chemotherapy. Such a trial may provide definitive answers and potentially establish a new standard of care.

Currently, the large majority of ongoing trials of neoadjuvant therapy for early-stage colon cancer, according to data available at ClinicalTrials.gov, have pathological complete response as the primary end point with new combination immunotherapies. Although these therapies may be interesting scientifically, it is difficult to imagine that they will meaningfully improve outcomes in combination with surgery in this patient population. Overall survival remains the most important end point.

The pathological responses observed with neoadjuvant immune checkpoint blockade become increasingly meaningful and have the potential for greater clinical effect when patients can be monitored with nonoperative management instead of undergoing surgery. Among patients with colon cancer, however, surgical resection is associated with substantially less morbidity than that with rectal cancer, and therefore, organ preservation may not be as important for all patients.

Given the notable responses of early-stage dMMR tumors to immunotherapy, we must shift the focus to carefully designed clinical trials that leverage this sensitivity in order to achieve improved outcomes for patients. At the present time, we have two options for trials: to pursue organ preservation or to better determine which patients benefit from neoadjuvant immune checkpoint blockade and surgery.

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Success in Sight for Gene Editing

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The development of efficient new gene-editing techniques has improved the prospect of curative genetic medicines. In 2012, Jinek and colleagues described an adaptive immune system in single-cell organisms, in which clustered regularly interspaced short palindromic repeat (CRISPR) sequences target foreign DNA for cleavage by CRISPR-associated (Cas) proteins, highlighting the potential of this system for gene editing.[1] CRISPR-Cas (also referred to as Cas9–guide RNA [gRNA]) technology has since been widely adopted as a versatile laboratory tool. In 2023, the European Medicines Agency and the Food and Drug Administration approved the CRISPR-based therapy exagamglogene autotemcel (Casgevy), which is administered to harvested blood stem cells ex vivo before reinfusion, for the treatment of sickle cell disease and transfusion-dependent β-thalassemia.[2,3]

In this issue of the *Journal*, Pierce et al.[4] describe the use of Cas9-gRNA gene editing to delete a harmful variant in a gene expressed in the retina. They report a positive outcome that provides proof of principle for the therapeutic potential of this approach in retinal disease and represents a milestone in the use of CRISPR-Cas9 technology for in vivo therapy.

Genetic diseases of the retina cause sight impairment, affecting millions of children and adults worldwide. Until relatively recently, management has been wholly limited to supportive measures. During recent decades, however, rapid advances in molecular biology and microsurgery have revealed key disease mechanisms and enabled the development of novel targeted interventions. The most compelling successes to date have involved gene-supplementation approaches, in which a genetic deficiency is compensated by the sustained local expression of the deficient protein. This outcome is achieved with the use of a DNA vector as a means to usher complementary DNA (encoding the therapeutic "replacement" gene) into surviving cells. In 2017, the first gene-supplementation therapy was approved by the Food and Drug Administration. The treatment — voretigene neparvovec-rzyl — is a recombinant adeno-associated virus (AAV) vector for genetic deficiency of RPE65, a retinal enzyme that is essential for recycling of visual pigment to photoreceptor cells.[5]

The most common form of genetic retinal disease in children is attributable to pathogenic variants in the gene encoding centrosomal protein 290 (CEP290), which is essential for the structural integrity and functioning of the sensory cilium of the photoreceptor cell.[6] The most common pathogenic variant in *CEP290* results in aberrant splicing of pre–messenger RNA (mRNA) and the inclusion of an aberrant sequence in the mature mRNA, which thereby disrupts the expression of the CEP290 protein. A gene-supplementation approach is not feasible for CEP290-associated retinal disease because the size of the *CEP290* gene exceeds the capacity of current vector systems. The masking of the pathogenic inclusion by means of repeated intraocular injections of an antisense oligonucleotide can improve photoreceptor function and visual acuity.[7] The development of Cas9-gRNA gene editing, however, offers the possibility of sustained benefit after a single intervention to delete the pathogenic gene variant itself.

In 2019, Maeder et al. reported the development of EDIT-101, an AAV5 vector encoding Cas9 and two gRNAs designed to delete the harmful *CEP290* gene variant in human photoreceptor cells.[8] In experimental models, the administration of EDIT-101 enabled the expression of normal CEP290. Now, Pierce at al. describe the effect of EDIT-101 in adults and children with *CEP290*-associated inherited retinal degeneration.[4] The potential for harm due to unintentional off-target effects of gene editing is an important concern, particularly because AAV5-mediated expression of Cas9-gRNA is sustained, but early indications of safety of EDIT-101 are favorable. Using full-field stimulus testing, the authors found strong evidence of sustained improvements in cone photoreceptor function. This finding is consistent with productive gene editing, which enabled improved expression of CEP290 and represents a landmark in the use of Cas9-gRNA technology for in vivo therapy.

The authors note that the improved cone photoreceptor function on full-field stimulus testing was not consistently associated with improvements in more conventional measures of vision, such as visual acuity. This discrepancy is unexplained and demands elucidation if a meaningful benefit is to be achieved consistently. The results of the study showed that the greatest benefit of EDIT-101 was in younger participants with severe sight impairment before the intervention and that treatment early in the course of the disease is likely to be most effective. Recruitment to the study was suspended prematurely, when only two of the proposed eight children were enrolled. Had more children been included, a more consistent effect on visual acuity may have been observed. The questions of long-term safety, scalability, and accessibility must also be addressed if all who stand to benefit can expect to do so.

This major achievement provides hope for people affected by CEP290-associated sight impairment and other genetic eye diseases. As proof of concept for in vivo gene editing in a stable neuronal tissue, the findings of this study represent an important advance toward realizing the potential for curative genetic medicines.

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