44,45]

More recently, phase 1 and 2 trials of stem-cell gene therapy, involving patients with β-thalassemia, showed safety and a reduced frequency of transfusion.[41,46] Clinical efficacy was correlated with gene-transfer efficacy, with the mean proviral copy number in transduced cells, and with the dose of genetically corrected hematopoietic stem cells and was inversely correlated with the hemoglobin transfusion requirement. One of these two trials,[41] as well as ongoing phase 3 studies of a vector encoding a variant $\beta^{A\text{-}T87Q}$-globin gene, showed transfusion independence for up to 56 months, which was considered durable; this led to conditional EMA approval of Zynteglo (Bluebird Bio) for patients 12 years of age or older with transfusion-dependent β-thalassemia who do not have a β^0/β^0 genotype.[47] Four gene-therapy trials targeting different genes and using different vectors for sickle cell anemia are ongoing (ClinicalTrials.gov numbers, NCT03282656, NCT02247843, NCT02186418, and NCT02151526).

IN VIVO GENE THERAPY

In vivo gene-transfer studies, in which the vector is injected directly into the patient, have been performed for monogenic diseases with a range of gene-delivery vehicles; AAV vectors are used in most current studies. Recombinant AAV vector is engineered from a nonpathogenic, nonenveloped parvovirus. Vectors are generated by placing the therapeutic gene, driven by an appropriate promoter, between two noncoding viral packaging signals (Fig. 2).[48] The efficiency of packaging the transgene into the vector drops off precipitously with sequences longer than 5 kb, one of the few limitations of the AAV vector-delivery system.[49] The majority of the AAV vector DNA is maintained in the cell as a stable episome (it is not integrated into the patient's genome). Thus, the risk of insertional mutagenesis for AAV vectors is low.

A red flag was raised when hepatocellular carcinoma developed in neonatal mice injected with high doses of AAV vector.[50] Subsequent studies have shown that the risk of insertional mutagenesis is dose-dependent and is increased in neonatal mice, in which rapid cell division in the liver is accompanied by relatively frequent chromosomal breaks, which are the preferred sites of AAV vector integration.[51,52] Hepatocellular carcinoma has not been observed in clinical studies, but experience with AAV vectors in infants is limited, and continued surveillance is warranted.

Early clinical studies identified the human immune response as a barrier to systemic administration of AAV-based therapies.[6] Many people have been exposed to wild-type AAV and thus have both circulating antibodies to AAV and capsid-specific memory T cells.[53,54] The development of methods to circumvent neutralization by preexisting antibodies and to control cellular immune responses has been key to successful wider clinical application.[55]

The first AAV vector commercial product and first gene therapy for genetic disease, alipogene tiparvovec (Glybera, uniQure), was approved by the EMA in 2012 for the treatment of recurrent or severe pancreatitis in persons with a rare genetic lipid disorder, lipoprotein lipase deficiency. Owing to weak commercial uptake of the drug, the sponsor allowed the approval to lapse in 2017. Nonetheless, its approval established that an AAV-based product could meet regulatory requirements, which heightened interest in the development of other AAV vector products (Table 2).

VISION LOSS

More recently, both the FDA and the EMA have approved another AAV vector product, voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics), for the treatment of a rare form of autosomal recessive blindness caused by mutations in *RPE65*, which encodes an enzyme critical to the

visual cycle. Without treatment, this disease eventually progresses to complete blindness in most affected persons, and many are visually impaired from birth.[56] The retina is an attractive target for vector-mediated gene transfer, because it is a relatively "immunoprivileged" space (i.e., a tissue that can tolerate introduction of antigen without development of an inflammatory immune response) and because low vector doses impose only a mild manufacturing burden. AAV vectors can be administered by means of injection beneath the neural retina in an outpatient surgical procedure (Fig. 2). Studies in a naturally occurring dog model of *RPE65* deficiency showed convincing proof of concept (treatment-restored vision),[57,58] and early-phase clinical testing by several groups showed evidence of improvement in vision.[59-61] These studies formed the basis of a randomized, controlled phase 3 trial of gene therapy: patients who received the drug had improvement in functional vision and increases in full-field light sensitivity and visual field.[62] Follow-up at 4 years suggested that the effect was durable.[63] However, other phase 1 and 2 trials documented only a transient effect, with loss of efficacy at time points as early as 1 year after vector injection.[10,16,64] The approval of voretigene neparvovec-rzyl has fueled efforts to address other forms of congenital blindness with the use of a similar approach, and trials are now under way for a variety of inherited retinal dystrophies.[65-68]

SYSTEMIC DELIVERY, HEMOPHILIA, AND THE IMMUNE RESPONSE

Systemic intravascular administration of AAV vector to target the liver or other organs has resulted in positive clinical outcomes in several serious inherited diseases. An early trial of intravascular administration of recombinant AAV vector involved men with severe hemophilia B. It defined the two major immunologic hurdles: preexisting antibodies to AAV, which are prevalent in 20 to 40% of the adult population, can neutralize the vector and thereby reduce efficacy; and a delayed cellular immune response to the AAV capsid, occurring 4 to 12 weeks after vector infusion, can result in destruction of the transduced cells and loss of therapeutic efficacy.[6] Both problems stem from the fact that humans are natural hosts for wild-type AAV and thus may carry antibodies or memory T cells that arise from infections of the respiratory tract during childhood.

The first problem has been addressed in the short term by excluding patients with preexisting antibodies from treatment: clearly, a better solution is needed. The clinical presentation of the delayed cellular immune response[6] was an asymptomatic self-limited increase in aminotransferase levels, accompanied by a gradual but complete loss of factor IX expression from the transgene. Testing of peripheral-blood mononuclear cells showed that they secreted interferon-γ in response to AAV capsid peptides, leading to the hypothesis that pharmacologic immunosuppression would permit a therapeutic effect because capsid-derived peptides should be present only transiently.[6] This hypothesis was proved in a second trial, in which participants who had an increase in aminotransferase levels or a decrease in factor IX levels received a tapering course of glucocorticoids.[69] Six participants who received an infusion of the highest dose tested had long-term expression of factor IX and a 90% reduction in both bleeding episodes and factor IX usage over a 3-year observation period.[70] The use of a high-specific-activity variant of factor IX[71] in a subsequent trial permitted a smaller dose (one quarter the high dose used in the earlier trial) to be used and led to a much higher mean factor IX activity level and a lower frequency of immune responses,[12] probably because the immune response is dose-dependent.

Owing to the size limitation on the length of complementary DNA (cDNA) that can be incorporated into AAV vectors, clinical trials of gene therapy for hemophilia A, which is caused by mutated *F8* (a very large gene), have taken longer to initiate. Clinical trials in progress make use of cDNA encoding a truncated form of factor VIII. One of these trials has recently yielded results: a report of the first nine patients indicated that six of the seven men who received the highest dose of vector had factor VIII activity levels ranging from 12% to more than 200% at 20 weeks (with 50 to 150% representing a normal level of activity),[7] but the levels declined over time (with follow-up over 3 years).[72] The declining factor VIII levels, along with the propensity of factor VIII to misfold, which can lead to cell stress, have raised questions about obtaining a durable response in persons with hemophilia A. Nonetheless, a robust effect on the

Table 2. Regulatory Milestones in Gene Therapy.*

Year and Milestone	Regulatory Authority	Indication	Vector†	Route of Administration
2003: approval of recombinant human p53 adenovirus for injection (Gendicine, Sibiono GeneTech)	NMPA	Head and neck squamous-cell carcinoma	Ad–p53	Intratumoral injection; intracavity or intravascular injection
2012: approval of alipogene tiparvovec (Glybera, uniQure)	EMA‡	Lipoprotein lipase deficiency	AAV1–LPL	Intramuscular injection
2015: approval of talimogene laherparepvec (Imlygic, Amgen)	EMA and FDA	Melanoma	HSV–GM-CSF	Intratumoral injection
2016: approval of autologous CD34+ cells encoding adenosine deaminase cDNA sequence (Strimvelis, Orchard Therapeutics)	EMA	Adenosine deaminase–deficient SCID	RV–ADA	Transplantation of autologous gene-modified CD34+ cells
2017				
Approval of tisagenlecleucel (Kymriah, Novartis)	FDA	Patients younger than 25 yr of age with relapsed or refractory ALL	LV–CD19	Intravenous infusion of autologous gene-modified T cells
Approval of axicabtagene ciloleucel (Yescarta, Kite Pharma)	FDA	Certain types of non-Hodgkin's lymphoma	RV–CD19	Intravenous infusion of autologous gene-modified T cells
Approval of voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics)	FDA	Biallelic *RPE65*-associated retinal dystrophy	AAV2–RPE65	Subretinal injection
2018				
Approval of tisagenlecleucel (Kymriah)	EMA	Patients younger than 25 yr of age with relapsed or refractory ALL	LV–CD19	Intravenous infusion of autologous gene-modified T cells
Approval of axicabtagene ciloleucel (Yescarta)	EMA	Certain types of non-Hodgkin's lymphoma	RV–CD19	Intravenous infusion of autologous gene-modified T cells
Review of gene-therapy IND applications in United States streamlined to single reviewing agency, the FDA	FDA and NIH	—	—	—
Approval of voretigene neparvovec (Luxturna)	EMA	Biallelic *RPE65*-associated retinal dystrophy	AAV2–RPE65	Subretinal injection
2019				
Conditional approval of autologous CD34+ cells encoding $\beta^{A\text{-}T87Q}$-globin gene (Zynteglo, Bluebird Bio)	EMA	Patients older than 12 yr of age with transfusion-dependent β-thalassemia without β^0/β^0 genotype	LV–β-globin	Transplantation of autologous gene-modified CD34+ cells
Approval of onasemnogene abeparvovec-xioi (Zolgensma, AveXis)	FDA	Patients younger than 2 yr of age with spinal muscular atrophy	AAV9–SMN1	Intravenous infusion

* ALL denotes acute lymphoblastic leukemia, cDNA complementary DNA, EMA European Medicines Agency, FDA U.S. Food and Drug Administration, IND investigational new drug, NIH National Institutes of Health, and NMPA National Medicine Products Administration (China).
† Vector designations indicate the type of vector (adeno-associated viral [AAV], adenoviral (Ad), herpes simplex viral [HSV], lentiviral [LV], or retroviral [RV]) and the gene transduced.
‡ Regulatory approval was allowed to lapse by the sponsor in 2017.

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annualized bleeding rate was found over 2 to 3 years.

The safety data in all these studies has been encouraging. Vector-related findings, including the presence of vector DNA in body fluids, have been transient, and adverse events such as asymptomatic transient increases in aminotransferase levels have generally responded to a tapering course of glucocorticoids. Phase 3 trials of AAV vector–mediated gene transfer for hemophilia are now under way (NCT03370913, NCT03861273, and NCT03569891).

SPINAL MUSCULAR ATROPHY

Another successful application of systemically administered AAV has been the treatment of spinal muscular atrophy, a disease caused by mutations in *SMN1*, which encodes the survival motor neuron protein. The disease is divided into four subtypes based on age at onset and severity. Spinal muscular atrophy type 1 is the most common genetic cause of death in infants. The median age at death or the need for mechanical ventilation for at least 16 hours per day for a period of at least 2 weeks is 10.5 months.[73] In 2016, the FDA approved the use of an antisense oligonucleotide (nusinersen [Spinraza, Biogen]) for the treatment of the disease. The drug requires repetitive intrathecal administration. In 2017, the results of a single intravenous administration of an AAV9 vector expressing *SMN1* in 15 infants between 1 and 8 months of age were reported, and in 2019 the treatment was approved by the FDA.[8,74] Although the transduction target is the spinal motor neuron, *SMN1* is ubiquitously expressed, and so the transduction of cells in other tissues may also be beneficial. All 15 infants in the initial trial were alive and free of ventilator support at 20 months of age, and of the 12 children in the higher-dose cohort, 11 sat unassisted, 9 rolled over, and 11 fed orally and could speak. Two grade 4 adverse effects were reported, both of which were elevations in aminotransferase levels (the most common adverse event caused by systemic administration of an AAV vector), which were alleviated by treatment with glucocorticoids. Expansion of the trials to more than 100 infants and children has generally confirmed these results. However, there have been two deaths, one related to progression of the underlying disease and the other with autopsy results still pending.[75]

FUTURE CONSIDERATIONS

Two developments in the regulatory landscape support the continuing maturation of gene therapy as a class of therapeutics. The first development is the recent announcement by National Institutes of Health (NIH) Director Francis Collins and former FDA Commissioner Scott Gottlieb that, after years of a dual review system involving both the NIH Recombinant DNA Advisory Committee and the FDA, gene-therapy investigational new drugs will be reviewed solely by the FDA, as is the case for other classes of therapeutics.[76] The other development is the issuance in 2018 of six new draft guidance documents by the FDA Office of Tissue and Advanced Therapies, which synthesize and codify approaches to multiple disease targets on the basis of the growing experience and consensus in the field regarding the best approaches in the preclinical, clinical, and manufacturing aspects of gene therapy.[77]

The cost of these treatments has been flagged as an issue that may hinder the development of gene therapies as commercially viable therapeutics. A challenge for all cell and gene therapies is that these "one time," high-value treatments are emerging into a reimbursement landscape that was developed around medicines that were administered in the long term. Most would agree that, given similar outcomes, single-administration treatments are preferable to drugs that must be repetitively administered. Therefore, the expectation is that the long-term benefits of these one-time therapies will justify the high costs. This is evident in hemophilia, for example, for which the current standard of care — clotting factor replacement — can cost as much as $400,000 per year or more per patient. When advances in gene therapy lead to new treatments for classes of diseases that have formerly lacked any therapeutic agents, there will not be direct cost offsets to the health care system. The issue of paying for these innovative treatments will therefore need to be addressed. Outcomes-based rebate arrangements, whereby the manufacturer provides a rebate if prespecified therapeutic outcomes are not achieved, are already in place for some gene-therapy products. Annuity payments that are made as long as the therapeutic effect persists have also been proposed.

For ex vivo gene therapy, future goals include

better lentiviral vector design to further improve safety and transgene control, efficient large-scale production and analytical characterization of vectors, and the development of less toxic conditioning regimens that permit robust engraftment of gene-corrected stem cells, including replacement of chemotherapy conditioning with antibody-based methods to reduce complications.[25,26] For in vivo gene therapy with AAV vectors, efforts in the next decade will focus on the elucidation and management of the human immune response to the vector and continued improvements in AAV vector design and development to improve targeting and permit lower doses that achieve in vivo efficacy.[78]

In conclusion, advances in gene therapy have uncovered exciting new therapeutic opportunities for many heretofore incurable diseases. However, a strong and continued collaborative effort will be required to surmount the challenges presented by this new class of medicines and to realize their full therapeutic potential.

An audio interview with Dr. High is available at NEJM.org

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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