The NEW ENGLAND JOURNAL of MEDICINE

Notable Articles of 2022

A collection of articles from the *New England Journal of Medicine* selected by NEJM editors

NEJM GROUP

The NEW ENGLAND JOURNAL of MEDICINE

December 2022

Dear Reader,

It's always interesting to look back at the trials we published in the preceding year and select the most notable. When I started as editor-in-chief in September, 2019, I had no idea that four months later we would begin to discuss a novel coronavirus in editorial meetings and that this would consume our pages and our thoughts for over two years.

At the end of 2022, it is good to acknowledge that for now, Covid-19 has evolved into a steadier state. This year's Notable Articles collection reflects this shift. Covid makes one appearance on the list: an Original Article published in February that reported the results of a randomized, controlled trial of oral nirmatrelvir plus ritonavir (Paxlovid) for high-risk adults with Covid-19. The availability of Paxlovid for newly diagnosed, high-risk patients was a welcome addition to our treatment options.

Many of the articles on this year's list received widespread news coverage. We published articles on intermittent fasting (according to this trial, it's not more beneficial than daily calorie restriction), an effective weekly drug to treat obesity, and an oral JAK inhibitor that showed promise in a phase 2 trial involving adults with severe alopecia.

What stands out in my memory of this year's news coverage was the reaction to a trial of a checkpoint PD-1 blockade in patients with locally advanced rectal cancer. Twelve patients received dostarlimab for 6 months, followed by 6 months of MRI monitoring. All twelve had a clinical complete response, with no evidence of tumor. Longer follow-up is needed, but the news of these initial results provided, as our editorialist said, "an early glimpse of a revolutionary treatment shift." News stories published in June reported on the joy of the patients in the trial; we shared their appreciation of their remarkable outcome.

Other Original Articles in this year's collection report on a new gene therapy for sickle cell disease, a shorter treatment course for children with TB (which changed WHO guidelines two months after it was published), and the treatment of mild hypertension in pregnancy, which reduced adverse pregnancy outcomes without impairing fetal growth. As is the nature of science, most of the Original Articles in this year's list involved improvements in the way things are done.

We hope that you enjoy reviewing the past year with us. We look forward to a new year, where we hope to be your trusted companion as you deliver the best care to your patients.

Sincerely,
Eric J. Rubin, M.D., Ph.D.
Editor-in-Chief, New England Journal of Medicine

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BONUS CONTENT

Explore these bonus notable articles from *NEJM Evidence* and *NEJM Catalyst Innovations in Care Delivery.*

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Betibeglogene Autotemcel Gene Therapy for Non–β^0/β^0 Genotype β-Thalassemia

Franco Locatelli, M.D., Ph.D., Alexis A. Thompson, M.D., M.P.H., Janet L. Kwiatkowski, M.D., John B. Porter, M.D., Adrian J. Thrasher, M.D., Ph.D., Suradej Hongeng, M.D., Martin G. Sauer, M.D., Isabelle Thuret, M.D., Ashutosh Lal, M.D., Mattia Algeri, M.D., Jennifer Schneiderman, M.D., Timothy S. Olson, M.D., Ph.D., Ben Carpenter, M.D., Persis J. Amrolia, M.D., Ph.D., Usanarat Anurathapan, M.D., Axel Schambach, M.D., Ph.D., Christian Chabannon, M.D., Ph.D., Manfred Schmidt, Ph.D., Ivan Labik, M.Sc., Heidi Elliot, Ruiting Guo, M.S., Mohammed Asmal, M.D., Ph.D., Richard A. Colvin, M.D., Ph.D., and Mark C. Walters, M.D.

ABSTRACT

BACKGROUND

Betibeglogene autotemcel (beti-cel) gene therapy for transfusion-dependent β-thalassemia contains autologous CD34+ hematopoietic stem cells and progenitor cells transduced with the BB305 lentiviral vector encoding the β-globin ($\beta^{A\text{-}T87Q}$) gene.

METHODS

In this open-label, phase 3 study, we evaluated the efficacy and safety of beti-cel in adult and pediatric patients with transfusion-dependent β-thalassemia and a non–β^0/β^0 genotype. Patients underwent myeloablation with busulfan (with doses adjusted on the basis of pharmacokinetic analysis) and received beti-cel intravenously. The primary end point was transfusion independence (i.e., a weighted average hemoglobin level of ≥9 g per deciliter without red-cell transfusions for ≥12 months).

RESULTS

A total of 23 patients were enrolled and received treatment, with a median follow-up of 29.5 months (range, 13.0 to 48.2). Transfusion independence occurred in 20 of 22 patients who could be evaluated (91%), including 6 of 7 patients (86%) who were younger than 12 years of age. The average hemoglobin level during transfusion independence was 11.7 g per deciliter (range, 9.5 to 12.8). Twelve months after beti-cel infusion, the median level of gene therapy–derived adult hemoglobin (HbA) with a T87Q amino acid substitution (HbA^{T87Q}) was 8.7 g per deciliter (range, 5.2 to 10.6) in patients who had transfusion independence. The safety profile of beti-cel was consistent with that of busulfan-based myeloablation. Four patients had at least one adverse event that was considered by the investigators to be related or possibly related to beti-cel; all events were nonserious except for thrombocytopenia (in 1 patient). No cases of cancer were observed.

CONCLUSIONS

Treatment with beti-cel resulted in a sustained HbA^{T87Q} level and a total hemoglobin level that was high enough to enable transfusion independence in most patients with a non–β^0/β^0 genotype, including those younger than 12 years of age. (Funded by Bluebird Bio; HGB-207 ClinicalTrials.gov number, NCT02906202.)

The authors' affiliations are listed in the Appendix. Dr. Locatelli can be contacted at franco.locatelli@opbg.net or at the Departments of Pediatric Hematology and Oncology and of Cell and Gene Therapy, IRCCS Ospedale Pediatrico Bambino Gesù, Sapienza, University of Rome, Piazza Sant'Onofrio, 4, 00165 Rome, Italy.

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EDITORIAL

Efficacy and Safety of Gene Therapy for β-Thalassemia

Emmanuel Payen, Ph.D.

β-Thalassemia results from insufficient production of the hemoglobin subunit β-globin (β^+) or from the absence of β-globin (β^0). Low levels of adult hemoglobin (HbA, or $\alpha_2\beta_2$) are exacerbated by excess free α-globin chains in erythroid cells, leading to dyserythropoiesis and shortening red-cell survival. Patients with transfusion-dependent β-thalassemia, the most severe clinical form of this disorder, receive repeated red-cell transfusions in order to prevent severe anemia and increase survival. However, iron overload caused by transfusions often leads to dysfunction in the heart, endocrine glands, and liver.

Allogeneic hematopoietic stem-cell transplantation, which is routinely used in children with β-thalassemia, can increase overall survival to greater than 90% and β-thalassemia–free survival to greater than 83%. Health-related quality of life can be better with allogeneic hematopoietic stem-cell transplantation than with conventional treatment, at a reasonable cost, but the lack of suitable donors and risks of stem-cell rejection and graft-versus-host disease restrict its use.

Hematopoietic stem-cell gene therapy, in which a functional β-globin gene is inserted into the patient's own hematopoietic stem cells, is advantageous because it does not require finding compatible donor cells and does not lead to an immune reaction. However, hematopoietic stem and progenitor cells must be sorted, genetically engineered, and reinfused into the patient after myeloablative conditioning. Therapeutic efficacy depends on the proportion of genetically modified hematopoietic stem cells and on the level of transgene expression in the transduced cell progeny. Patient safety depends on the number and quality of hematopoietic stem and progenitor cells in the hematopoietic cell pool after culture and on the genotoxicity of the genetic engineering tool.

Betibeglogene autotemcel (beti-cel) gene therapy for transfusion-dependent β-thalassemia involves the infusion of autologous CD34+ cells transduced with BB305, a self-inactivating lentiviral vector[1] derived from the HPV569 vector.[2] Both the BB305 and the HPV569 vectors express a β-globin chain with a T87Q amino acid substitution (β^{T87Q}). In an early clinical study, red-cell transfusions were discontinued in a patient with transfusion-dependent β-thalassemia who had received HPV569-transduced cells,[3] but the total hemoglobin level remained low (8 to 9 g per deciliter) because of low transduction efficiency. The use of BB305 increased the vector titer and the rate of hematopoietic-cell transduction.[1]

In two phase 1–2 clinical studies (HGB-204 and HGB-205)[4] evaluating the safety and efficacy of gene therapy with BB305 in patients with transfusion-dependent β-thalassemia, 11 of 13 patients (85%) with β^+ transfusion-dependent β-thalassemia gained transfusion independence (i.e., a weighted mean hemoglobin level of ≥9 g per deciliter without red-cell transfusions for ≥12 months). The vector copy number, a measure of the number of integrated transgenes in cells, ranged from 0.1 to approximately 4 copies per diploid genome in peripheral-blood leukocytes, and the weighted average hemoglobin levels after infusion ranged from 9.1 to 13.2 g per deciliter. Nevertheless, 7 of 11 patients with β^+ transfusion-dependent β-thalassemia who gained transfusion independence had mean hemoglobin levels below 11.0 g per deciliter, and most patients

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with β^0 transfusion-dependent β-thalassemia did not gain transfusion independence.[5,6] A cutoff hemoglobin level of 11.0 g per deciliter substantially corrected dyserythropoiesis, and the vector copy number in the drug product was associated with the level of therapeutic HbA (HbA^{T87Q}, or $\alpha_2\beta^{T87Q}{}_2$) in vivo.[4]

After the completion of the HGB-204 and HGB-205 studies, the sponsor decided to add transduction enhancers to the hematopoietic stem and progenitor cells in the manufacturing process.[7] In HGB-207, a multicenter, global, phase 3 study described by Locatelli and colleagues[8] in this issue of the *Journal*, the benefits of this manufacturing modification are evident in 23 patients with transfusion-dependent β-thalassemia and a non–β^0/β^0 genotype. In this study, the vector copy number in beti-cel ranged from 1.9 to 5.6 copies per diploid genome (as compared with 0.3 to 2.1 copies per diploid genome in the HGB-204 and HGB-205 studies[4]). It is remarkable that the vector copy number in peripheral-blood mononuclear cells exceeded 1 copy per diploid genome 6 months after transplantation in 15 of 23 patients (65%), as compared with 3 of 22 patients (14%) in the previous studies.[4] Transfusion independence occurred in 20 of 22 evaluable patients (91%), including 6 of 7 patients who were younger than 12 years of age, and 15 patients who gained transfusion independence had hemoglobin levels above 11.0 g per deciliter at the last study visit. The vector copy numbers and total hemoglobin levels remained stable for up to 4 years after beti-cel infusion.

In this study, erythropoiesis and liver iron concentrations improved, but levels of erythropoietic activity remained high and iron overload persisted in some patients. Long-term analyses of these findings are warranted. Modification of the manufacturing process for beti-cel did not alter the engraftment characteristics of the hematopoietic stem and progenitor cells. Transfusion independence did not occur in two patients who had a low vector copy number in peripheral-blood mononuclear cells, probably for several reasons that remain unclear. Transduction enhancers decreased transduction variability and increased hemoglobin levels. If a long-term reduction in iron overload is confirmed, then beti-cel gene therapy may be considered to be at least as effective as allogeneic hematopoietic stem-cell transplantation, with the added benefit of no risks of graft rejection and graft-versus-host disease.

One of the risks of transgene integration is the activation of endogenous oncogenic genes, and this risk would be expected to increase with the number of vector insertion events. The vector copy number per cell was high, reaching a mean of 5.5 in leukocytes, with no evidence of a tumor risk. However, one of the most frequently targeted genes of the lentivirus construct is *HMGA2*. In an early study, insertion of HPV569 into this gene resulted in the emergence of a dominant clone in a patient with transfusion-dependent β-thalassemia who received gene therapy.[3] The patients in the HGB-207 study were not found to have clonal dominance, probably because of highly diverse, polyclonal reconstitution. Additional follow-up is warranted to assess long-term safety. Combinatorial approaches[9] with several therapeutic genes expressed from the same vector may yield beneficial effects at a lower vector copy number and reduce the risks associated with insertional mutagenesis.

These encouraging results should have led to the rapid development of lentiviral gene therapy for transfusion-dependent β-thalassemia. However, such hopes have been dashed in Europe by continuing disagreements between Bluebird Bio (the sponsor of the HGB-207 study) and payment agencies more than 2 years after beti-cell received conditional marketing authorization from the European Commission. This situation shows that if patients are to have affordable access to treatment, a fair balance among the costs of drug development and manufacturing, the return on investment for shareholders, and the pricing of cell therapy and gene therapy products is necessary.[10] Other clinical trials of the reactivation of fetal hemoglobin by lentiviral vectors or genome editing are under way.[11] Pricing will clearly play a key role in this new competitive market.

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

From the Division of Innovative Therapies, Infectious Diseases Models for Innovative Therapies Research Center and Unité Mixte de Recherche–1184, French Alternative Energies and Atomic Energy Commission Fontenay-aux-Roses, INSERM, Université Paris-Saclay, Fontenay-aux-Roses, France.

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The NEW ENGLAND JOURNAL of MEDICINE

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Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease

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ABSTRACT

BACKGROUND

Sickle cell disease is characterized by the painful recurrence of vaso-occlusive events. Gene therapy with the use of LentiGlobin for sickle cell disease (bb1111; lovotibeglogene autotemcel) consists of autologous transplantation of hematopoietic stem and progenitor cells transduced with the BB305 lentiviral vector encoding a modified β-globin gene, which produces an antisickling hemoglobin, HbA^{T87Q}.

METHODS

In this ongoing phase 1–2 study, we optimized the treatment process in the initial 7 patients in Group A and 2 patients in Group B with sickle cell disease. Group C was established for the pivotal evaluation of LentiGlobin for sickle cell disease, and we adopted a more stringent inclusion criterion that required a minimum of four severe vaso-occlusive events in the 24 months before enrollment. In this unprespecified interim analysis, we evaluated the safety and efficacy of LentiGlobin in 35 patients enrolled in Group C. Included in this analysis was the number of severe vaso-occlusive events after LentiGlobin infusion among patients with at least four vaso-occlusive events in the 24 months before enrollment and with at least 6 months of follow-up.

RESULTS

As of February 2021, cell collection had been initiated in 43 patients in Group C; 35 received a LentiGlobin infusion, with a median follow-up of 17.3 months (range, 3.7 to 37.6). Engraftment occurred in all 35 patients. The median total hemoglobin level increased from 8.5 g per deciliter at baseline to 11 g or more per deciliter from 6 months through 36 months after infusion. HbA^{T87Q} contributed at least 40% of total hemoglobin and was distributed across a mean (±SD) of 85±8% of red cells. Hemolysis markers were reduced. Among the 25 patients who could be evaluated, all had resolution of severe vaso-occlusive events, as compared with a median of 3.5 events per year (range, 2.0 to 13.5) in the 24 months before enrollment. Three patients had a nonserious adverse event related or possibly related to LentiGlobin that resolved within 1 week after onset. No cases of hematologic cancer were observed during up to 37.6 months of follow-up.

CONCLUSIONS

One-time treatment with LentiGlobin resulted in sustained production of HbA^{T87Q} in most red cells, leading to reduced hemolysis and complete resolution of severe vaso-occlusive events. (Funded by Bluebird Bio; HGB-206 ClinicalTrials.gov number, NCT02140554.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Tisdale can be contacted at johntis@mail.nih.gov or at the Cellular and Molecular Therapeutics Branch NHLBI–NIDDK, National Institutes of Health, Bethesda, MD 20814.

Drs. Kanter and Walters contributed equally to this article.

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RESEARCH SUMMARY

Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease

Kanter J et al. DOI: 10.1056/NEJMoa2117175

CLINICAL PROBLEM

Patients with sickle cell disease often have vaso-occlusive events, progressive vasculopathy, and chronic hemolytic anemia, which are associated with an increased risk of complications and early death. HLA-matched sibling allogeneic hematopoietic stem-cell (HSC) transplantation is one treatment option, but its potential use is limited. Gene therapy with lovotibeglogene autotemcel (LentiGlobin) — consisting of autologous transplantation of hematopoietic stem and progenitor cells transduced with a lentiviral vector encoding a modified β-globin gene, resulting in the production of the antisickling hemoglobin HbA^{T87Q} — presents another therapeutic option.

CLINICAL TRIAL

Design: An unprespecified interim analysis of a phase 1–2 trial evaluated the efficacy and safety of LentiGlobin in patients with sickle cell disease.

Intervention: 35 patients received a single infusion of LentiGlobin and were followed for up to 37.6 months. Efficacy outcomes included levels of total hemoglobin, HbA^{T87Q}, and hemolysis markers and the incidence of vaso-occlusive events.

RESULTS

Efficacy: During a median follow-up of 17.3 months, median total hemoglobin increased and HbA^{T87Q} expression was observed in most red cells. Markers of hemolysis were reduced overall. Among 25 patients who met criteria for evaluation of vaso-occlusive events, 3 had events after infusion; there were no severe events, a reduction from the rate during the 2 years before infusion.

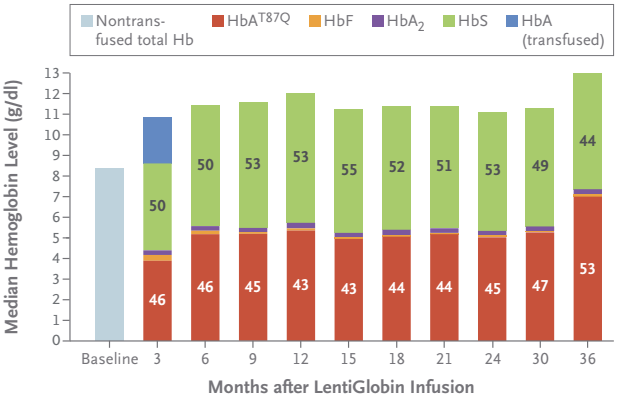
Safety: One third of patients had serious adverse events after infusion; the most frequent were abdominal pain, drug withdrawal syndrome, nausea, and vomiting. In 3 patients, adverse events were judged to be related to LentiGlobin infusion.

LIMITATIONS AND REMAINING QUESTIONS

Limitations of the study include the following:

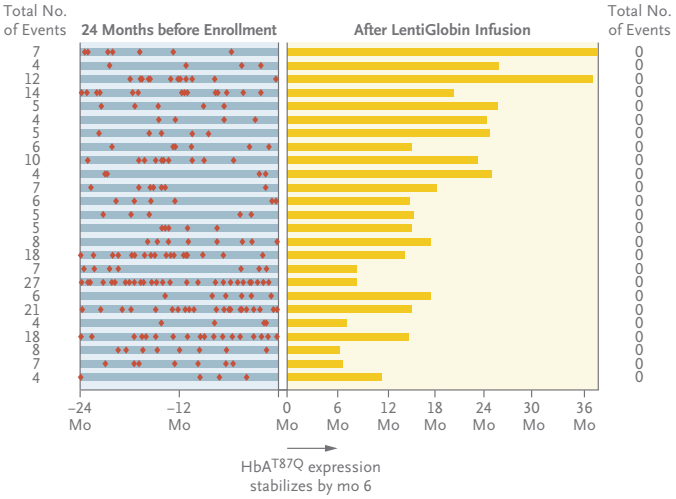
- The small number of patients
- Limited duration of follow-up
- The lack of a control group

Hemoglobin Fractions



No. of Patients	22	35	30	23	25	19	14	12	12	6	2
Total Hemoglobin, Median (g/dl)	8.5	11.4	11.6	11.9	12.1	11.7	11.7	11.0	11.4	11.5	13.0

Severe Vaso-Occlusive Events



Median Annualized Rate for Severe Vaso-Occlusive Events (range)	
3.5 (2.0–13.5)	0.0 (0.0–0.0)

CONCLUSIONS

One-time gene therapy with LentiGlobin resulted in sustained production of the antisickling hemoglobin HbA^{T87Q} in patients with sickle cell disease.

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EDITORIAL

Fetal-like Hemoglobin in Sickle Cell Anemia

Martin H. Steinberg, M.D.

Sickle hemoglobin polymerizes when it is deoxygenated, thereby damaging the sickle erythrocyte and initiating vascular occlusion and hemolysis. Preventing the polymerization of sickle hemoglobin should avert the secondary pathophysiological consequences of polymerization-induced vaso-occlusion and hemolytic anemia; it is a preferred approach to disease-modifying treatment[1] (Fig. 1A). In this issue of the *Journal*, Kanter and colleagues[2] report that the production of high levels of a polymerization-blocking hemoglobin by engineered autologous hematopoietic stem and progenitor cells can reverse the common complications of sickle cell disease.

Nearly 75 years ago, researchers discovered that high levels of fetal hemoglobin appeared to prevent the complications of sickle cell disease in babies. This finding raised a series of related questions. How does fetal hemoglobin prevent deoxy-sickle hemoglobin polymerization? Which differences in amino acids between fetal and adult hemoglobin are critical to such antisickling effects? Could the postnatal switch from fetal to adult hemoglobin be reversed?

Fetal hemoglobin has powerful antipolymerization properties because its γ-globin subunits form mixed hybrid tetramers of two α-globin chains with one γ-globin and one sickle β-globin chain that are largely excluded from the polymer.[1] It was calculated that if the hemoglobin of each sickle erythrocyte consisted of approximately 30% fetal hemoglobin, the complications of sickle cell disease could be prevented or reversed. Different iterations of cell-based gene therapies have approached or achieved this goal.[3-5]

Gene therapy for hemoglobin disorders begins with the collection of hematopoietic stem and progenitor cells that are removed from the patient's bone marrow with drugs (Fig. 1B). These cells are then modified so that they either produce more fetal hemoglobin or express a fetal-like hemoglobin encoded by a normal β-globin gene containing a glutamine (Q) residue in place of threonine (T) at position 87 (HbA^{T87Q}). This glutamine residue is one of the amino acids of fetal hemoglobin with antipolymerization properties and thus makes HbA^{T87Q} fetal-like. After chemotherapeutic ablation of the bone marrow, the engineered cells are reinfused into the patient, which is followed by engraftment, replication, production of hemoglobin, and (it is hoped) lifelong persistence.

Using a lentiviral vector called LentiGlobin, Kanter et al. infused such engineered cells into 35 patients with severe sickle cell disease (which they defined as a minimum of four vaso-occlusive events in the 24 months before enrollment) and evaluated the outcomes for safety and efficacy. Among the 25 patients who could be evaluated at 6 months, severe sickle vaso-occlusive events had stopped, hemoglobin levels had increased to more than 11 g per deciliter, and HbA^{T87Q} was being detected in 40% of total hemoglobin. Approximately 15% of red cells did not contain HbA^{T87Q}. However, reticulocyte counts remained above normal, indicating continued hemolysis.

Vaso-occlusive events, such as acute painful episodes and acute chest syndrome, are the most prominent features of sickle cell disease and are the most troubling for both the patients and their physicians. Intravascular hemolysis causes longer-term, initially subclinical complications, such as pulmonary vascular disease and nephropathy, which are associated with an increased risk of death and complications.[6] The observed continued hemolytic anemia in the study patients was probably caused by the fraction of cells that

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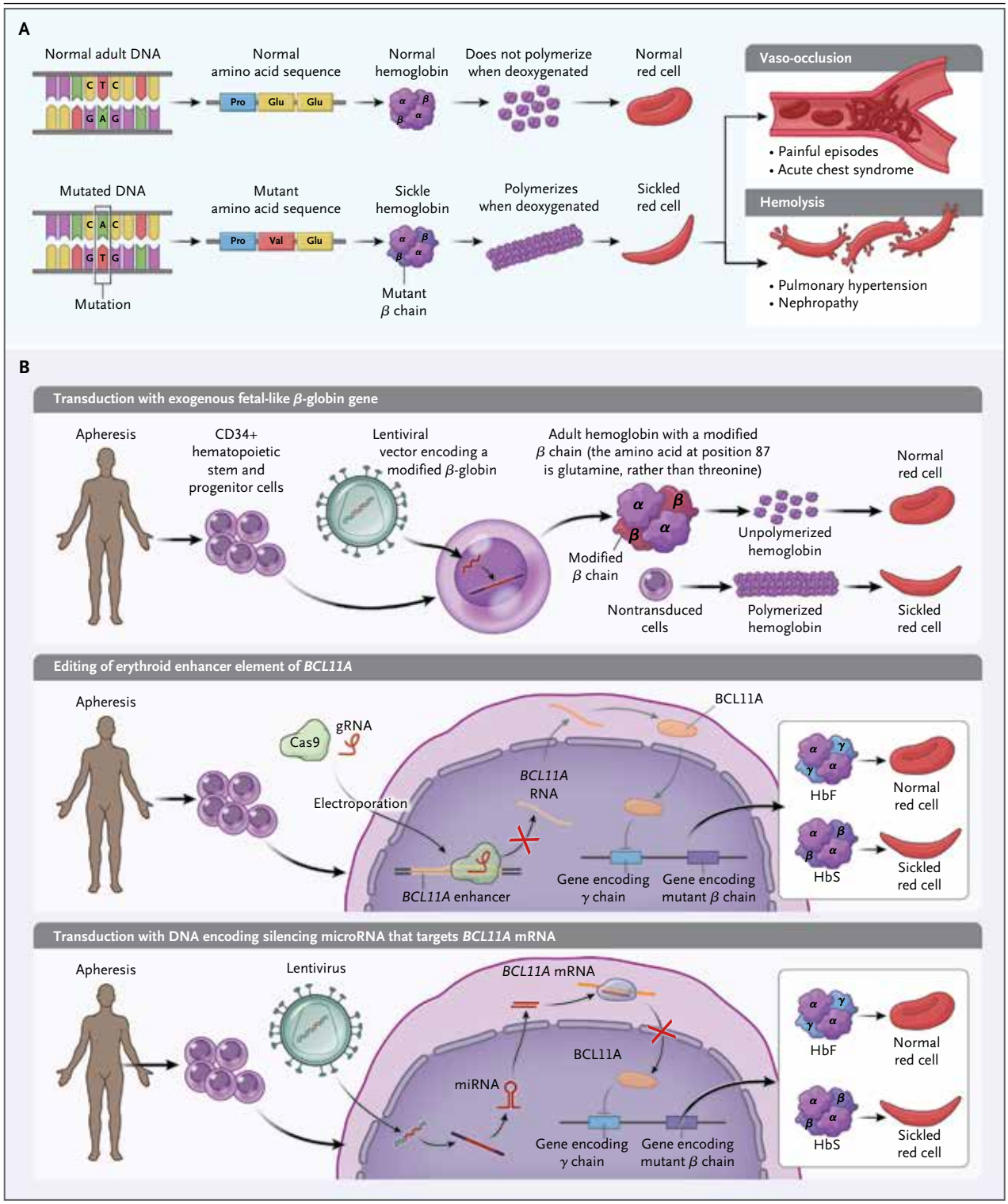

contained no or low levels of HbA^{T87Q} and that were unprotected from destruction. This finding raises the question of whether vascular injury will continue to occur in patients receiving modified hematopoietic stem and progenitor cells, because the clinical importance of persistent low-grade hemolysis remains to be determined. Moreover, whether the antipolymerization effect of hybrid

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Figure 1 (facing page). Paths to the Prevention of Erythrocyte Sickling.

Panel A shows the transformation of normal DNA into mutated DNA by the substitution of glutamic acid with valine in the sixth amino acid position of the β-globin chain, a process that results in the production of sickle hemoglobin (HbS), which polymerizes when it is deoxygenated. This transformation damages the sickle erythrocyte and causes the vaso-occlusion and hemolytic anemia that produce the phenotype of sickle cell disease. Vaso-occlusive complications include acute painful episodes and acute chest syndrome. Hemolysis-related complications include pulmonary hypertension and nephropathy resulting from intravascular lysis and heme release.

Panel B shows three novel approaches to the treatment of sickle cell disease. The approach described by Kanter et al. involves the semirandom introduction into the genome of an exogenous fetal-like β-globin gene with the use of a lentivirus vector. Two other approaches involve the suppression of the expression of *BCL11A* by targeted genetic modification. The BCL11A protein is a repressor of fetal hemoglobin (HbF) production. Common to the three approaches is the use of autologous CD34+ hematopoietic stem and progenitor cells (HSPCs), which are collected by apheresis after mobilization into peripheral circulation from the bone marrow. The cells are then genetically engineered by one of three methods: the addition of a fetal-like β-globin gene through transduction with a lentiviral vector (top diagram), genome editing of the *BCL11A* erythroid enhancer by means of electroporation of an engineered form of the Cas9 enzyme and guide RNA (gRNA) (middle diagram), or knockdown of *BCL11A* messenger RNA (mRNA) through an inhibitory microRNA (miRNA) encoded by the lentiviral vector (bottom diagram). The modified HSPCs are then returned to the patient. It is also possible to correct the sickle hemoglobin mutation, but clinical studies of this approach are just beginning.

tetramers containing HbA^{T87Q} is equivalent to that of fetal hemoglobin is unknown. It is possible that the effect of fetal-like HbA^{T87Q} on hemolysis-related vasculopathic complications will be diminished as compared with its effect on vaso-occlusive complications; longer-term data are needed to determine whether this is so. Perhaps intravascular lysis of only a small number of unprotected cells (by increasing plasma heme concentrations and thus reducing nitric oxide bioavailability) is sufficient to promote sickle vasculopathy.[7,8]

The safety profile for gene therapy mirrors that of hematopoietic stem-cell transplantation. Acute myeloid leukemia developed in 2 patients after LentiGlobin gene therapy in studies preceding the trial by Kanter et al., probably for reasons unrelated to lentivirus integration. Other factors — including a higher risk of myeloid cancers in patients with sickle cell disease, myeloablative conditioning, the presence of known driver mutations for leukemia, and stress erythropoiesis — may have caused these leukemias.

In the longer term, will induction of high levels of antisickling hemoglobin prevent all disease complications and justify the rigors and expense of this procedure? Allogeneic hematopoietic stem-cell transplantation from HLA-identical sibling donors is potentially curative. More than 90% of patients who are treated by this procedure have event-free survival, but less than 20% of patients have a donor.[9] Gene therapy with autologous stem cells extends the possibility of a cure to all patients without the need for immunosuppression. Unfortunately, any highly efficacious gene-based treatment is unlikely to improve the health of most people with sickle cell disease, because the greatest burden of disease is in countries where access to highly technological health care is limited.[10] Drugs that achieve even modest levels of fetal hemoglobin expression in most sickle erythrocytes have a higher likelihood of benefiting populations suffering the most from this disease.[11]

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

From Boston University School of Medicine, Boston.

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The NEW ENGLAND JOURNAL of MEDICINE

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Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlleron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. Welch, S.M. Graham, A.C. Hesseling, D.M. Gibb, and A.M. Crook, for the SHINE Trial Team*

ABSTRACT

BACKGROUND

Two thirds of children with tuberculosis have nonsevere disease, which may be treatable with a shorter regimen than the current 6-month regimen.

METHODS

We conducted an open-label, treatment-shortening, noninferiority trial involving children with nonsevere, symptomatic, presumably drug-susceptible, smear-negative tuberculosis in Uganda, Zambia, South Africa, and India. Children younger than 16 years of age were randomly assigned to 4 months (16 weeks) or 6 months (24 weeks) of standard first-line antituberculosis treatment with pediatric fixed-dose combinations as recommended by the World Health Organization. The primary efficacy outcome was unfavorable status (composite of treatment failure [extension, change, or restart of treatment or tuberculosis recurrence], loss to follow-up during treatment, or death) by 72 weeks, with the exclusion of participants who did not complete 4 months of treatment (modified intention-to-treat population). A noninferiority margin of 6 percentage points was used. The primary safety outcome was an adverse event of grade 3 or higher during treatment and up to 30 days after treatment.

RESULTS

From July 2016 through July 2018, a total of 1204 children underwent randomization (602 in each group). The median age of the participants was 3.5 years (range, 2 months to 15 years), 52% were male, 11% had human immunodeficiency virus infection, and 14% had bacteriologically confirmed tuberculosis. Retention by 72 weeks was 95%, and adherence to the assigned treatment was 94%. A total of 16 participants (3%) in the 4-month group had a primary-outcome event, as compared with 18 (3%) in the 6-month group (adjusted difference, −0.4 percentage points; 95% confidence interval, −2.2 to 1.5). The noninferiority of 4 months of treatment was consistent across the intention-to-treat, per-protocol, and key secondary analyses, including when the analysis was restricted to the 958 participants (80%) independently adjudicated to have tuberculosis at baseline. A total of 95 participants (8%) had an adverse event of grade 3 or higher, including 15 adverse drug reactions (11 hepatic events, all but 2 of which occurred within the first 8 weeks, when the treatments were the same in the two groups).

CONCLUSIONS

Four months of antituberculosis treatment was noninferior to 6 months of treatment in children with drug-susceptible, nonsevere, smear-negative tuberculosis. (Funded by the U.K. Medical Research Council and others; SHINE ISRCTN number, ISRCTN63579542.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Turkova can be contacted at a.turkova@ucl.ac.uk or at the Medical Research Council Clinical Trials Unit, University College London, 90 High Holborn, London WC1V 6LJ, United Kingdom.

*The members of the SHINE Trial Team are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Gibb and Crook contributed equally to this article.

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RESEARCH SUMMARY

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

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CLINICAL PROBLEM

Most children with tuberculosis (TB) have nonsevere disease, which probably could be treated with shorter regimens than the currently recommended 6 months. However, data from randomized trials of this approach in children are limited.

CLINICAL TRIAL

Design: An open-label, parallel-group, randomized, controlled trial examined whether 4 months of treatment would be noninferior to 6 months of treatment in children with nonsevere, symptomatic, presumably drug-susceptible, smear-negative TB in sub-Saharan Africa and India.

Intervention: 1204 children younger than 16 years of age were randomly assigned to 4 or 6 months of standard first-line anti-TB treatment with World Health Organization–recommended pediatric doses. The primary efficacy outcome was unfavorable status — defined as treatment failure or change, loss to follow-up during treatment, TB recurrence, or death — by 72 weeks.

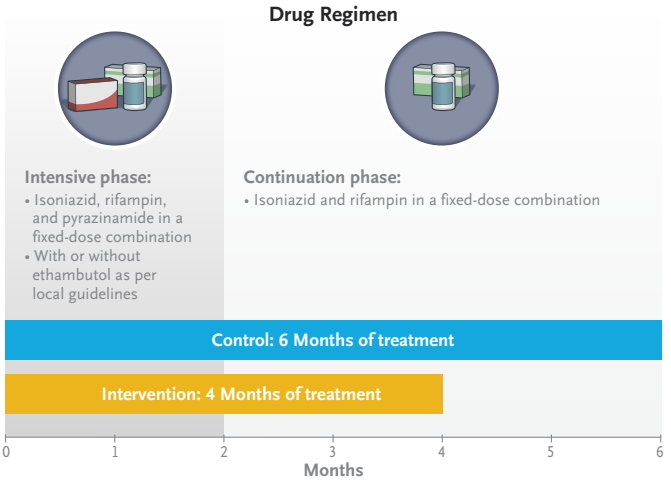
RESULTS

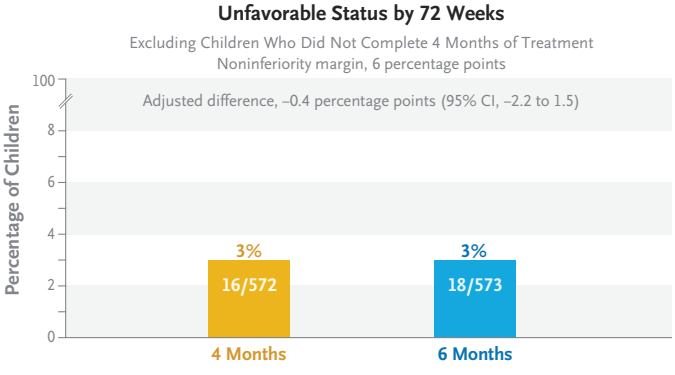
Efficacy: The percentage of children with an unfavorable status by week 72 did not differ significantly between the groups, showing noninferiority of the shorter regimen.

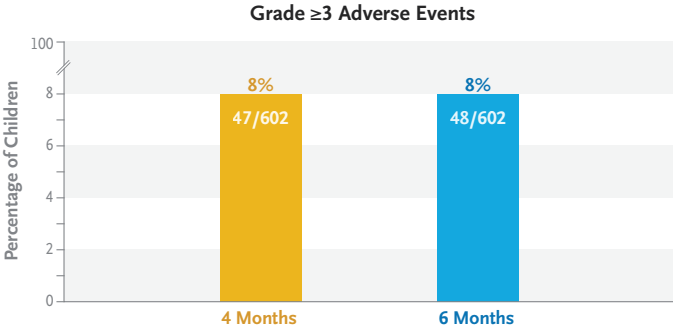
Safety: The percentage of children with an adverse event of grade 3 or higher during treatment or in the 30 days after treatment did not differ significantly between the groups. Pneumonia or other chest infections were the most common such events.

LIMITATIONS AND REMAINING QUESTIONS

- The open-label design of the trial may have led to more treatment extensions with the 4-month regimen.
- It is unknown whether the results would apply to sites without radiographic capabilities to confirm nonsevere TB.







CONCLUSIONS

Among children with nonsevere, drug-susceptible, smear-negative TB, a 4-month treatment regimen was noninferior to a 6-month regimen at 72 weeks of follow-up.

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EDITORIAL

Childhood Tuberculosis — Time for Shorter and Differentiated Treatment

Madhukar Pai, M.D., Ph.D., and Heather J. Zar, M.B., B.Ch., Ph.D.

Well before the Covid-19 pandemic disrupted tuberculosis care,[1] long treatment duration has been a weak link in the continuum of care. But the past decade has been a turning point in the pioneering of shorter treatment and differentiated care, as opposed to the traditional, one-size-fits-all approach. Shortening of treatment is being achieved by exploiting longer-acting drugs, adding new drugs, or, for persons with nonsevere disease, targeting shorter regimens.[2]

For latent *Mycobacterium tuberculosis* infection, several shorter alternatives to the traditional 6 to 9 months of isoniazid therapy now exist, including a 3-month regimen of weekly rifapentine plus isoniazid or a 4-month regimen of daily rifampin.[3] For drug-resistant tuberculosis, 6 months of oral-only regimens such as bedaquiline, pretomanid, and linezolid[4] or these drugs plus moxifloxacin[5] could replace the 24-month standard regimen. For drug-sensitive tuberculosis in adults, a 4-month rifapentine-based regimen containing moxifloxacin was noninferior to the standard 6-month regimen in a recent trial.[6]

Where does this leave children, a vulnerable group that is often excluded from randomized trials of new treatments? According to the World Health Organization, 1.1 million children worldwide became ill with tuberculosis in 2020, predominantly in low- and middle-income countries.[7] Increasingly, childhood tuberculosis is also identified in the context of acute lower respiratory tract infection or pneumonia.[8] However, difficulties in confirming a diagnosis of tuberculosis (particularly a lack of microbiologic confirmation), a long duration of treatment, lack of easy access to fixed-dose palatable pediatric formulations, pill burden, and medication side effects are big challenges in treating children. It is therefore timely and commendable that Turkova et al. present in this issue of the *Journal*[9] the results of the SHINE trial — a trial that included only children and showed that 4 months of treatment provided similar efficacy to a standard 6-month regimen for nonsevere tuberculosis.

This multicenter, open-label trial involved 1204 children with symptomatic, nonsevere (as assessed radiologically), smear-negative tuberculosis. The median age of the participants was 3.5 years, and 11% of them had human immunodeficiency virus (HIV) infection. In children with microbiologic confirmation of tuberculosis (14% of the trial population), only those with drug-susceptible cases were included. Participants were randomly assigned in a 1:1 ratio to receive either 4 months (16 weeks) or 6 months (24 weeks) of antituberculosis therapy. All the participants received 8 weeks of standard treatment with isoniazid, rifampin, and pyrazinamide as a fixed-dose formulation, with or without ethambutol; this treatment was followed by either 8 weeks or 16 weeks of isoniazid and rifampin in a fixed-dose combination. The primary outcome was unfavorable status (defined as treatment failure [extension, change, or restart of treatment or tuberculosis recurrence], loss to follow-up during treatment, or death) by 72 weeks.

In the primary analysis, the 4-month regimen was found to be noninferior to the standard 6-month regimen. Findings in all the subgroup analyses, including those stratified according to

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age, HIV infection status, sex, geographic region, body weight, use of ethambutol, or positivity on microbiologic testing, were similar to those in the primary analysis. Results of the safety analyses were similar in the two treatment groups, with adverse events occurring in approximately 8% of the participants in each group, with most events occurring during the first 8 weeks of treatment (during which the treatments were identical in the two groups). Adherence was high in each group, with 94% adherence to at least 80% of the doses throughout the assigned treatment duration. Retention in this trial was impressive, with 95% of the expected participants attending the 72-week visit. Besides the benefits of adherence and reduction in pill burden over time, a cost-effectiveness analysis indicated lower health care costs with the shorter regimen.

The next steps for implementation of the regimen used in the SHINE trial would include revision of global guidelines, adoption by countries, and scaling up of better diagnostic tools as well as pediatric fixed-dose formulations. Although the findings of this trial are applicable only to nonsevere tuberculosis, most cases of tuberculosis in children initially manifest as nonsevere disease, with low bacillary burden on smears and molecular tests.[10] Thus, the trial findings will be applicable to most children with tuberculosis and can be adopted by national programs with the use of fixed-drug formulations that are already available.

However, a key barrier to implementation would be the identification of children with nonsevere tuberculosis. The use of microscopy to rule out smear-positive cases is probably unnecessary, given the low sensitivity in children and the replacement of microscopy with molecular tests such as Xpert MTB/RIF Ultra.[10] Low, very low, or trace positive values on Xpert testing are most common in children with microbiologically confirmed tuberculosis[10] and could be used as a proxy for smear-negative tuberculosis and to simultaneously rule out rifampin resistance. It is therefore imperative that countries invest more in microbiologic diagnosis with molecular testing for childhood tuberculosis, building on the laboratory capacity developed for Covid-19.[1]

Reliance on radiography of the chest to identify nonsevere disease may be a challenge in areas where radiology facilities are limited; interobserver variability in interpretation is also an issue. However, these concerns may be addressed with newer, ultra-portable digital radiography systems and artificial intelligence–based software for reading radiographs, with the latter requiring validation in children.[11] Given the wide usefulness of radiographs beyond tuberculosis care, greater efforts are needed to make digital radiography more affordable and accessible, as an essential diagnostic tool in primary health care.

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

From the McGill International TB Centre, McGill School of Population and Global Health, McGill University, Montreal (M.P.); and the Department of Paediatrics and Child Health, South African Medical Research Council Unit on Child and Adolescent Health, University of Cape Town, Cape Town, South Africa (H.J.Z.).

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Endovascular Therapy for Acute Stroke with a Large Ischemic Region

S. Yoshimura, N. Sakai, H. Yamagami, K. Uchida, M. Beppu, K. Toyoda, Y. Matsumaru, Y. Matsumoto, K. Kimura, M. Takeuchi, Y. Yazawa, N. Kimura, K. Shigeta, H. Imamura, I. Suzuki, Y. Enomoto, S. Tokunaga, K. Morita, F. Sakakibara, N. Kinjo, T. Saito, R. Ishikura, M. Inoue, and T. Morimoto

ABSTRACT

BACKGROUND

Endovascular therapy for acute ischemic stroke is generally avoided when the infarction is large, but the effect of endovascular therapy with medical care as compared with medical care alone for large strokes has not been well studied.

METHODS

We conducted a multicenter, open-label, randomized clinical trial in Japan involving patients with occlusion of large cerebral vessels and sizable strokes on imaging, as indicated by an Alberta Stroke Program Early Computed Tomographic Score (ASPECTS) value of 3 to 5 (on a scale from 0 to 10, with lower values indicating larger infarction). Patients were randomly assigned in a 1:1 ratio to receive endovascular therapy with medical care or medical care alone within 6 hours after they were last known to be well or within 24 hours if there was no early change on fluid-attenuated inversion recovery images. Alteplase (0.6 mg per kilogram of body weight) was used when appropriate in both groups. The primary outcome was a modified Rankin scale score of 0 to 3 (on a scale from 0 to 6, with higher scores indicating greater disability) at 90 days. Secondary outcomes included a shift across the range of modified Rankin scale scores toward a better outcome at 90 days and an improvement of at least 8 points in the National Institutes of Health Stroke Scale (NIHSS) score (range, 0 to 42, with higher scores indicating greater deficit) at 48 hours.

RESULTS

A total of 203 patients underwent randomization; 101 patients were assigned to the endovascular-therapy group and 102 to the medical-care group. Approximately 27% of patients in each group received alteplase. The percentage of patients with a modified Rankin scale score of 0 to 3 at 90 days was 31.0% in the endovascular-therapy group and 12.7% in the medical-care group (relative risk, 2.43; 95% confidence interval [CI], 1.35 to 4.37; P=0.002). The ordinal shift across the range of modified Rankin scale scores generally favored endovascular therapy. An improvement of at least 8 points on the NIHSS score at 48 hours was observed in 31.0% of the patients in the endovascular-therapy group and 8.8% of those in the medical-care group (relative risk, 3.51; 95% CI, 1.76 to 7.00), and any intracranial hemorrhage occurred in 58.0% and 31.4%, respectively (P<0.001).

CONCLUSIONS

In a trial conducted in Japan, patients with large cerebral infarctions had better functional outcomes with endovascular therapy than with medical care alone but had more intracranial hemorrhages. (Funded by Mihara Cerebrovascular Disorder Research Promotion Fund and the Japanese Society for Neuroendovascular Therapy; RESCUE-Japan LIMIT ClinicalTrials.gov number, NCT03702413.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Morimoto can be contacted at t-morimoto@umin.net or at the Department of Clinical Epidemiology, Hyogo College of Medicine, 1-1 Mukogawa, Nishinomiya, Hyogo 663-8501, Japan.

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RESEARCH SUMMARY

Endovascular Therapy for Acute Stroke with a Large Ischemic Region

Yoshimura S et al. DOI: 10.1056/NEJMoa2118191

CLINICAL PROBLEM

Although endovascular therapy is standard treatment for ischemic stroke caused by large-vessel occlusion, it is not typically used in patients with a large ischemic region because of a lack of data from randomized trials and concern about the risk of hemorrhage with reperfusion.

CLINICAL TRIAL

Design: An open-label, multicenter, randomized clinical trial in Japan compared endovascular therapy with medical therapy alone in patients with large-vessel stroke and a large ischemic area.

Intervention: 203 patients underwent randomization; 100 patients assigned to endovascular therapy and 102 assigned to medical care alone completed follow-up. The primary outcome was a modified Rankin scale score of 0 (no disability) to 3 (moderate disability but ambulatory) at 90 days after stroke onset.

RESULTS

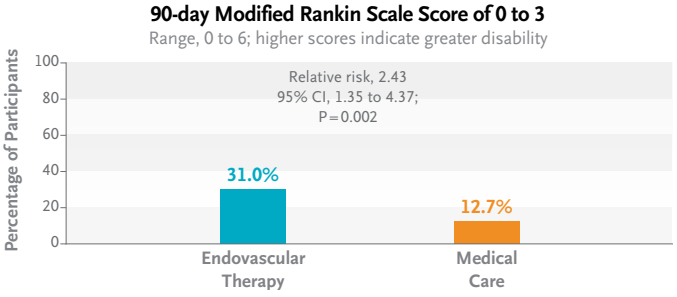
Efficacy: The percentage of patients with a modified Rankin scale score of 0 to 3 at 90 days was significantly higher with endovascular therapy than with medical care alone.

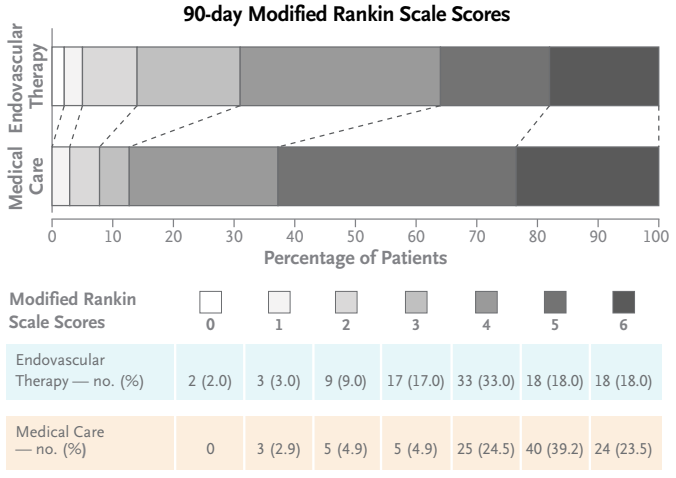
Safety: The percentage of patients who had any intracranial hemorrhage within 48 hours after randomization was significantly higher with endovascular therapy than with medical care alone. However, the percentage of patients who had symptomatic intracranial hemorrhage within 48 hours, decompressive craniectomy within 7 days, or ischemic stroke recurrence within 90 days or who died within 90 days did not differ significantly between the groups.

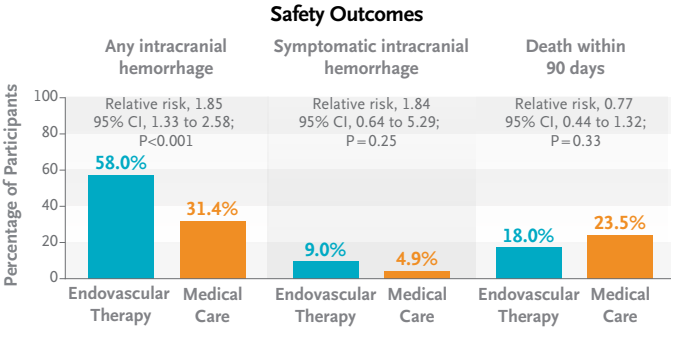
LIMITATIONS AND REMAINING QUESTIONS

Further study is required to understand the following:

- The difference in how ischemic area is determined by computed tomography, as is common practice in the United States, and by diffusion-weighted magnetic resonance imaging, which was used more often in this trial, should be considered.
- Generalizability of the findings is limited outside Japan; approximately 27% of the patients in each group received intravenous thrombolysis at a dose of 0.6 mg per kilogram according to Japanese guidelines — a lower dose than that used in some other countries.
- Whether causes of death were related to the assigned trial treatment could not be determined.







CONCLUSIONS

Patients with large cerebral infarctions had better functional outcomes but more overall intracranial hemorrhages with endovascular therapy added to medical therapy than with medical therapy alone.

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EDITORIAL

In Stroke, When Is a Good Outcome Good Enough?

Lee H. Schwamm, M.D.

In this issue of the *Journal*, Yoshimura and colleagues[1] report the favorable results of a well-conducted randomized trial comparing mechanical thrombectomy (endovascular therapy) with medical care in patients with large-vessel occlusion and large cerebral infarctions. Previous trials of endovascular therapy in selected populations of patients with small and medium-sized strokes have shown beneficial treatment effects, thereby setting the stage for randomized trials of endovascular therapy in patients with large infarctions.[2]

Neurologists have been reluctant to perform endovascular therapy in patients with large infarctions because of the putative risk of bleeding into the infarction and the likelihood that outcomes would be poor with any treatment. On account of the latter reason, trials involving patients with large infarctions may use an expanded definition of a "good outcome" that is based on a modified Rankin scale score of 0 to 3 (on a scale from 0 to 6, with higher scores indicating greater disability; a score of 3 indicates moderate disability).[3] The results of a meta-analysis of the effect of endovascular therapy in patients with large strokes, as gauged by an Alberta Stroke Program Early Computed Tomographic Score (ASPECTS) of 3 to 5 (on a scale from 0 to 10, with lower scores indicating larger infarction), favored endovascular therapy over standard treatment.[4] The patients in the current trial by Yoshimura and colleagues generally had greater stroke severity and larger infarct volumes than patients in the meta-analysis. These factors make the choice of a modified Rankin scale score of 0 to 3 at 90 days as the primary end point in this trial seem reasonable on the surface. The trial showed a benefit with endovascular therapy as compared with standard medical care for stroke, with a relative risk of this "good outcome" of 2.43.

The trial by Yoshimura and colleagues is distinguished from other trials of endovascular therapy by the following four factors. First, a good outcome was defined as a modified Rankin scale score of 0 to 3 instead of the range of 0 to 2 that is typically used. Second, ASPECTS scoring of the infarct size during screening was predominantly based on the results of magnetic resonance imaging rather than of computed tomography (CT). Third, the trial population comprised patients who were enrolled either 6 hours or less after the onset of stroke or 6 to 24 hours after the time they were last known to be well but had imaging results indicating that the stroke was recent. And fourth, alteplase was used infrequently and at a lower dose (0.6 mg per kilogram of body weight, which is the dose typically used in Japan, where the trial was conducted) than in many other countries. There are several details of the criteria that defined large strokes in this trial that should be considered in the interpretation of the trial results. Because magnetic resonance angiography may overestimate the degree of cerebral large-vessel stenosis as compared with CT angiography and because Japanese patients often have intracranial atherosclerosis with partial stenosis of these vessels, it is unclear how many patients had incomplete large-vessel occlusion and might have been excluded from the trial if CT had been used instead. There are important differences in how the patients in this trial were treated as compared with real-world practice in countries other than Japan. In the United States and other countries, most patients are evaluated by means of CT-based methods

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and receive intravenous thrombolysis more often and at higher doses (0.9 mg per kilogram vs. the 0.6-mg-per-kilogram dose administered in the trial). If the patients in this trial had received thrombolysis more often and at higher doses, it is possible that a higher percentage of patients in the medical-care group would have had good outcomes, thereby diminishing the treatment effect of endovascular therapy.

The between-group difference among the survivors in the distribution of disability according to modified Rankin scale scores also bears consideration: more patients survived, but at what cost? From a society-centered utilitarian perspective, the goal is to provide the greatest benefit for the greatest number of patients; the shift in modified Rankin scale scores toward lower (better) outcomes indicates a benefit with endovascular therapy in this trial. But from a patient-centered (or deontological) perspective, the goal is to prevent individual patient harm; this means that even though society overall might benefit from endovascular therapy for patients with large cerebral infarction, if many patients end up surviving but severely disabled in the process, the conclusion would be that the ends do not justify the means.[5] A preserved ability to walk that is accompanied by residual disability due to aphasia or depression (an outcome consistent with a modified Rankin scale score of 3) may not be acceptable. Because the modified Rankin scale prioritizes impairments in physical rather than cognitive, emotional, or self-care domains, it underestimates the true burden of disease borne by patients and caregivers.[6] For example, more than half the patients with stroke who have a modified Rankin scale score of 0 to 2 may have cognitive impairment and limitations in social participation, and one third of patients have depression 2 to 3 years after stroke. Furthermore, in this trial, more than one third of patients who underwent endovascular therapy survived with moderately severe or severe disability (a modified Rankin scale score of 4 or 5, respectively), which indicates an inability to walk or attend to their bodily needs or be bedridden and in need of constant nursing care. Studies have shown that the estimation by the treating physicians of the risk of death or an unfavorable functional outcome among patients with severe stroke is relatively inaccurate, and the prediction of quality of life is even more imprecise.[7]

When an attempt is made to convert the modified Rankin scale to a utility-weighted instrument, these problems may be compounded. The method of applying utility weighting and the results obtained and their interpretation vary according to the scale used for weighting and the patient population from which the weighting values are obtained. When survivors of stroke are interviewed, they rate the utility (or quality) of their impaired outcome very low if they perceive themselves as being dependent and placing a burden on a caregiver.[8] Similar to trials of endovascular therapy, trials of decompressive hemicraniectomy for severe stroke have shown an increase in the percentage of patients with a modified Rankin scale score of 0 to 3 but at the expense of more survivors living with substantial disability.[9] Both these interventions for large strokes raise an ethical question about trading death for functional disability. Therefore, real-world disability that is not captured by the modified Rankin scale creates challenges in describing the potential benefits and risks when obtaining consent for endovascular therapy in patients with large strokes, especially when the definition of a good outcome is expanded beyond a disability-free or functionally independent state.

For all these reasons, I believe that equipoise remains in the decision-making process of whether to use endovascular therapy in patients with large cerebral infarctions. More large trials are needed — and some are under way — to provide a sufficient sample size and evidence of benefit of endovascular therapy in this important population of patients with stroke.

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

From the Stroke Service, Massachusetts General Hospital, and Harvard Medical School, Boston.

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The NEW ENGLAND JOURNAL of MEDICINE

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Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

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ABSTRACT

BACKGROUND

Nirmatrelvir is an orally administered severe acute respiratory syndrome coronavirus 2 main protease (M^{pro}) inhibitor with potent pan–human-coronavirus activity in vitro.

METHODS

We conducted a phase 2–3 double-blind, randomized, controlled trial in which symptomatic, unvaccinated, nonhospitalized adults at high risk for progression to severe coronavirus disease 2019 (Covid-19) were assigned in a 1:1 ratio to receive either 300 mg of nirmatrelvir plus 100 mg of ritonavir (a pharmacokinetic enhancer) or placebo every 12 hours for 5 days. Covid-19–related hospitalization or death from any cause through day 28, viral load, and safety were evaluated.

RESULTS

A total of 2246 patients underwent randomization; 1120 patients received nirmatrelvir plus ritonavir (nirmatrelvir group) and 1126 received placebo (placebo group). In the planned interim analysis of patients treated within 3 days after symptom onset (modified intention-to treat population, comprising 774 of the 1361 patients in the full analysis population), the incidence of Covid-19–related hospitalization or death by day 28 was lower in the nirmatrelvir group than in the placebo group by 6.32 percentage points (95% confidence interval [CI], −9.04 to −3.59; P<0.001; relative risk reduction, 89.1%); the incidence was 0.77% (3 of 389 patients) in the nirmatrelvir group, with 0 deaths, as compared with 7.01% (27 of 385 patients) in the placebo group, with 7 deaths. Efficacy was maintained in the final analysis involving the 1379 patients in the modified intention-to-treat population, with a difference of −5.81 percentage points (95% CI, −7.78 to −3.84; P<0.001; relative risk reduction, 88.9%). All 13 deaths occurred in the placebo group. The viral load was lower with nirmatrelvir plus ritonavir than with placebo at day 5 of treatment, with an adjusted mean difference of −0.868 $\log_{10}$ copies per milliliter when treatment was initiated within 3 days after the onset of symptoms. The incidence of adverse events that emerged during the treatment period was similar in the two groups (any adverse event, 22.6% with nirmatrelvir plus ritonavir vs. 23.9% with placebo; serious adverse events, 1.6% vs. 6.6%; and adverse events leading to discontinuation of the drugs or placebo, 2.1% vs. 4.2%). Dysgeusia (5.6% vs. 0.3%) and diarrhea (3.1% vs. 1.6%) occurred more frequently with nirmatrelvir plus ritonavir than with placebo.

CONCLUSIONS

Treatment of symptomatic Covid-19 with nirmatrelvir plus ritonavir resulted in a risk of progression to severe Covid-19 that was 89% lower than the risk with placebo, without evident safety concerns. (Supported by Pfizer; ClinicalTrials.gov number, NCT04960202.)

From Global Product Development, Pfizer, Collegeville, PA (J.H., H.L.-T.); Global Product Development (A.G.) and Early Clinical Development (M.L.B.), Pfizer, Cambridge, MA; Global Product Development, Pfizer, New York (P.A., W.B., B.D., R.P.); Global Product Development, Pfizer, Lake Forest, IL (W.W.); Medical and Safety, Pfizer, Sandwich, United Kingdom (V.M.H.); Köhler and Milstein Research, Mérida, Yucatan, Mexico (A.S.-C.); and Global Product Development, Pfizer, Tampa, FL (J.M.R.). Dr. Hammond can be contacted at jennifer.hammond@pfizer.com, or at Pfizer, 500 Arcola Rd., Collegeville, PA 19426.

*A list of the EPIC-HR investigators is provided in the Supplementary Appendix.

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RESEARCH SUMMARY

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Hammond J et al. DOI: 10.1056/NEJMoa2118542

CLINICAL PROBLEM

Safe and effective oral therapies for mild-to-moderate Covid-19 are needed for symptomatic, unvacccinated outpatients at high risk for progression to severe disease. Although monoclonal antibodies are currently available for this indication, they require administration and monitoring in a health care setting and may not work as well against emerging SARS-CoV-2 variants.

CLINICAL TRIAL

Design: An international, phase 2–3, double-blind, randomized, controlled trial assessed the efficacy and safety of the antiviral agent nirmatrelvir plus ritonavir (a pharmacokinetic enhancer) in preventing disease progression in unvaccinated adults with mild-to-moderate Covid-19 who were at high risk for progression to severe Covid-19.

Intervention: 2246 adults with confirmed SARS-CoV-2 infection were randomly assigned to receive nirmatrelvir (300 mg) plus ritonavir (100 mg) or matching placebo every 12 hours for 5 days, beginning within 5 days after the onset of Covid-19 symptoms. The primary outcome of the final analysis involving 1379 patients was the incidence of Covid-19–related hospitalization or death from any cause by day 28 in patients receiving treatment within 3 days after symptom onset.

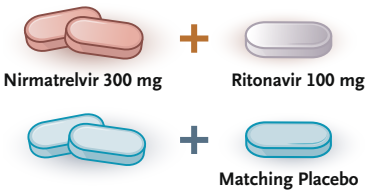
RESULTS

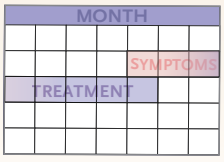
Efficacy: Nirmatrelvir plus ritonavir resulted in risk of progression to hospitalization or death at 28 days that was significantly lower than the risk with placebo.

Safety: The incidence of adverse events during or after treatment was similar in the two groups. Dysgeusia and diarrhea were more frequent with nirmatrelvir plus ritonavir than with placebo.

LIMITATIONS

- The trial was restricted to unvaccinated patients and those at high risk of progression to severe Covid-19.





Every 12 hours for 5 days beginning ≤3 days after symptom onset

Treated ≤3 Days after Onset of Symptoms through Day 28 (modified intention-to-treat population)

	Nirmatrelvir Group N = 697	Placebo Group N = 682
Total number of patients with event	5	44
Covid-19–related hospitalization	5	44
Death from any cause	0	9
Estimated percentage with event (95% CI)	0.72 (0.30–1.73)	6.53 (4.90–8.68)
Difference ±SE from placebo — percentage points	−5.81±1.01	
Relative risk reduction	88.9%	

Adverse Events during Treatment Period (safety-analysis population)

	Nirmatrelvir Group N = 1109	Placebo Group N = 1115
No. of adverse events	476	525
Patients with any adverse event — no. (%)	251 (22.6)	266 (23.9)
Serious adverse event	18 (1.6)	74 (6.6)
Maximum grade 3 or 4 adverse event	45 (4.1)	93 (8.3)
Maximum grade 5 adverse event	0	13 (1.2)
Discontinued drug or placebo because of adverse event	23 (2.1)	47 (4.2)
Had dose reduction or temporary discontinuation owing to adverse event	4 (0.4)	4 (0.4)

CONCLUSIONS

As compared with placebo, nirmatrelvir plus ritonavir reduced the risk of Covid-19–related hospitalization or death from any cause in symptomatic, unvaccinated, nonhospitalized patients at high risk for progression to severe Covid-19.

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EDITORIAL

The Potential of Intentional Drug Development

Eric J. Rubin, M.D., Ph.D., and Lindsey R. Baden, M.D.

At the start of the Covid-19 pandemic more than 2 years ago, hopes were high for rapid interventions that could lessen the severity of disease and save lives. Several approved and investigational drugs had some in vitro activity against the causative virus, SARS-CoV-2. Many repurposed medications were quickly enlisted but ultimately did not have meaningful clinical activity against Covid. Two investigational agents, remdesivir and molnupiravir, eventually showed some clinical efficacy. But both have considerable drawbacks; remdesivir is available only as a parenteral formulation, and molnupiravir has only a modest effect. Studies of these drugs, along with monoclonal antibodies, did make one point clear: intervention with antiviral agents is possible, but only early in the course of disease.[1]

Investigators now report in the *Journal* the first small-molecule antiviral agent designed specifically to inhibit SARS-CoV-2.[2] The active component, nirmatrelvir, is an inhibitor of the SARS-CoV-2 3-chymotrypsin–like cysteine protease enzyme, one of two essential proteases encoded by the virus. Protease inhibitors have a record of success in treating viral infections that dates from their introduction for the treatment of HIV. Like the antiretroviral medications, nirmatrelvir is rapidly metabolized by cytochrome P450 3A4 (CYP3A4) and is therefore administered together with a low dose of the potent inhibitor of that enzyme, ritonavir. Nirmatrelvir blocks viral replication in vitro at low concentrations and, when given with ritonavir, achieves effective plasma levels.

In this phase 3 randomized, controlled trial, nirmatrelvir plus ritonavir or placebo was administered to unvaccinated outpatients who were infected with SARS-CoV-2, were at high risk for progression to severe disease, and had symptom onset within 5 days before randomization. The primary outcome was a composite of progression to hospitalization for Covid-19 and death from any cause through day 28 in patients whose first dose was administered within 3 days after symptom onset and who had not received monoclonal antibody therapy. The trial was designed to include about 3000 patients, but it was terminated at the time of a planned interim analysis by the data monitoring committee because the efficacy end point had been reached. This report includes all enrolled patients — those who had reached the interim analysis point and those subsequently enrolled who had not yet reached the day 28 assessment, a total of 2246 patients split between the nirmatrelvir and placebo groups.

Nirmatrelvir plus ritonavir was associated with mild dysgeusia and diarrhea, but no particularly troubling safety concerns were identified. Treatment with the drug had a substantial effect on the primary outcome. In the final analysis population, which largely mirrored that of the interim analysis, 5 of 697 (0.72%) in the nirmatrelvir group were hospitalized or died, as compared with 44 of 682 (6.45%) in the placebo group. There were no deaths in the nirmatrelvir group and 9 in the placebo group. This effectiveness held up in a secondary analysis that included all participants whose first dose occurred within 5 days after symptom onset, with 8 of 1039

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(0.77%) who received nirmatrelvir plus ritonavir and 66 of 1046 (6.31%) who received placebo reaching the composite end point. That the results from the interim analysis were consistent with those of the final analysis is reassuring; it has not been the case for every Covid-19 trial.[3]

The results are clear, but nonetheless it is worth considering the difference between absolute and relative risk reduction. Although the relative risk reductions were large and similar across most subgroups (at about 89%), those at lower risk had a very small absolute benefit. For example, in patients who were SARS-CoV-2 seronegative at baseline, the absolute risk reduction was about 10 percentage points. However, in those who were SARS-CoV-2 seropositive at baseline, either because they had been infected in the past or had already undergone seroconversion from their current infection, the absolute risk reduction was about 1 percentage point. Thus, although all groups seem to have a similar relative benefit, the greatest absolute benefit is among those at highest risk.

This trial was performed between mid-July and early December 2021, a period when the delta variant was most likely responsible for the majority of infections. We do not yet know how nirmatrelvir plus ritonavir will perform as new variants, such as omicron, emerge. In vitro studies, however, suggest that the activity of nirmatrelvir is preserved across all tested viral strains.[4] We have not yet seen resistance to the new agent, but just as newer variants have evolved to be less susceptible to immune control (including control by monoclonal antibodies), it is likely that resistance to a single agent such as nirmatrelvir will become an issue.

Given that likelihood, how can we best use this effective drug? Supplies are currently constrained and are likely to remain so for some time. Who then should receive this scant resource? Here the new study provides some guidance: the absolute benefit will accrue primarily to patients at highest risk for disease progression, particularly those with multiple and serious coexisting conditions and those unable to mount sufficient immune responses. The timing of nirmatrelvir therapy is probably critical as well. Although the trial showed little difference between initiating treatment within 3 days and initiating it within 5 days after the onset of symptoms, initiating therapy much later than 5 days is very likely to be less effective. This is certainly true for other antiviral agents, such as remdesivir, which has only a small effect in hospitalized patients[5] but has a much greater effect when given early in the course of infection.[6] It will be very important to assess patients individually, since ritonavir interferes with the metabolism of many therapeutic agents, from antiseizure to immunosuppressive to anticoagulant medications. And, finally, until we have a better idea of the potential for the emergence of resistance, we need to be good stewards of this medication. By limiting its use to those most likely to benefit, we can potentially prolong its useful life.

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

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The NEW ENGLAND JOURNAL of MEDICINE

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Calorie Restriction with or without Time-Restricted Eating in Weight Loss

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ABSTRACT

BACKGROUND

The long-term efficacy and safety of time-restricted eating for weight loss are not clear.

METHODS

We randomly assigned 139 patients with obesity to time-restricted eating (eating only between 8:00 a.m. and 4:00 p.m.) with calorie restriction or daily calorie restriction alone. For 12 months, all the participants were instructed to follow a calorie-restricted diet that consisted of 1500 to 1800 kcal per day for men and 1200 to 1500 kcal per day for women. The primary outcome was the difference between the two groups in the change from baseline in body weight; secondary outcomes included changes in waist circumference, body-mass index (BMI), amount of body fat, and measures of metabolic risk factors.

RESULTS

Of the total 139 participants who underwent randomization, 118 (84.9%) completed the 12-month follow-up visit. The mean weight loss from baseline at 12 months was −8.0 kg (95% confidence interval [CI], −9.6 to −6.4) in the time-restriction group and −6.3 kg (95% CI, −7.8 to −4.7) in the daily-calorie-restriction group. Changes in weight were not significantly different in the two groups at the 12-month assessment (net difference, −1.8 kg; 95% CI, −4.0 to 0.4; P=0.11). Results of analyses of waist circumferences, BMI, body fat, body lean mass, blood pressure, and metabolic risk factors were consistent with the results of the primary outcome. In addition, there were no substantial differences between the groups in the numbers of adverse events.

CONCLUSIONS

Among patients with obesity, a regimen of time-restricted eating was not more beneficial with regard to reduction in body weight, body fat, or metabolic risk factors than daily calorie restriction. (Funded by the National Key Research and Development Project [No. 2018YFA0800404] and others; ClinicalTrials.gov number, NCT03745612.)

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Dr. Liu, Ms. Huang, and Drs. Huang, Yang, and H. Zhang contributed equally to this article.

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RESEARCH SUMMARY

Calorie Restriction with or without Time-Restricted Eating in Weight Loss

Liu D et al. DOI: 10.1056/NEJMoa2114833

CLINICAL PROBLEM

Daily calorie restriction is a primary weight-loss strategy for patients with obesity, but most diet trials have shown only modest weight loss after a year, and maintaining weight loss is challenging. Time-restricted eating — a form of intermittent fasting involving a shortened daily eating period — has shown promise in pilot studies, but data on long-term efficacy and safety are lacking.

CLINICAL TRIAL

Design: A randomized trial examined the effects of time-restricted eating plus daily calorie restriction as compared with daily calorie restriction alone in obese patients.

Intervention: 139 patients in Guangzhou, China, with a body-mass index of 28 to 45 were randomly assigned to time-restricted eating (eating only between 8:00 a.m. and 4:00 p.m.) plus daily calorie restriction or to daily calorie restriction alone. All the patients were instructed to follow a diet of 1500 to 1800 kcal per day (for men) or 1200 to 1500 kcal per day (for women) for 12 months. The primary outcome was the difference between the two groups in the change from baseline in body weight at 12 months.

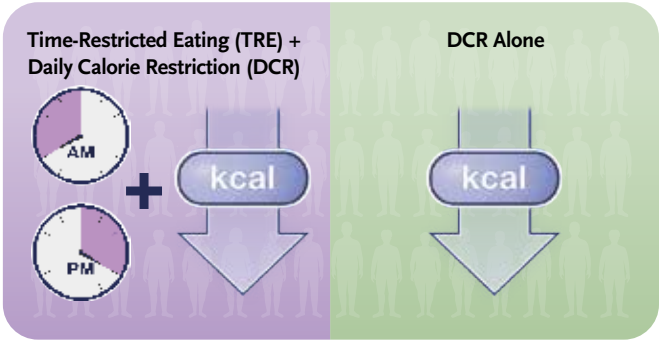
RESULTS

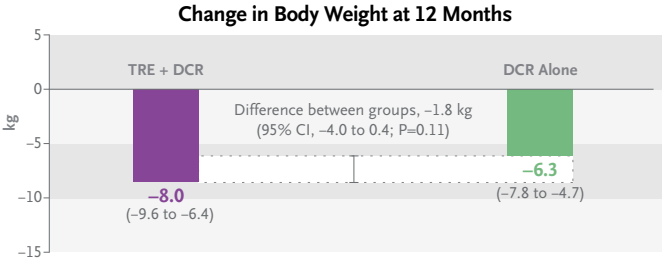
Efficacy: Among 118 patients who completed the 12-month follow-up visit, there was no significant difference in mean weight loss between the group assigned to time-restricted eating plus daily calorie restriction and the group assigned to daily calorie restriction alone.

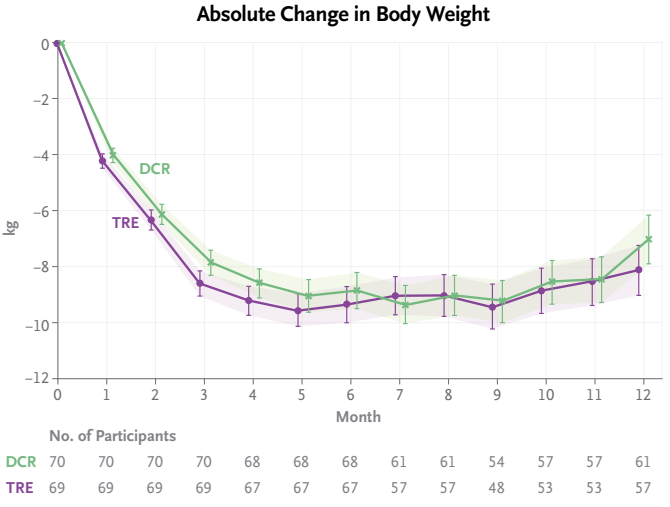
Safety: There were no substantial differences between the two groups in the number of adverse events. No deaths or serious adverse events were reported.

LIMITATIONS AND REMAINING QUESTIONS

- The findings cannot be generalized to other ethnic groups, to patients with diabetes or cardiovascular disease, or to different time-restricted–eating regimens.
- Total energy expenditure, which might have helped to explain individual differences in weight loss, was not measured.







CONCLUSIONS

Among patients with obesity, daily calorie restriction with a regimen of time-restricted eating offered no weight-loss benefit as compared with daily calorie restriction alone.

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EDITORIAL

Calorie and Time Restriction in Weight Loss

Blandine Laferrère, M.D., Ph.D., and Satchidananda Panda, Ph.D.

Weight loss with calorie restriction is the recommended approach for treatment of obesity, but this approach is resource-intensive and difficult to sustain over time.[1] Time-restricted eating is a potentially low-cost and sustainable lifestyle in which daily intake of calories is restricted to a consistent time period of less than 10 hours without explicit attempts to modify diet composition or reduce calories.

Chronic disruption of the circadian rhythm increases the risk of obesity and metabolic diseases. Restricting the window of time for eating sustains circadian rhythms and improves metabolism by prolonging the daily fast, which in turn activates cellular pathways that are implicated in mediating the benefits of calorie restriction.[2] Experiments in mice have shown that time-restricted eating can reduce adiposity and improve metabolism with or without weight loss.[3] A comparison of calorie restriction with and without time restriction is difficult to perform, because calorie-restriction protocols in mice inadvertently implement time restriction. In one study, mice that were fed a calorie-restricted diet received their daily ration in one meal consumed within a 6-hour time period. Mice that were fed the same diet at night lost more weight than those fed during the day, which suggests that timing of food consumption matters.[4]

In humans in free living conditions, time-restricted eating results in some degree of calorie restriction.[2] In this issue of the *Journal*, Liu et al.[5] report their findings from a randomized, controlled trial of calorie restriction alone as compared with calorie restriction plus time-restricted eating in weight loss in 139 patients with obesity whose average time window for eating was 10 hours and 23 minutes at baseline. All the patients were assigned a diet that represented a 25% calorie reduction from baseline to be followed for 12 months. The trial tested whether 8-hour time-restricted eating plus calorie restriction was superior to calorie restriction alone. In this trial, Liu et al. used effective strategies to reinforce adherence to calorie restriction and time-restricted eating. Nearly 85% of patients completed the trial, and adherence to calorie restriction and time-restricted eating was approximately 80%. The percent weight loss from baseline to 12 months was 9.0% (8.0 kg) in the time-restriction group and 7.2% (6.3 kg) in the calorie-restriction-only group, and superiority of time restriction was not established (group difference, –1.8 kg; P=0.11). Waist circumference, body-mass index, body fat, blood pressure, and biomarker levels decreased significantly over the trial time period with no substantial differences between the groups. The results of the trial suggest that calorie restriction combined with time restriction, when delivered with intensive coaching and monitoring, is an approach that is as safe, sustainable, and effective for weight loss as calorie restriction alone.

In this trial, the habitual time period for eating for patients at baseline was relatively short — 10 hours and 23 minutes.[2,6] Hence, the effective reduction of the eating window to 8 hours in the time-restriction group was modest (approximately 2 hours). Persons whose habitual time period for eating is long are likely to benefit

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the most from time-restricted eating. Furthermore, the intensive calorie-restriction intervention resulted in greater weight loss (approximately 9%) than weight loss that has been shown to occur with time-restricted eating alone (2 to 4%).[2] Moreover, the reduced caloric intake may have blunted any effect of time-restricted eating independent of calorie restriction. Finally, the patients were relatively healthy, a factor that left little room to test whether time-restricted eating plus calorie restriction has a significantly greater effect on cardiometabolic risks than calorie restriction alone, as has been observed in studies that involved patients with metabolic syndrome.[7]

The trial was relatively small, and the results have not precluded the possibility of a clinically important benefit of the time-restricted intervention. At 12 months, the 95% confidence interval for the difference between the trial groups in change in weight from baseline did not exclude a benefit as large as 4 kg (difference in weight change between groups was –1.8 kg; 95% CI, −4.0 to 0.4; P=0.11).

The applicability of this trial to wider populations is debatable. The short time period for eating at baseline may be specific to the population studied, since investigators outside China have reported longer time windows.[6,8,9] The rigorous coaching and monitoring by trial staff also leaves open the question of whether time-restricted eating is easier to adhere to than intentional calorie restriction. Such cost–benefit analyses are important for the assessment of the scalability of a lifestyle intervention.

Despite these limitations, this trial offers an important benchmark for a dietary lifestyle intervention that combines quality, quantity, and timing of nutrition, and it shows the evolving use of digital platforms that incorporate self-monitoring by patients and frequent feedback to deliver the intervention.

The concept of time-restricted eating is evolving. Future studies will determine the appropriate duration of the time window for eating, who is most likely to benefit from this approach, how to implement time-restricted eating and the potential mechanisms for doing so, and the effects of time-restricted eating early in the day as compared with late in the day. From a public health point of view, time-restricted eating may turn out to be an approach to accomplish calorie restriction and improve metabolic health without the resource-intensive approach of intentional calorie restriction.

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

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The NEW ENGLAND JOURNAL of MEDICINE

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Two Phase 3 Trials of Baricitinib for Alopecia Areata

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ABSTRACT

BACKGROUND

Alopecia areata is an autoimmune condition characterized by rapid hair loss in the scalp, eyebrows, and eyelashes, for which treatments are limited. Baricitinib, an oral, selective, reversible inhibitor of Janus kinases 1 and 2, may interrupt cytokine signaling implicated in the pathogenesis of alopecia areata.

METHODS

We conducted two randomized, placebo-controlled, phase 3 trials (BRAVE-AA1 and BRAVE-AA2) involving adults with severe alopecia areata with a Severity of Alopecia Tool (SALT) score of 50 or higher (range, 0 [no scalp hair loss] to 100 [complete scalp hair loss]). Patients were randomly assigned in a 3:2:2 ratio to receive once-daily baricitinib at a dose of 4 mg, baricitinib at a dose of 2 mg, or placebo. The primary outcome was a SALT score of 20 or less at week 36.

RESULTS

We enrolled 654 patients in the BRAVE-AA1 trial and 546 in the BRAVE-AA2 trial. The estimated percentage of patients with a SALT score of 20 or less at week 36 was 38.8% with 4-mg baricitinib, 22.8% with 2-mg baricitinib, and 6.2% with placebo in BRAVE-AA1 and 35.9%, 19.4%, and 3.3%, respectively, in BRAVE-AA2. In BRAVE-AA1, the difference between 4-mg baricitinib and placebo was 32.6 percentage points (95% confidence interval [CI], 25.6 to 39.5), and the difference between 2-mg baricitinib and placebo was 16.6 percentage points (95% CI, 9.5 to 23.8) ($P<0.001$ for each dose vs. placebo). In BRAVE-AA2, the corresponding values were 32.6 percentage points (95% CI, 25.6 to 39.6) and 16.1 percentage points (95% CI, 9.1 to 23.2) ($P<0.001$ for each dose vs. placebo). Secondary outcomes for baricitinib at a dose of 4 mg but not at a dose of 2 mg generally favored baricitinib over placebo. Acne, elevated levels of creatine kinase, and increased levels of low- and high-density lipoprotein cholesterol were more common with baricitinib than with placebo.

CONCLUSIONS

In two phase 3 trials involving patients with severe alopecia areata, oral baricitinib was superior to placebo with respect to hair regrowth at 36 weeks. Longer trials are required to assess the efficacy and safety of baricitinib for alopecia areata. (Funded by Eli Lilly under license from Incyte; BRAVE-AA1 and BRAVE-AA2 ClinicalTrials.gov numbers, NCT03570749 and NCT03899259.)

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*The BRAVE-AA Investigators are listed in the Supplementary Appendix, available at NEJM.org.

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RESEARCH SUMMARY

Two Phase 3 Trials of Baricitinib for Alopecia Areata

King B et al. DOI: 10.1056/NEJMoa2110343

CLINICAL PROBLEM

Current treatments for alopecia areata — an autoimmune disorder that causes rapid, nonscarring hair loss — have variable efficacy. Baricitinib is an oral, selective, reversible inhibitor of Janus kinases (JAKs) 1 and 2 that showed promise in a phase 2 trial involving adults with severe alopecia areata, but additional data are needed.

CLINICAL TRIAL

Design: Two multinational, randomized, placebo-controlled, phase 3 trials (BRAVE-AA1 and BRAVE-AA2) examined the effects of baricitinib on hair regrowth in adults with severe alopecia areata.

Intervention: In the two trials combined, 1200 patients (men ≤60 years of age and women ≤70 years of age) with Severity of Alopecia Tool (SALT) scores ≥50 and a current alopecia episode were randomly assigned to once-daily baricitinib (2 mg or 4 mg) or placebo for 36 weeks. (SALT scores range from 0 to 100, with 0 indicating no scalp hair loss and 100 indicating complete scalp hair loss.) The primary outcome was the percentage of patients with a SALT score ≤20, indicating meaningful hair regrowth, at week 36.

RESULTS

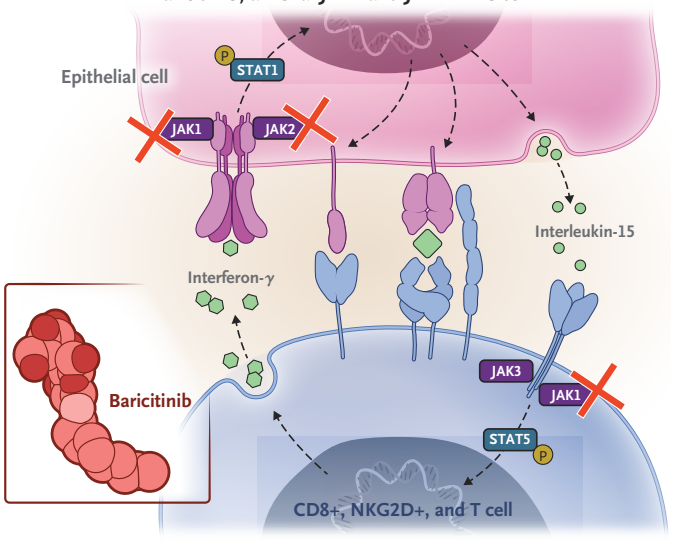
Efficacy: The percentage of patients with a SALT score ≤20 was significantly higher with both doses of baricitinib than with placebo.

Safety: Most adverse events were mild or moderate. Acne, an elevated creatine kinase level, and increased lipid levels were more common with baricitinib than with placebo.

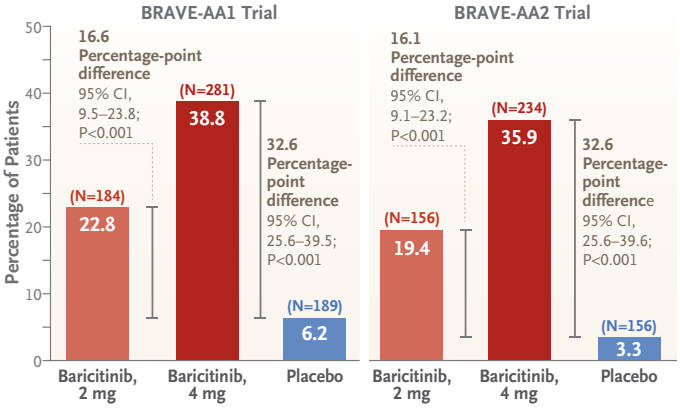
LIMITATIONS AND REMAINING QUESTIONS

- Longer-term trials are needed to assess the efficacy and safety of baricitinib for alopecia areata.
- Patients with a previous inadequate response to oral JAK inhibitors and those with an alopecia episode lasting ≥8 years without hair regrowth were excluded; thus, the benefits or harms of baricitinib in these patients are unknown.
- Patients with androgenetic alopecia might have been included, despite efforts to exclude them.

Baricitinib, an Oral JAK1 and JAK2 Inhibitor



SALT Score ≤20 at 36 Weeks



Safety Outcomes for Baricitinib

	BRAVE-AA1 Trial		BRAVE-AA2 Trial	
Outcome	2 mg	4 mg	2 mg	4 mg
Acne	5.5%	5.7%	5.8%	4.7%
Increased creatine kinase	1.6%	5.7%	0.0%	3.0%
LDL cholesterol ≥130 mg/dl	20.5%	27.7%	24.8%	30.3%
HDL cholesterol ≥60 mg/dl	42.3%	41.7%	35.6%	43.0%

CONCLUSIONS

Among adults with severe alopecia areata, the oral JAK inhibitor baricitinib was superior to placebo with respect to hair regrowth after 36 weeks of treatment.

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EDITORIAL

Baricitinib in Alopecia Areata

Andrew Messenger, M.D., and Matthew Harries, Ph.D.

For many people, alopecia areata is a transient problem, in which small patches of hair loss recover spontaneously within a few months. But for others, the reality is rather different. An Italian study showed that one third of patients with scalp hair loss of 25 to 50% still had active patchy disease at long-term follow-up, with a further third having progression to alopecia totalis or alopecia universalis, terms that vividly capture the extreme extent of disease and from which recovery is rare.[1] For many patients with severe disease, medical treatments do not work, and they face difficulty in coping with their hair loss, a challenge that many find extremely difficult owing to its unpredictable course. Several studies attest to the adverse effect of alopecia areata on health-related quality of life,[2] with emotional and psychosocial disabilities as highlighted in a population study in which anxiety, depression, absenteeism, and unemployment were more prevalent in those with alopecia areata than in matched controls.[3]

But there is hope. In this issue of the *Journal*, King and colleagues report hair regrowth with the oral Janus kinase (JAK) inhibitor baricitinib in two phase 3 trials involving a total of 1200 patients with severe alopecia areata.[4] This is an important milestone — to our knowledge, these are the first phase 3 trials of a JAK inhibitor involving patients with alopecia areata and represent the first published phase 3 trials of any treatment for this condition. The research underpinning these trials involved a mouse model of alopecia areata and was published in 2014[5]; it suggested that the cytokines interferon-γ and interleukin-15 play key roles in disease pathogenesis. The investigators found that inhibition of JAKs, a family of four intracellular tyrosine kinases that transduce cytokine-mediated signals, not only prevented the development of hair loss but also reversed alopecia once established.[5] In the same study, near-complete regrowth of hair was seen in three patients with alopecia areata treated with the JAK1 and JAK2 inhibitor ruxolitinib. This was followed by case reports and series describing successful treatment of alopecia areata by JAK inhibitors, mostly using tofacitinib (a JAK3 inhibitor).

Two phase 2 trials of ritlecitinib (an inhibitor of JAK3 and tyrosine kinase expressed in hepatocellular carcinoma) and brepocitinib (an inhibitor of JAK1 and tyrosine kinase 2)[6] and of baricitinib (a JAK1 and JAK2 inhibitor)[7] have been published, both with positive results. The two trials published in the current issue of the *Journal* (BRAVE-AA1 and BRAVE-AA2) include the phase 3 extension of the phase 2 baricitinib trial with a larger sample size. All the patients had severe alopecia areata, and nearly half had alopecia universalis. After 36 weeks, 39% of the patients in BRAVE-AA1 and 36% of those in BRAVE-AA2 who received baricitinib at a dose of 4 mg daily had at least 80% scalp coverage with hair. The percentage of patients in the two trials who had complete or near-complete hair regrowth (23%) was similar to that previously reported for ritlecitinib (25%)[6] and also for tofacitinib (20%) in an uncontrolled series.[8] These results are impressive. Of existing treatments, only topical immunotherapy has shown similar, but widely

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varying, incidences of reported response among patients with extensive disease,[9] with evidence derived from low-quality, noncomparative studies only. Furthermore, restrictive protocols and the limited availability of topical immunotherapy to specialist centers prevent widespread access to this treatment.

Adverse events in patients taking JAK inhibitors for alopecia areata have been relatively mild, but it is apparent that most patients need to continue treatment to maintain hair growth and that long-term safety will need to be monitored, probably through pharmacovigilance disease registries. Furthermore, JAK inhibitors are expensive, so it may not be feasible to treat all affected patients with these agents. Analyses will need to address cost in relation to the disability caused by this disease. Alopecia areata occasionally causes physical disability (e.g., in those with severe nail disease or loss of eyelashes), but in most patients, the overriding effect is on quality of life. Some studies, though not all, have shown a negative correlation between the extent of hair loss and quality of life,[2] and it seems reasonable to assume that restoring hair growth would alleviate suffering, but this needs to be shown in a formal way. The inclusion of assessments of health-related quality of life in clinical trials was one of two main recommendations of the 2008 Cochrane review on interventions for alopecia areata (the other being a call for good-quality trials).[10] The omission of quality-of-life measures in the current trials, except perhaps for the use of the Hospital Anxiety and Depression Scale, is a missed opportunity. It could be argued that such measures, rather than hair regrowth, should be the primary end points.

The experience with JAK agents has ignited interest and investment in treatment for alopecia areata and has led to a better understanding of its pathogenesis, therapeutic targets, and effect on patients. As has happened in other chronic inflammatory skin diseases after biologic drugs first appeared, we hope that the trials published in the *Journal* are at the front of a long line of new targeted therapies for this long-neglected condition.

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

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The NEW ENGLAND JOURNAL of MEDICINE

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PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

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ABSTRACT

BACKGROUND

Neoadjuvant chemotherapy and radiation followed by surgical resection of the rectum is a standard treatment for locally advanced rectal cancer. A subset of rectal cancer is caused by a deficiency in mismatch repair. Because mismatch repair–deficient colorectal cancer is responsive to programmed death 1 (PD-1) blockade in the context of metastatic disease, it was hypothesized that checkpoint blockade could be effective in patients with mismatch repair–deficient, locally advanced rectal cancer.

METHODS

We initiated a prospective phase 2 study in which single-agent dostarlimab, an anti–PD-1 monoclonal antibody, was administered every 3 weeks for 6 months in patients with mismatch repair–deficient stage II or III rectal adenocarcinoma. This treatment was to be followed by standard chemoradiotherapy and surgery. Patients who had a clinical complete response after completion of dostarlimab therapy would proceed without chemoradiotherapy and surgery. The primary end points are sustained clinical complete response 12 months after completion of dostarlimab therapy or pathological complete response after completion of dostarlimab therapy with or without chemoradiotherapy and overall response to neoadjuvant dostarlimab therapy with or without chemoradiotherapy.

RESULTS

A total of 12 patients have completed treatment with dostarlimab and have undergone at least 6 months of follow-up. All 12 patients (100%; 95% confidence interval, 74 to 100) had a clinical complete response, with no evidence of tumor on magnetic resonance imaging, ^{18}F-fluorodeoxyglucose–positron-emission tomography, endoscopic evaluation, digital rectal examination, or biopsy. At the time of this report, no patients had received chemoradiotherapy or undergone surgery, and no cases of progression or recurrence had been reported during follow-up (range, 6 to 25 months). No adverse events of grade 3 or higher have been reported.

CONCLUSIONS

Mismatch repair–deficient, locally advanced rectal cancer was highly sensitive to single-agent PD-1 blockade. Longer follow-up is needed to assess the duration of response. (Funded by the Simon and Eve Colin Foundation and others; ClinicalTrials.gov number, NCT04165772.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Cercek can be contacted at cerceka@mskcc.org or at Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065. Dr. Diaz can be contacted at ldiaz@mskcc.org or at Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065.

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RESEARCH SUMMARY

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

Cercek A et al. DOI: 10.1056/NEJMoa2201445

CLINICAL PROBLEM

Standard treatment for locally advanced rectal cancer includes neoadjuvant chemotherapy and radiation, followed by surgical resection of the rectum. This approach, however, is associated with substantial complications and toxic effects. Research suggests that immune checkpoint blockade alone is highly effective in patients with mismatch repair–deficient metastatic colorectal cancer; whether this strategy is effective in mismatch repair–deficient, locally advanced rectal cancer is unknown.

CLINICAL TRIAL

Design: A prospective, phase 2, single-group study examined the efficacy and safety of neoadjuvant therapy with the programmed death 1 (PD-1) inhibitor dostarlimab in patients with mismatch repair–deficient stage II or III rectal adenocarcinoma.

Intervention: Adult patients received intravenous dostarlimab every 3 weeks for 6 months, to be followed by chemoradiotherapy and total mesorectal excision. Patients with a clinical complete response to dostarlimab could forgo chemoradiotherapy and surgery. A key primary end point was overall response to dostarlimab alone or to dostarlimab plus chemoradiotherapy, determined on the basis of rectal magnetic resonance imaging, endoscopic visualization, and digital rectal examination.

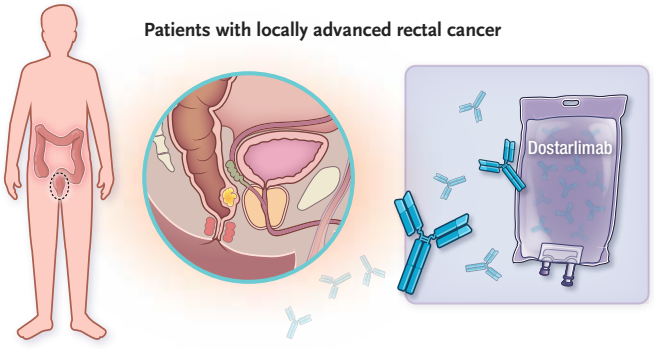
RESULTS

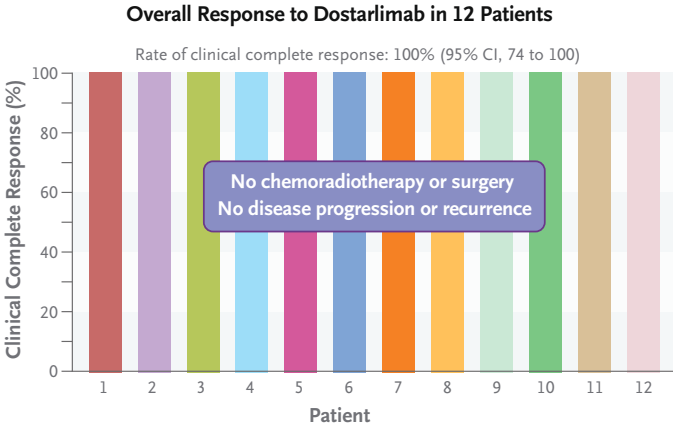
Efficacy: 12 of 16 enrolled patients have already completed 6 months of dostarlimab. All 12 had a clinical complete response, with no evidence of tumor on any diagnostic test. During a median follow-up of 12 months, no patient received chemoradiotherapy or underwent surgery, and none had disease progression or recurrence.

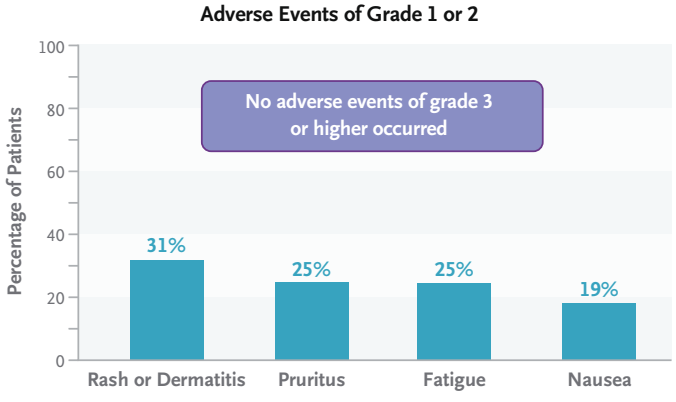
Safety: No adverse events of grade 3 or higher have occurred. The most common adverse events of grade 1 or 2 included rash or dermatitis, pruritus, fatigue, and nausea.

LIMITATIONS AND REMAINING QUESTIONS

- The study was small and limited to a single institution, and most of the patients were White.
- Longer-term follow-up is needed to evaluate the duration of response.







CONCLUSIONS

All patients with mismatch repair–deficient, locally advanced rectal cancer who were treated with the PD-1 inhibitor dostarlimab alone for 6 months had a clinical complete response, although longer follow-up is warranted.

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EDITORIAL

Improving Treatment Approaches for Rectal Cancer

Hanna K. Sanoff, M.D., M.P.H.

The cure rate for nonmetastatic rectal cancer has been improving for decades. Treatment for stage II and III rectal adenocarcinomas now routinely includes surgery, radiation therapy, and chemotherapy. The results of recent phase 3 trials have led to an increase in the intensity of treatment to include multiagent chemotherapy in addition to radiation therapy before proctectomy is performed; such treatment has resulted in a 3-year disease-free survival rate as high as 77%.[1,2] Unfortunately, this treatment approach is grueling and can cause substantial long-term sequelae, including neuropathy, infertility, and bowel and sexual dysfunction. However, this more aggressive preoperative treatment also opens the door for a paradigm-shifting way to mitigate some of the long-term consequences — nonoperative management.

With nonoperative management, treatment begins with chemotherapy and radiation therapy. Thereafter, in patients without detectable residual cancer, treatment consists of only careful observation, with surgery reserved for patients with cancer regrowth. Implementation of this strategy avoids the functional consequences of proctectomy in patients who have a sustained response to chemotherapy and radiation. In the OPRA (Organ Preservation of Rectal Adenocarcinoma) nonoperative management trial, at 3 years, the percentage of patients in whom the rectum was preserved was 43% in the group that received chemotherapy followed by chemoradiotherapy and 59% in the group that received the same treatments in reverse.[3]

Unfortunately, for the 5 to 10% of patients with cancers that are molecularly characterized as deficient in DNA mismatch-repair enzymes, the chance of rectal preservation may be lower because of a diminished response to chemotherapy and radiation therapy.[4,5] A second paradigm shift in colorectal cancer — the transition from chemotherapy to immunotherapy as primary treatment for metastatic mismatch repair–deficient cancers — presents a potential means to allow these patients to consider nonoperative approaches. In the KEYNOTE-177 trial, in which the immune checkpoint inhibitor pembrolizumab was compared with standard chemotherapy, treatment with pembrolizumab resulted in a longer duration of cancer control and a greater chance for cancer regression than standard chemotherapy.[6]

Cercek and colleagues[7] now report in the *Journal* the results of a small but compelling study that brings these two treatment advances together. In this study, immunotherapy with the programmed death 1 (PD-1) inhibitor dostarlimab was followed by nonoperative care in patients with mismatch repair–deficient stage II or III rectal cancer. Twelve patients received dostarlimab for 6 months with careful monitoring of clinical response by magnetic resonance imaging, ^{18}F-fluorodeoxyglucose–positron-emission tomography, and endoscopy. Patients who did not have a complete response were to receive subsequent standard radiation therapy and chemotherapy; however, all 12 patients had complete tumor resolution with dostarlimab. At a median follow-up of 1 year, none of the 12 patients had needed other treatment, and none had had cancer regrowth. None of the patients had adverse events of grade 3 or higher.

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These results are cause for great optimism, but such an approach cannot yet supplant our current curative treatment approach. The end point presented, clinical complete response, is an imperfect surrogate for long-term cancer control. Patients who have a clinical complete response after chemotherapy and radiation therapy have a better prognosis than those who do not have a clinical complete response, yet cancer regrowth occurs in 20 to 30% of such patients when the cancer is managed nonoperatively.[4,8] Furthermore, although responses to PD-1 inhibition can last for years, only 55% of patients treated with pembrolizumab for mismatch repair–deficient metastatic colorectal cancer in the KEYNOTE-177 trial were reported to be alive without cancer progression at 12 months; responses lasted longer among the patients who had an initial strong response, but only approximately 70% had an ongoing response 3 years later.[6] These recurrence dynamics may (or may not) differ between immunotherapy and chemoradiotherapy and between early- and late-stage disease. In fact, very little is known about the duration of time needed to find out whether a clinical complete response to dostarlimab equates to cure.

Whether the results of this small study conducted at Memorial Sloan Kettering Cancer Center will be generalizable to a broader population of patients with rectal cancer is also not known. In order to provide more information regarding which patients might benefit from immunotherapy, subsequent trials should aim for heterogeneity in age, coexisting conditions, and tumor bulk. Enrollment of patients from diverse communities could address variations in the composition of the gut microbiome, which are known to influence response to immunotherapy.[9] Diversity in the clinical practice setting is also critical to ensuring that this is a safe approach to implement on a large scale. Safe nonoperative management involves access to specialty care for direct intraluminal visualization and expertise in interpretation of rectal magnetic resonance imaging. Such expertise is not available in all communities, and without it, patients could miss the opportunity for curative resection if tumor regrowth occurred.

Despite these uncertainties, Cercek and colleagues and their patients who agreed to forgo standard treatment for a promising but unknown future with immunotherapy have provided what may be an early glimpse of a revolutionary treatment shift. Although the incidence of severe toxic effects (i.e., adverse events of grade 3 or higher) with PD-1 inhibitors is usually higher than that seen in this study — closer to 10% — lasting consequences are uncommon.[10] Thus, if immunotherapy can be a curative treatment for rectal cancer, eligible patients may no longer have to accept functional compromise in order to be cured.

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

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Tirzepatide Once Weekly for the Treatment of Obesity

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ABSTRACT

BACKGROUND

Obesity is a chronic disease that results in substantial global morbidity and mortality. The efficacy and safety of tirzepatide, a novel glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, in people with obesity are not known.

METHODS

In this phase 3 double-blind, randomized, controlled trial, we assigned 2539 adults with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or more, or 27 or more and at least one weight-related complication, excluding diabetes, in a 1:1:1:1 ratio to receive once-weekly, subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) or placebo for 72 weeks, including a 20-week dose-escalation period. Coprimary end points were the percentage change in weight from baseline and a weight reduction of 5% or more. The treatment-regimen estimand assessed effects regardless of treatment discontinuation in the intention-to-treat population.

RESULTS

At baseline, the mean body weight was 104.8 kg, the mean BMI was 38.0, and 94.5% of participants had a BMI of 30 or higher. The mean percentage change in weight at week 72 was –15.0% (95% confidence interval [CI], –15.9 to –14.2) with 5-mg weekly doses of tirzepatide, –19.5% (95% CI, –20.4 to –18.5) with 10-mg doses, and –20.9% (95% CI, –21.8 to –19.9) with 15-mg doses and –3.1% (95% CI, –4.3 to –1.9) with placebo (P<0.001 for all comparisons with placebo). The percentage of participants who had weight reduction of 5% or more was 85% (95% CI, 82 to 89), 89% (95% CI, 86 to 92), and 91% (95% CI, 88 to 94) with 5 mg, 10 mg, and 15 mg of tirzepatide, respectively, and 35% (95% CI, 30 to 39) with placebo; 50% (95% CI, 46 to 54) and 57% (95% CI, 53 to 61) of participants in the 10-mg and 15-mg groups had a reduction in body weight of 20% or more, as compared with 3% (95% CI, 1 to 5) in the placebo group (P<0.001 for all comparisons with placebo). Improvements in all prespecified cardiometabolic measures were observed with tirzepatide. The most common adverse events with tirzepatide were gastrointestinal, and most were mild to moderate in severity, occurring primarily during dose escalation. Adverse events caused treatment discontinuation in 4.3%, 7.1%, 6.2%, and 2.6% of participants receiving 5-mg, 10-mg, and 15-mg tirzepatide doses and placebo, respectively.

CONCLUSIONS

In this 72-week trial in participants with obesity, 5 mg, 10 mg, or 15 mg of tirzepatide once weekly provided substantial and sustained reductions in body weight. (Supported by Eli Lilly; SURMOUNT-1 ClinicalTrials.gov number, NCT04184622.)

From the Section of Endocrinology and Metabolism, Department of Medicine, and the Section of Pediatric Endocrinology, Department of Pediatrics, Yale University School of Medicine, New Haven, CT (A.M.J.); the Comprehensive Weight Control Center, Division of Endocrinology, Diabetes, and Metabolism, Weill Cornell Medicine, New York (L.J.A.); Eli Lilly, Indianapolis (N.N.A., S.Z., B.L., M.C.B., A.S.); McMaster University, Hamilton, and York University and Wharton Weight Management Clinic, Toronto — all in Ontario, Canada (S.W.); Intend Research, Norman, OK (L.C.); Centro Paulista De Investigação Clínica (Cepic), Sao Paulo (B.A.); and Tokyo-Eki Center-Building Clinic, Tokyo (A.K.). Dr. Jastreboff can be contacted at ania.jastreboff@yale.edu or at Yale University School of Medicine, Endocrinology and Metabolism, 333 Cedar St., P.O. Box 208020, New Haven, CT 06520.

*The SURMOUNT-1 Investigators are listed in the Supplementary Appendix, available at NEJM.org.

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RESEARCH SUMMARY

Tirzepatide Once Weekly for the Treatment of Obesity

Jastreboff AM et al. DOI: 10.1056/NEJMoa2206038

CLINICAL PROBLEM

Several clinical guidelines recommend pharmacotherapy for obesity. Tirzepatide — a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist recently approved in the United States to treat type 2 diabetes — induced clinically relevant weight reduction in phase 2 studies of people with diabetes. However, its efficacy for weight reduction in those without diabetes is unknown.

CLINICAL TRIAL

Design: An international, phase 3, double-blind, randomized, placebo-controlled trial examined the efficacy and safety of tirzepatide in adults with obesity or overweight who did not have diabetes.

Intervention: 2539 adults with a body-mass index of 30 or higher, or 27 or higher with at least one weight-related complication, were assigned to once-weekly subcutaneous tirzepatide at one of three doses (5 mg, 10 mg, or 15 mg) or placebo, in addition to lifestyle intervention. Treatment included a dose-escalation phase and lasted for 72 weeks. The coprimary end points were the percentage change in weight from baseline to week 72 and weight reduction of at least 5% by week 72.

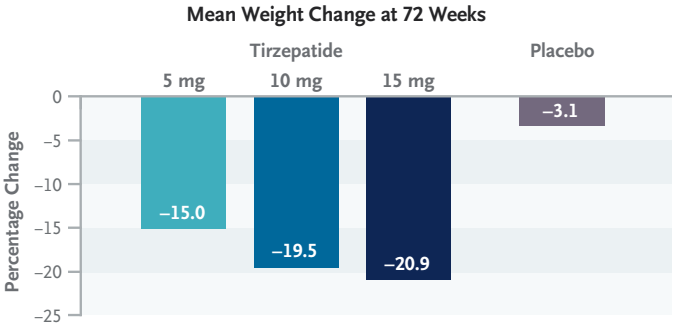
RESULTS

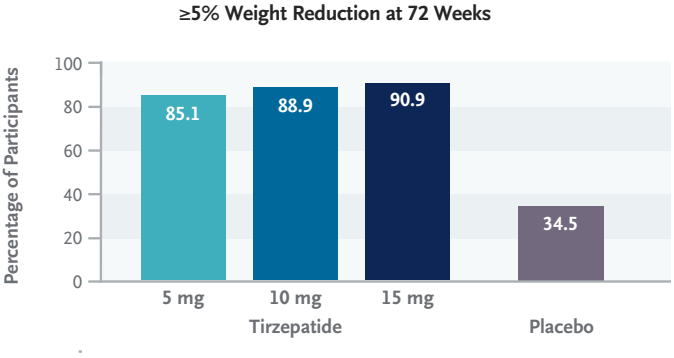
Efficacy: Both the percentage change in weight and the percentage of participants with at least 5% weight reduction were significantly greater with all three doses of tirzepatide than with placebo.

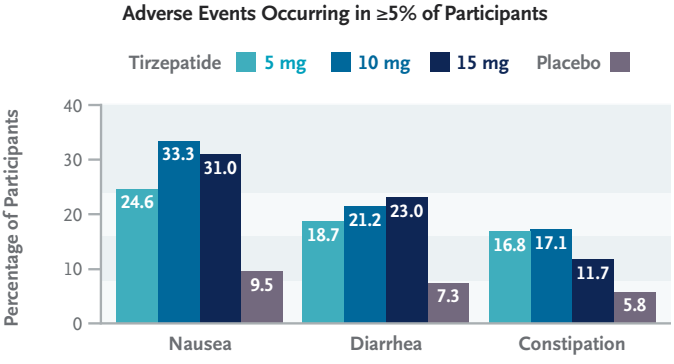
Safety: Gastrointestinal events, including nausea, diarrhea, and constipation, were the most common adverse events seen with tirzepatide; the majority of events were transient and mild to moderate in severity.

LIMITATIONS AND REMAINING QUESTIONS

- Enrolled participants may have been more committed to weight management than many people with obesity.
- Cardiometabolic variables (e.g., blood pressure and lipid levels) were relatively normal at baseline, so the ability to show a potential improvement within the time frame of this study was limited.
- The number of participants with overweight plus at least one weight-related complication was small (140 of the 2539 participants; 5.5%), which prevented definitive conclusions in this subgroup.







CONCLUSIONS

All three doses of once-weekly subcutaneous tirzepatide led to clinically meaningful and sustained weight reduction in obese adults who did not have diabetes.

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EDITORIAL

Shifting Tides Offer New Hope For Obesity

Clifford J. Rosen, M.D., and Julie R. Ingelfinger, M.D.

Obesity is a chronic disease affecting millions of people — in 2020, the Centers for Disease Control and Prevention (CDC) reported that the overall prevalence of obesity in the United States during the period from 2017 through 2018 was 42.5%.[1] The development of type 2 diabetes is a complication of obesity that leads to greater mortality primarily due to a higher incidence of cancer, cardiovascular disease, and kidney disease[2] The medical effects of obesity, especially type 2 diabetes, have a greater impact on some groups — particularly Black, Hispanic, and Native Americans — than on others, adding to notable health care disparities.

The pathophysiology of obesity is complex and multifactorial, but adipocyte expansion leads to an underlying inflammatory state, which — coupled with lipotoxic insulin signaling, glucotoxicity, insulin resistance, oxidative stress, and appetite dysregulation — can cause irreversible tissue damage.[3] Hence, a need exists for both prevention and treatment strategies. Lifestyle therapies fail for most people, though there is continued interest in delivering new programs in coaching, group therapy, and cognitive behavioral therapy.[4] Intermittent fasting or circadian timed feeding has recently garnered attention, although the benefits have not been firmly established.

In the past, few medications were approved to treat obesity, and those that were approved were plagued by weak efficacy and troubling side effects. Some agents, such as phentermine with fenfluramine, sibutramine, and lorcaserin, were actually withdrawn, owing to risks of serious cardiac valvulopathy, stroke, and cancer, respectively. Endoscopic gastric bypass and glucose-lowering agents have become favored approaches for both clinicians and patients. Gastric bypass can lead to major weight loss and long-term remission from type 2 diabetes.[5] At present, six agents are approved by the Food and Drug Administration (FDA) for use by adult patients with obesity (fewer have been approved for children and adolescents): orlistat, phentermine, phentermine–topiramate, bupropion, liraglutide, and semaglutide. The latter two are approved by the FDA as an adjunct to lifestyle modification for weight loss. However, some drugs used to treat type 2 diabetes, such as exenatide, as well as sodium–glucose contransporter 2 (SGLT2) antagonists, have not, to date, been approved by the FDA for weight loss.

Glucose-lowering agents that cause weight loss are agonists in the incretin analogue family. The naturally occurring incretins are glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1). GLP-1 stimulates insulin release and inhibits glucagon secretion, whereas GIP also stimulates insulin release but inhibits glucagon release, but only during hyperglycemia.[6] Together, their secretion constitutes an "incretin effect" — that is, insulin secretion two to three times higher after oral glucose intake than that after an equivalent intravenous glucose administration. Both these hormones directly activate the GLP-1 receptor and produce remarkable improvements in glucose tolerance as well as modest weight loss.

The mechanisms related to weight loss with GLP-1 receptor agonists are incompletely understood. GIP, GLP-1, and their receptors are widely expressed, particularly in the brain.[7] GLP-1 increases satiety and decreases gastric emptying.

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It also has direct effects on adipocytes, as well as cardiovascular tissue and bone. GIP has fewer organ-specific actions than GLP-1, but it may positively influence adipose tissue regulation of lipid storage, and it has direct activity in the central nervous system.

The possibility of combining the properties of both incretins as a single co-agonist became apparent during development of the GLP-1 receptor agonists, and findings from phase I–II studies were promising for patients with type 2 diabetes. The leading molecule of these GLP-1–GIP co-agonists was tirzepatide, a 39-amino-acid peptide whose basic structure originated from the GIP sequence but was modified to include substitution of a second amino acid, to avoid dipeptidyl peptidase 4 proteolysis, and the addition of a fatty di-acid acyl chain for albumin binding and once-weekly subcutaneous dosing.[8] In a large randomized trial in patients with type 2 diabetes, SURPASS-2, tirzepatide was found to be superior to semaglutide with respect to the mean change in glycated hemoglobin from baseline to 40 weeks.[9] Tirzepatide also induced greater weight loss than semaglutide (relative difference, −5.5 kg), though with the expected gastrointestinal side effects. Notwithstanding, the trade-off seemed worth it; few participants dropped out in that study.

Jastreboff et al. now report in the *Journal* findings from SURMOUNT-1, a 72-week phase III, multicenter, randomized clinical trial in overweight or obese persons, comparing three different doses of tirzepatide with placebo.[10] Weight loss in the active group at 72 weeks was an astonishingly 15% with the lowest dose (5 mg) and 21% with the highest dose (15 mg). Tirzepatide treatment also reduced waist circumference and lowered systolic and diastolic blood pressure, lipids, fasting insulin, and glycated hemoglobin. Serious and nonserious adverse events were limited to gastrointestinal symptoms, such as nausea, diarrhea, and constipation, similar to those associated with the other "tide" therapies for weight loss.

Until now, the most effective approach to weight loss has been bariatric surgery (often termed metabolic surgery), owing to changes in gastric hormones and other mediators. More than 250,000 people in the United States and 600,000 people worldwide underwent bariatric surgery in 2019; there are now active bariatric surgery programs in virtually all medical centers. Such programs focus on postsurgical maintenance of weight loss through long-term follow-up. However, the lifetime complications from bariatric surgery require further study, particularly as younger persons undergo the procedure. It is remarkable that the magnitude of weight loss with tirzepatide was similar to that with gastric bypass, which raises the potential for alternative medical approaches to the treatment of obesity.

In the SURMOUNT-1 trial, the relatively large number of participants, the racial and ethnic balance, and the lack of major off-target side effects suggest that the results from this trial could have major ramifications for people with obesity. Of course, there remain unanswered questions. For example, is there a distinct mechanism of action for tirzepatide-induced weight loss relative to other first-generation incretin mimetics beyond the effects of GIP? Also, are major adverse cardiovascular events reduced with tirzepatide treatment? Because the trial was of short duration and the cohort was relatively young and not at particularly high risk for cardiovascular disease, future trials will be needed to address this important question. Further, will the gastrointestinal effects moderate over time or lead to new health issues and, ultimately, stopping of the drug? Will tirzepatide "holidays" be feasible, with the agent used at intervals? Will unforeseen concerns appear over time? Notwithstanding, the "tides" are shifting, and there are now more options for people with obesity to lose weight and maintain euglycemia.

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

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The NEW ENGLAND JOURNAL of MEDICINE

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Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes

Bionic Pancreas Research Group*

ABSTRACT

BACKGROUND

Currently available semiautomated insulin-delivery systems require individualized insulin regimens for the initialization of therapy and meal doses based on carbohydrate counting for routine operation. In contrast, the bionic pancreas is initialized only on the basis of body weight, makes all dose decisions and delivers insulin autonomously, and uses meal announcements without carbohydrate counting.

METHODS

In this 13-week, multicenter, randomized trial, we randomly assigned in a 2:1 ratio persons at least 6 years of age with type 1 diabetes either to receive bionic pancreas treatment with insulin aspart or insulin lispro or to receive standard care (defined as any insulin-delivery method with unblinded, real-time continuous glucose monitoring). The primary outcome was the glycated hemoglobin level at 13 weeks. The key secondary outcome was the percentage of time that the glucose level as assessed by continuous glucose monitoring was below 54 mg per deciliter; the prespecified noninferiority limit for this outcome was 1 percentage point. Safety was also assessed.

RESULTS

A total of 219 participants 6 to 79 years of age were assigned to the bionic-pancreas group, and 107 to the standard-care group. The glycated hemoglobin level decreased from 7.9% to 7.3% in the bionic-pancreas group and did not change (was at 7.7% at both time points) in the standard-care group (mean adjusted difference at 13 weeks, −0.5 percentage points; 95% confidence interval [CI], −0.6 to −0.3; P<0.001). The percentage of time that the glucose level as assessed by continuous glucose monitoring was below 54 mg per deciliter did not differ significantly between the two groups (13-week adjusted difference, 0.0 percentage points; 95% CI, −0.1 to 0.04; P<0.001 for noninferiority). The rate of severe hypoglycemia was 17.7 events per 100 participant-years in the bionic-pancreas group and 10.8 events per 100 participant-years in the standard-care group (P=0.39). No episodes of diabetic ketoacidosis occurred in either group.

CONCLUSIONS

In this 13-week, randomized trial involving adults and children with type 1 diabetes, use of a bionic pancreas was associated with a greater reduction than standard care in the glycated hemoglobin level. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; ClinicalTrials.gov number, NCT04200313.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Russell can be contacted at sjrussell@mgh.harvard.edu or at the Diabetes Research Center, Massachusetts General Hospital, 50 Staniford St., Suite 301, Boston, MA 02114.

*The authors' full names, academic degrees, and affiliations are listed in the Appendix.

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RESEARCH SUMMARY

Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes

Bionic Pancreas Research Group DOI: 10.1056/NEJMoa2205225

CLINICAL PROBLEM

Commercially available, hybrid closed-loop insulin-delivery systems require substantial patient input, including basal insulin rates to start therapy and meal carbohydrate counts to determine mealtime insulin doses. In contrast, the bionic pancreas, currently in development by various entities, is highly automated; its technology relies only on body weight to initiate treatment and determine doses and uses qualitative carbohydrate estimates rather than counts at mealtime. Trials comparing the bionic pancreas with standard insulin-delivery methods are needed.

CLINICAL TRIAL

Design: A multicenter, parallel-group, unblinded, randomized trial examined the efficacy and safety of a bionic pancreas as compared with standard care in children and adults with type 1 diabetes.

Intervention: 326 participants 6 to 79 years of age who had been using insulin for at least 1 year were assigned either to automated glucose control with the bionic pancreas (with insulin aspart or insulin lispro) or to standard care with their current insulin-delivery method (multiple injections, pump, or hybrid closed-loop system) plus a continuous glucose monitor. The primary outcome was the glycated hemoglobin level at 13 weeks.

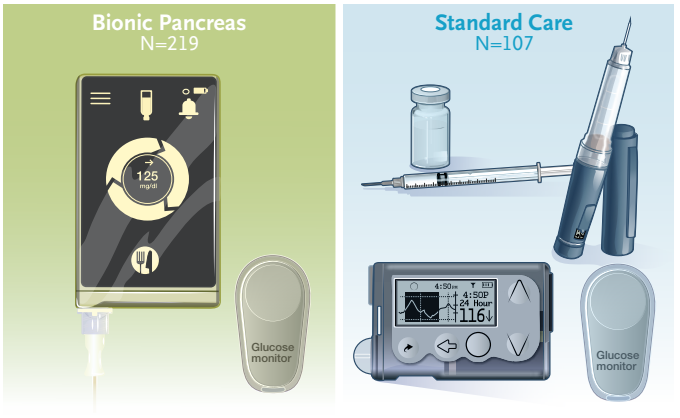
RESULTS

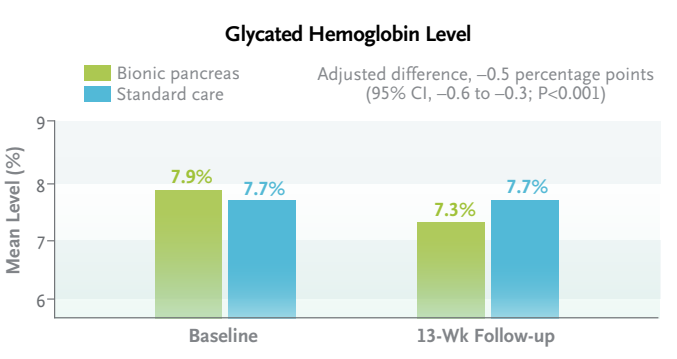
Efficacy: The mean glycated hemoglobin level decreased over the 13-week trial in the bionic-pancreas group and remained unchanged in the standard-care group, which resulted in a significant difference between the groups at 13 weeks.

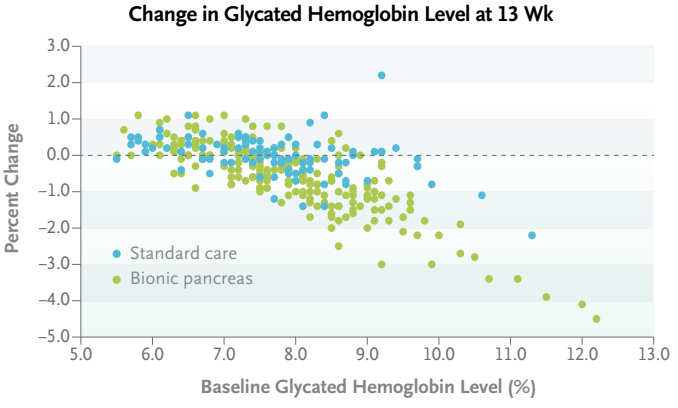
Safety: The rate of severe hypoglycemia did not differ significantly between the groups. There were no episodes of diabetic ketoacidosis in either group.

LIMITATIONS

- Hypoglycemia as measured at baseline by continuous glucose monitors was infrequent; thus, the effects of the bionic pancreas on reducing the risk and severity of hypoglycemia could not be assessed.
- Approaches to managing and reporting hyperglycemia and ketosis differed between the two groups.







CONCLUSIONS

In children and adults with type 1 diabetes, use of a bionic pancreas for 13 weeks resulted in a greater reduction in the glycated hemoglobin level than standard care, with no apparent safety concerns.

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EDITORIAL

Seeking Simpler Solutions with Diabetes Technology

Jennifer Sherr, M.D., Ph.D.

In January 1922, the management of type 1 diabetes was forever altered when Leonard Thompson became the first person to receive an injection of insulin extract.[1] Although treatment with insulin therapy has been possible for more than a century, providers and persons with type 1 diabetes are faced with the grim reality that the attainment of glycemic targets remains elusive for many, increasing the risk of microvascular and macrovascular complications.[2]

To aid with diabetes management, various technologies have been developed. Some are aimed at measuring glucose, with continuous glucose monitors that currently offer a plethora of data on which to make treatment decisions, whereas others work to deliver insulin, with insulin pumps that provide more fine-tuned and precise doses than what is feasible with multiple daily injections. From these foundational components, automated insulin-delivery systems (also known as closed-loop systems) provide a more physiologic approach to diabetes management, tying insulin delivery to sensor glucose values on the basis of algorithms. Insulin delivery with such devices can be interrupted to avert hypoglycemia, and additional insulin can be autonomously delivered to mitigate hyperglycemia. A clear picture has emerged regarding the benefits of automated insulin delivery — evident improvements in glycemia, especially overnight.[3] Although the ultimate goal for these systems is full automation, given the limitations of subcutaneously delivered rapid-acting insulin analogues, a hybrid approach has been used, whereby the person with diabetes needs to note (i.e., announce) meals, often by entering discrete amounts of carbohydrates about to be consumed. To date, three such systems have received regulatory approval in the United States, with five systems receiving CE marking.[4]

In this issue of the *Journal*, Russell and colleagues[5] present the results of a 13-week, multicenter trial in which patients were randomly assigned in a 2:1 ratio to receive either an insulin-only configuration of the bionic pancreas or standard care, which could be any method of insulin delivery but necessitated the use of a real-time continuous glucose monitor. The iLet bionic pancreas (Beta Bionics) differentiates itself from others in that the initiation of automated insulin delivery requires only the entry of a patient's body weight and its simplified qualitative approach to meal announcements. The cohort of participants who were enrolled in this trial ranged in age from 6 to 79 years and had baseline glycated hemoglobin levels ranging from 5.5% to 13.1%. The mode of insulin delivery before enrollment varied among the participants — automated insulin-delivery systems, conventional pumps, and multiple daily injections — and the trial participants were diverse in their racial, ethnic, and educational backgrounds, with more than 15% of the cohort being insured by Medicare, Medicaid, or other government insurance.

During the 13-week trial period, the participants in the bionic-pancreas group had a reduction in the glycated hemoglobin level, from 7.9% to 7.3%, whereas those in the standard-care group had no change in the glycated hemoglobin level (which was 7.7% at both time points).

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The time with the glucose level in the target range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter) was 11 percentage points higher with use of the bionic pancreas, a finding that reflects, on average, an increase of more than 2.5 hours per day in the target range.

Although the glycemic outcomes in this trial echo what has been shown with other systems, what makes these findings critically important is that the criteria that are required for use of this mode of insulin delivery actually constitute just one thing: having type 1 diabetes. With the representation of characteristics that mirror the actual experience of a person with type 1 diabetes, these findings can be more easily generalized to real-world application of the technology when regulatory approval is obtained. Indeed, one can suppose that with much of the math that plagues diabetes management being alleviated with the bionic pancreas, numeracy skills would not preclude system adoption. In addition, whereas endocrinologists tend to be concentrated in certain geographic regions in the United States, persons with type 1 diabetes live across the country, which means that many seek care from primary care providers. Although primary care providers may be eager to offer the best tools, the complexity of the available systems to date has not infrequently impeded prescription. The feasibility of simplified technologies to overcome this issue is palpable.

Academic societies have altered clinical practice guidelines and standards of medical care to highlight the recommendation that automated insulin delivery should be considered in all persons with diabetes who can safely use available technology.[6-8] Now, the goal will be to ensure that access to such technologies is not limited because of insurance coverage or perceptions about who may be an "ideal" candidate for such treatment. Recent registry data have highlighted the finding that the provision of subsidized continuous glucose monitors has led to an exponential growth in sensor use, with a concomitant reduction in glycated hemoglobin levels that were maintained over a 2-year period.[9] These results are impressive, but there is no doubt that automated insulin delivery will be even more promising in the outcomes that it will achieve. In fact, although population-based studies show that rates of death and cardiovascular disease have decreased over time among persons with type 1 diabetes, a gap exists when comparisons are made with rates in the general population.[10] The time is now to close this chasm, and simplified, automated insulin delivery, as with the bionic pancreas, may be the solution.

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

From the Department of Pediatrics, Yale School of Medicine, New Haven, CT.

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Treatment for Mild Chronic Hypertension during Pregnancy

A.T. Tita, J.M. Szychowski, K. Boggess, L. Dugoff, B. Sibai, K. Lawrence, B.L. Hughes, J. Bell, K. Aagaard, R.K. Edwards, K. Gibson, D.M. Haas, L. Plante, T. Metz, B. Casey, S. Esplin, S. Longo, M. Hoffman, G.R. Saade, K.K. Hoppe, J. Foroutan, M. Tuuli, M.Y. Owens, H.N. Simhan, H. Frey, T. Rosen, A. Palatnik, S. Baker, P. August, U.M. Reddy, W. Kinzler, E. Su, I. Krishna, N. Nguyen, M.E. Norton, D. Skupski, Y.Y. El-Sayed, D. Ogunyemi, Z.S. Galis, L. Harper, N. Ambalavanan, N.L. Geller, S. Oparil, G.R. Cutter, and W.W. Andrews, for the Chronic Hypertension and Pregnancy (CHAP) Trial Consortium*

ABSTRACT

BACKGROUND

The benefits and safety of the treatment of mild chronic hypertension (blood pressure, <160/100 mm Hg) during pregnancy are uncertain. Data are needed on whether a strategy of targeting a blood pressure of less than 140/90 mm Hg reduces the incidence of adverse pregnancy outcomes without compromising fetal growth.

METHODS

In this open-label, multicenter, randomized trial, we assigned pregnant women with mild chronic hypertension and singleton fetuses at a gestational age of less than 23 weeks to receive antihypertensive medications recommended for use in pregnancy (active-treatment group) or to receive no such treatment unless severe hypertension (systolic pressure, ≥160 mm Hg; or diastolic pressure, ≥105 mm Hg) developed (control group). The primary outcome was a composite of preeclampsia with severe features, medically indicated preterm birth at less than 35 weeks' gestation, placental abruption, or fetal or neonatal death. The safety outcome was small-for-gestational-age birth weight below the 10th percentile for gestational age. Secondary outcomes included composites of serious neonatal or maternal complications, preeclampsia, and preterm birth.

RESULTS

A total of 2408 women were enrolled in the trial. The incidence of a primary-outcome event was lower in the active-treatment group than in the control group (30.2% vs. 37.0%), for an adjusted risk ratio of 0.82 (95% confidence interval [CI], 0.74 to 0.92; P<0.001). The percentage of small-for-gestational-age birth weights below the 10th percentile was 11.2% in the active-treatment group and 10.4% in the control group (adjusted risk ratio, 1.04; 95% CI, 0.82 to 1.31; P=0.76). The incidence of serious maternal complications was 2.1% and 2.8%, respectively (risk ratio, 0.75; 95% CI, 0.45 to 1.26), and the incidence of severe neonatal complications was 2.0% and 2.6% (risk ratio, 0.77; 95% CI, 0.45 to 1.30). The incidence of any preeclampsia in the two groups was 24.4% and 31.1%, respectively (risk ratio, 0.79; 95% CI, 0.69 to 0.89), and the incidence of preterm birth was 27.5% and 31.4% (risk ratio, 0.87; 95% CI, 0.77 to 0.99).

CONCLUSIONS

In pregnant women with mild chronic hypertension, a strategy of targeting a blood pressure of less than 140/90 mm Hg was associated with better pregnancy outcomes than a strategy of reserving treatment only for severe hypertension, with no increase in the risk of small-for-gestational-age birth weight. (Funded by the National Heart, Lung, and Blood Institute; CHAP ClinicalTrials.gov number, NCT02299414.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Tita can be contacted at atita@uab.edu or at the Department of Obstetrics and Gynecology, Center for Women's Reproductive Health, Marnix E. Heersink School of Medicine, University of Alabama at Birmingham, 619 19th St. S., Birmingham, AL 35249.

*A complete list of the investigators in the CHAP Trial Consortium is provided in the Supplementary Appendix, available at NEJM.org.

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RESEARCH SUMMARY

Treatment for Mild Chronic Hypertension during Pregnancy

Tita AT et al. DOI: 10.1056/NEJMoa2201295

CLINICAL PROBLEM

Chronic hypertension during pregnancy increases risk of poor pregnancy and birth outcomes. Although pharmacologic antihypertensive therapy is standard treatment for severe hypertension during pregnancy, its benefits and safety are unclear for mild chronic hypertension in pregnant women.

CLINICAL TRIAL

Design: A U.S. multicenter, open-label, randomized, controlled trial assessed whether treatment of mild chronic hypertension in pregnant women, as compared with no treatment, would reduce adverse pregnancy outcomes without harming fetal growth.

Intervention: 2408 women with a known or new diagnosis of mild chronic hypertension and a singleton fetus at <23 weeks' gestation were randomly assigned to receive either active treatment with antihypertensive medications approved for pregnancy or standard treatment — i.e., no treatment, unless systolic blood pressure was ≥160 mm Hg or diastolic blood pressure was ≥105 mm Hg. The primary outcome was a composite of preeclampsia with severe features, medically indicated preterm birth at <35 weeks, placental abruption, fetal death, or neonatal death.

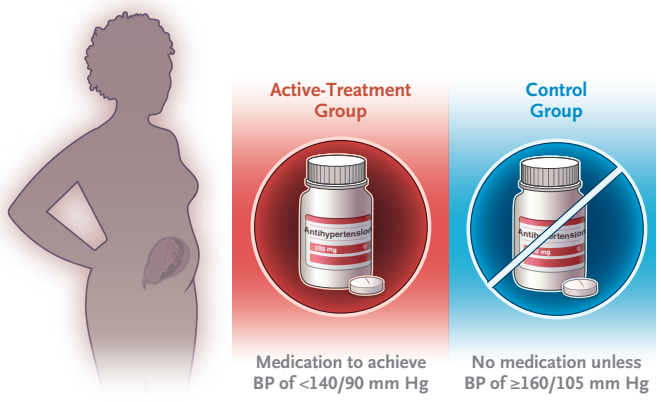
RESULTS

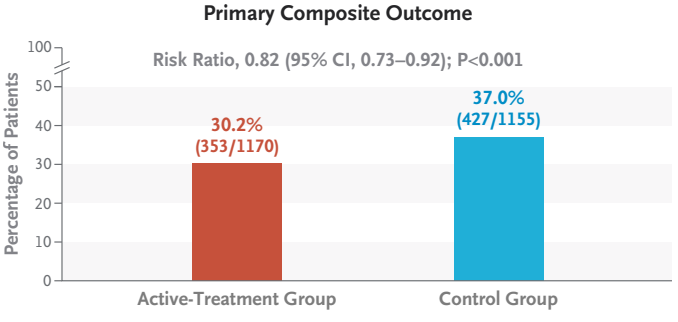
Efficacy: Active treatment of mild chronic hypertension reduced the frequency of primary outcome events.

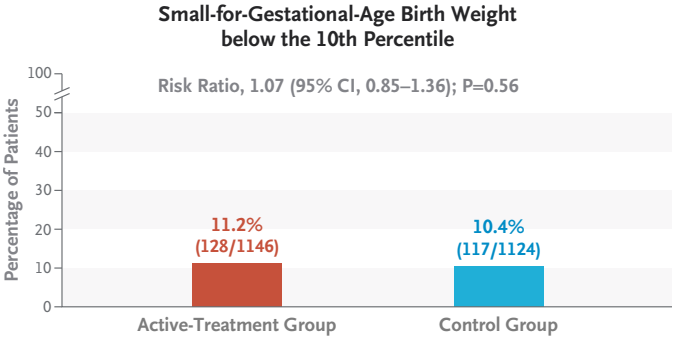
Safety: The percentage of infants who were small for gestational age (<10th percentile) was similar in the active-treatment and control groups.

LIMITATIONS AND REMAINING QUESTIONS

- Patients were aware of their treatment group.
- There was a high ratio of women screened to women enrolled (12:1).
- The study was not powered to assess treatment effects across subgroups.







CONCLUSIONS

Treating mild chronic hypertension in pregnancy reduced adverse pregnancy outcomes without impairing fetal growth.

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EDITORIAL

Treating Hypertension in Pregnancy

Michael F. Greene, M.D., and Winfred W. Williams, M.D.

The latest data from the National Center for Health Statistics indicate that in 2019 more than 83,000 pregnant women in the United States had chronic hypertension that antedated their pregnancies.[1] This number represents 2.2% of the more than 3.7 million births that were recorded that year. The rate of hypertension during pregnancy has been rising inexorably over five decades in parallel with the strongly associated covariates of a maternal age of more than 35 years and the presence of overweight or obesity, factors that were present in 55.9% of women who gave birth in 2019. In addition, hypertension is more than twice as common in Black women as in White women.

The consequences of hypertension in pregnancy for both mothers and their offspring are well known. They include increased maternal risks of preeclampsia or eclampsia, stroke, heart failure, pulmonary edema, acute kidney injury, placental abruption, and death and increased fetal risks of preterm birth, poor growth, and perinatal death. All these risks for adverse pregnancy outcomes are also greater among Black women.

Guidelines for treating hypertension in adults have been clear in recommending treatment at increasingly lower blood-pressure thresholds to minimize long-term risks of death and complications.[2] Recommendations in favor of treatment of hypertension in pregnancy have been clear for women with severe hypertension who are at risk for acute complications such as stroke and for those with coexisting conditions such as renal disease. However, early small studies of treatment of mild hypertension in pregnancy in otherwise healthy women have not shown clear or durable benefits of such treatment.[3,4] These findings have caused fraught decision making due to concern about the potential unintended fetal consequences of poor growth or death from lowering of placental perfusion pressure.

In the Control of Hypertension in Pregnancy Study (CHIPS)[5] comparing "tight" with "less tight" antihypertensive control in 987 pregnant women with mild hypertension, Magee et al. found that tight control could be achieved without the feared adverse consequences on fetal growth. However, the trial was neither designed nor powered to examine other potential treatment benefits.

In this issue of the *Journal*, Tita and colleagues[6] present the results of the large multicenter, open-label, randomized Chronic Hypertension and Pregnancy (CHAP) trial[4] conducted at 61 sites in the United States to compare the treatment of otherwise uncomplicated hypertension at two different blood-pressure thresholds. Enrolled in the trial were pregnant women who had mild hypertension, which was defined as a systolic blood pressure between 140 and 160 mm Hg and a diastolic blood pressure between 90 and 105 mm Hg. All the women had a singleton fetus of less than 23 weeks of gestation. The women were randomly assigned in a 1:1 ratio to receive either active treatment with an antihypertensive agent that targeted a blood pressure of less than 140/90 mm Hg or to receive standard (control) treatment, with initiation of treatment to the same target only if there was an increase in the systolic pressure beyond 160 mm Hg or in the diastolic pressure beyond 105 mm Hg (severe hypertension). The preferred first choice for an antihypertensive agent was labetalol or extended-release nifedipine. The primary outcome was a composite of preeclampsia with severe features, medically indicated preterm birth at less then 35 weeks of gestation, placental abruption, or

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perinatal death. The main safety outcomes were the incidences of small-for-gestational-age birth at less than the 10th percentile and at less than the 5th percentile.

The investigators screened 29,772 potential patients, the majority of whom were ineligible because their blood pressure was either too high or too low or they were too far along in gestation. Ultimately, data for 1208 women in the active-treatment group and 1200 in the control group were available for analysis. The groups were well balanced with respect to both demographic and clinical characteristics. Before enrollment, 45% of the patients in the two groups were taking aspirin, a percentage that increased to more than 75% at the time of delivery. At this point, some differences between the current trial and CHIPS are important. In the current trial, 47.5% of the women were Black, as compared with 12.5% in CHIPS, and the mean gestational age at randomization was 15.4 weeks with a treatment duration of 21 weeks, as compared with a mean gestational age of 24 weeks with a treatment duration of 13 weeks in CHIPS. In the current trial, the mean body-mass index at enrollment was 37.5, as compared with 31 in CHIPS.

In the CHAP trial, the incidence of the primary outcome was lower in the active-treatment group than in the control group (30.2% vs. 37.0%), for an adjusted risk ratio of 0.82 (95% confidence interval, 0.74 to 0.92; P<0.001). The primary-outcome result was driven by the incidences of preeclampsia with severe features and medically indicated preterm birth at less than 35 weeks of gestation. The infant safety outcomes of a size below the 10th percentile or below the 5th percentile for gestational age did not differ significantly between the two groups. The virtually identical values for placental weight in the two treatment groups give further assurance of the safety of the active treatment. The absence of any evidence of reduced fetal growth with more aggressive treatment is very reassuring and is consistent with the findings of the CHIPS investigators.

In the current trial, the relatively large number of secondary outcomes need to be interpreted with caution owing to the lack of adjustment for multiple comparisons. The lower rate of severe hypertension that was observed in the active-treatment group is consistent with the findings of six previous studies, including CHIPS.[7] The lower risks of preterm birth before 37 weeks and a birth weight of less than 2500 g in the active-treatment group are consistent with the lower incidence of medically indicated preterm birth before 35 weeks, which was a component of the primary outcome. The high incidence of cesarean delivery attracts attention but was the same in both groups and was identical to the incidence in CHIPS.

The most exciting finding in this trial (possibly the result of the large enrollment) is the apparent reduction in the incidence of various measures of preeclampsia in the active-treatment group, findings that have not been observed in eight previous randomized trials, including CHIPS.[7] As secondary outcomes not adjusted for multiplicity, these findings must be regarded with caution. However, if the results are confirmed in subsequent studies, such outcomes would be a compelling reason to change the recommendations for clinical practice regarding the treatment of mild hypertension during pregnancy.

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

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ORIGINAL ARTICLE

Safety and Efficacy of a Monoclonal Antibody against Malaria in Mali

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ABSTRACT

BACKGROUND

CIS43LS is a monoclonal antibody that was shown to protect against controlled *Plasmodium falciparum* infection in a phase 1 clinical trial. Whether a monoclonal antibody can prevent *P. falciparum* infection in a region in which the infection is endemic is unknown.

METHODS

We conducted a phase 2 trial to assess the safety and efficacy of a single intravenous infusion of CIS43LS against *P. falciparum* infection in healthy adults in Mali over a 6-month malaria season. In Part A, safety was assessed at three escalating dose levels. In Part B, participants were randomly assigned (in a 1:1:1 ratio) to receive 10 mg of CIS43LS per kilogram of body weight, 40 mg of CIS43LS per kilogram, or placebo. The primary efficacy end point, assessed in a time-to-event analysis, was the first *P. falciparum* infection detected on blood-smear examination, which was performed at least every 2 weeks for 24 weeks. At enrollment, all the participants received artemether–lumefantrine to clear possible *P. falciparum* infection.

RESULTS

In Part B, 330 adults underwent randomization; 110 were assigned to each trial group. The risk of moderate headache was 3.3 times as high with 40 mg of CIS43LS per kilogram as with placebo. *P. falciparum* infections were detected on blood-smear examination in 39 participants (35.5%) who received 10 mg of CIS43LS per kilogram, 20 (18.2%) who received 40 mg of CIS43LS per kilogram, and 86 (78.2%) who received placebo. At 6 months, the efficacy of 40 mg of CIS43LS per kilogram as compared with placebo was 88.2% (adjusted 95% confidence interval [CI], 79.3 to 93.3; P<0.001), and the efficacy of 10 mg of CIS43LS per kilogram as compared with placebo was 75.0% (adjusted 95% CI, 61.0 to 84.0; P<0.001).

CONCLUSIONS

CIS43LS was protective against *P. falciparum* infection over a 6-month malaria season in Mali without evident safety concerns. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT04329104.)

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*The members of the Mali Malaria mAb Trial Team are listed in the Supplementary Appendix, available at NEJM.org.

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RESEARCH SUMMARY

Safety and Efficacy of a Monoclonal Antibody against Malaria in Mali

Kayentao K et al. DOI: 10.1056/NEJMoa2206966

CLINICAL PROBLEM

In a recent phase 1 trial, a single intravenous infusion of the antimalarial monoclonal antibody CIS43LS protected adult volunteers from controlled *Plasmodium falciparum* infection. Whether CIS43LS can prevent *P. falciparum* infection in an area in which the infection is endemic is unknown.

CLINICAL TRIAL

Design: The double-blind, randomized, placebo-controlled part of a phase 2 trial assessed the safety and efficacy of CIS43LS in preventing *P. falciparum* infection in healthy adults over a 6-month malaria season in Mali.

Intervention: 330 adults were assigned to receive a single intravenous infusion of CIS43LS (10 mg per kilogram of body weight or 40 mg per kilogram) or placebo. All participants received artemether–lumefantrine 7 to 21 days before CIS43LS or placebo infusion to clear possible *P. falciparum* blood-stage infection. End points included safety through day 7 after infusion and efficacy against *P. falciparum* infection through week 24.

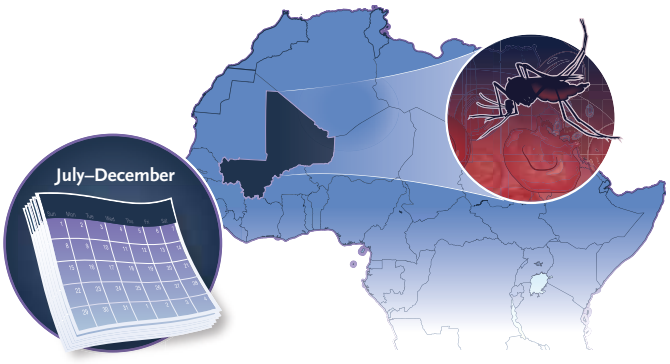
RESULTS

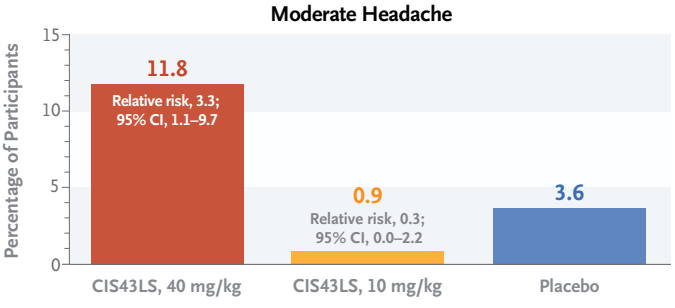
Safety: Most solicited local and systemic adverse events through day 7 day were rare, and all were mild to moderate in severity. Moderate headache occurred more often with CIS43LS than with placebo, and only with the dose of 40 mg per kilogram.

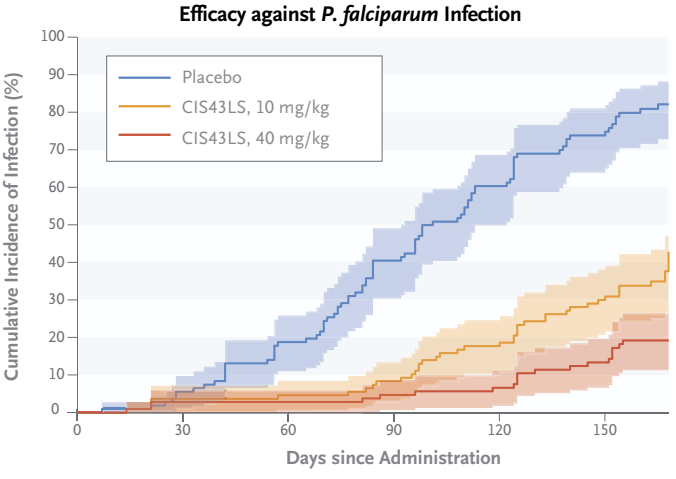
Efficacy: *P. falciparum* infection, detected on blood-smear examination, occurred significantly less often with either dose of CIS43LS than with placebo.

LIMITATIONS AND REMAINING QUESTIONS

- The duration of protection against *P. falciparum* infection and the relationship to dose of CIS43LS require further study.
- Additional trials are needed to assess the safety and efficacy of antimalarial monoclonal antibodies in children and pregnant women.







CONCLUSIONS

A single infusion of the antimalarial monoclonal antibody CIS43LS had no evident safety concerns and protected healthy adults against *P. falciparum* infection during a 6-month malaria season in Mali.

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EDITORIAL

Monoclonal Antibodies against Malaria

Umberto D'Alessandro, M.D., Ph.D.

Malaria is both a consequence and a cause of poverty and inequality.[1] A malaria-free world, in addition to preventing disease and deaths, would stimulate development and economic growth, improving the lives of hundreds of millions of people. Although the global malaria burden has decreased substantially during the past 20 years, progress has stalled since 2014; in 2020, 29 countries accounted for 96% of malaria cases globally, and 6 African countries accounted for approximately 55% of all cases globally.[2] Currently available interventions for malaria control are unlikely to achieve the vision of a malaria-free world. The drive toward the elimination and eventually eradication of malaria needs new tools; monoclonal antibodies could be one of these tools.

Kayentao et al. now report in the *Journal* the results of a phase 2 clinical trial in Mali in which they assessed the safety and efficacy of CIS43LS, a monoclonal antibody against the sporozoites of *Plasmodium falciparum*, the deadliest type of malaria.[3] After a small dose-escalation study that ensured the product was sufficiently safe, 330 healthy adults were randomly assigned to receive over 30 minutes a single intravenous infusion of 100 ml of normal saline with CIS43LS at a dose of either 10 mg per kilogram of body weight or 40 mg per kilogram or an infusion without CIS43LS. Participants attended follow-up visits 1, 3, 7, 14, 21, and 28 days later and then every 2 weeks until 24 weeks after the infusion. The follow-up covered the malaria transmission season, which occurs between July–August and December–January in Mali and surrounding countries, with malaria cases usually peaking in October or November. During these visits, a thick blood smear to identify malaria infections was systematically obtained. Artemether–lumefantrine, the first-line treatment in Mali, was administered to all trial participants before the infusion, to clear any possible infection, and to patients with clinical malaria diagnosed during the follow-up. During follow-up, infected but asymptomatic participants were not treated.

No safety concerns were identified, although the risk of headache was higher with 40 mg of CIS43LS per kilogram than with placebo. As for efficacy, each of the two CIS43LS groups was compared with the control group. For the primary end point (i.e., the first *P. falciparum* infection over the 24-week trial period, assessed in a time-to-event analysis), the efficacy as compared with placebo [(1 − hazard ratio) × 100] was 75% with 10 mg per kilogram and 88% with 40 mg per kilogram. A secondary efficacy analysis yielded similar (albeit lower) estimates. CIS43LS decreased the risk of infection, and there seemed to be a dose-dependent effect, with the incidence of infection starting to increase at approximately 90 days after the infusion of 10 mg per kilogram and at approximately 120 days after the infusion of 40 mg per kilogram.

No information on the incidence of clinical malaria is provided, because this was not a secondary end point. CIS43LS, by targeting *P. falciparum* sporozoites, the parasite stage transmitted by the vectors to humans, would primarily reduce the incidence of infections. Moreover, clinical malaria in this group of healthy volunteers would be less frequent than infection because they would have acquired substantial immunity against clinical disease owing to their lifelong exposure to malaria. Nevertheless, knowing the incidence of clinical malaria would have helped in understanding the effect that CIS43LS may have at the population level. Future trials should collect this in-

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formation; indeed, the phase 2 clinical trials currently ongoing in Mali (ClinicalTrials.gov number, NCT05304611) and Kenya (NCT05400655) on L9LS, a different monoclonal antibody against *P. falciparum* sporozoites, include the incidence of clinical malaria among the secondary end points.

The present trial provides proof of concept that monoclonal antibodies can protect against *P. falciparum* infection over a period of several months. Nevertheless, several issues should be resolved before monoclonal antibodies are included in the antimalarial arsenal. A major one is the route of administration, which for this trial was intravenous. It is difficult to conceive the large-scale implementation of an intervention administered as a single intravenous infusion of 100 ml over a period of 30 minutes. Subcutaneous administration would be easier to implement, but the volume that can be injected is limited. CIS43LS was vialed at a concentration of 100 mg per millimeter; for a target dose of 5 mg per kilogram, the volume for an adult would vary between 3 ml (60 kg) and 4 ml (80 kg) administered with different injections, each with a maximum volume of 2.5 ml.[4] In the ongoing trials, L9S is vialed at a higher concentration (150 mg per milliliter), thus requiring a lower volume to be injected.[5] Moreover, it is unclear what the cost of monoclonal antibodies would be, although an estimate of $50 per gram has been mentioned.[6]

Both CIS43LS and L9S target the same parasite stage as the malaria vaccines RTS,S/AS01 and R21/Matrix-M. The former vaccine, after its pilot implementation into the routine immunization system of three African countries, has recently been recommended for use by the World Health Organization.[7] The latter was recently tested in Burkina Faso in children; over a period of 2 years and after a booster dose, it had an efficacy of 78% against clinical malaria.[8] Moreover, combining RTS,S/AS01 with seasonal malaria chemoprevention decreased clinical malaria by approximately 60% as compared with seasonal malaria chemoprevention alone or RTS,S/AS01 alone, findings that support the concept that combining treatment and vaccine interventions translates into a larger effect than that obtained with each of the interventions alone.[9] Nevertheless, the initial supply of RTS,S/AS01 will probably be insufficient to meet the need.[10] The development of monoclonal antibodies such as CIS43LS and L9S should be seen within this context. They could be combined with drug-based interventions, such as seasonal malaria chemoprevention or mass drug-administration campaigns, or even with malaria vaccines because they could target different groups. Eventually, we will need as many interventions as possible to achieve the ambitious goal of malaria eradication.

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

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NEJM Evidence

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ORIGINAL ARTICLE

Computerized Games versus Crosswords Training in Mild Cognitive Impairment

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Abstract

BACKGROUND Mild cognitive impairment (MCI) increases the risk of dementia. The efficacy of cognitive training in patients with MCI is unclear.

METHODS In a two-site, single-blinded, 78-week trial, participants with MCI — stratified by age, severity (early/late MCI), and site — were randomly assigned to 12 weeks of intensive, home-based, computerized training with Web-based cognitive games or Web-based crossword puzzles, followed by six booster sessions. In mixed-model analyses, the primary outcome was change from baseline in the 11-item Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) score, a 70 point scale in which higher scores indicate greater cognitive impairment at 78 weeks, adjusted for baseline. Secondary outcomes included change from baseline in neuropsychological composite score, University of California San Diego Performance-Based Skills Assessment (functional outcome) score, and Functional Activities Questionnaire (functional outcome) score at 78 weeks, adjusted for baseline. Changes in hippocampal volume and cortical thickness on magnetic resonance imaging were assessed.

RESULTS Among 107 participants (n=51 [games]; n=56 [crosswords]), ADAS-Cog score worsened slightly for games and improved for crosswords at week 78 (least squares [LS] means difference, −1.44; 95% confidence interval [CI], −2.83 to −0.06; P=0.04). From baseline to week 78, mean ADAS-Cog score worsened for games (9.53 to 9.93) and improved for crosswords (9.59 to 8.61). The late MCI subgroup showed similar results (LS means difference, −2.45; SE, 0.89; 95% CI, −4.21 to −0.70). Among secondary outcomes, the Functional Activities Questionnaire score worsened more with games than with crosswords at week 78 (LS means difference, −1.08; 95% CI, −1.97 to −0.18). Other secondary outcomes showed no differences. Decreases in hippocampal volume and cortical thickness were greater for games than for crosswords (LS means difference, 34.07; SE, 17.12; 95% CI, 0.51 to 67.63 [hippocampal volume]; LS means difference, 0.02; SE, 0.01; 95% CI, 0.00 to 0.04 [cortical thickness]).

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EDITORIAL

Crossword Puzzles for Brain Training in Mild Cognitive Impairment

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Given the increasing prevalence and public health impact of dementia, it is imperative that we identify prevention strategies. One approach, broadly termed brain training, can be defined as guided drill-and-practice mental exercises targeting cognitive domains. We have evidence suggesting that brain training may prevent dementia in cognitively intact adults, including the well-validated protective effect of education early in life and the results of the ACTIVE (Advanced Cognitive Training for Independent and Vital Elderly) trial,[1] which showed not only a long-term cognitive benefit of training in processing speed but a possible decrease in dementia incidence and transfer of cognitive benefits to performance in everyday functioning (as measured by performance on instrumental activities of daily living). The benefits of brain training, however, are not as clear in mild cognitive impairment (MCI), which encompasses many persons with prodromal dementia. Meta-analyses suggest a moderate effect size (benefit) to some cognitive domains in MCI but smaller effect sizes to others.[2] Of most importance, many trials have studied in-person interventions (e.g., in the laboratory), which are inherently labor intensive. Remotely accessed computerized training is a better strategy for widespread dissemination. Thus, it remains an open question whether cognitive training can improve function in MCI.

This is the context for the COG-IT (Cognitive Training and Neuroplasticity in Mild Cognitive Impairment) trial, presented in this issue of *NEJM Evidence* by Devanand et al.[3] In a two-site, blinded, 78-week clinical trial, the authors compared the effectiveness of two computerized cognitive training interventions in 107 participants with MCI per the standard definition. Fifty-one participants were randomly assigned to play computerized games compared with 56 who were randomly assigned to do computerized crossword puzzles. The primary outcome was the Alzheimer's Disease Assessment Scale score. Secondary outcomes were a cognitive composite score, the University of California San Diego Performance-based Skills Assessment (primary functional outcome), the Functional Activities Questionnaire, and regional brain volumes. Cholinesterase inhibitors were allowed. The difficulty of the computerized games was scaled over time with the patient's performance, whereas crossword puzzles maintained medium difficulty without scaling over time. For the first 12 weeks, participants performed four 30-minute sessions weekly, plus booster sessions between 12 and 78 weeks, both at home and in the clinic. Adherence was monitored through computer sessions. Primary statistical analyses were linear mixed effects models comparing outcomes in participants randomly assigned to performing games versus crossword puzzles.

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The investigators hypothesized that a carefully curated selection of games would yield better results than crossword puzzles.[3] Instead, they found the opposite: scores on the Alzheimer's Disease Assessment Scale were superior at 12 weeks in the crossword puzzle group, and at 78 weeks had improved nearly 1 point in the crossword group versus a 0.4-point worsening in the games group. Whereas most secondary outcomes were roughly similar between treatment groups, function (as measured by using the University of California San Diego Performance-based Skills Assessment and the Functional Activities Questionnaire) and hippocampal volume were numerically better in the crossword puzzle group (although this trial was not powered to evaluate these secondary outcomes). The superiority of crossword puzzles was most apparent in the participants with late MCI. Adherence was good, and 12% to 17% of participants dropped out over 78 weeks, which points to good retention and, thus, relatively representative findings. Although the sample was racially and ethnically diverse, it was a highly educated sample, and future work will need to explore efficacy in those with less formal education.

These results[3] have practical everyday applications. First, it is gratifying to see cognitive improvement from computer-based cognitive training interventions that can be easily performed at home and that are inherently straightforward to disseminate. Second, it is helpful to have comparative effectiveness data in this field; there have been a wide variety of interventions evaluated, and it has not been clear which interventions stand out as practical and effective. In this regard, crossword puzzles are inherently attractive — they are already widely disseminated and can be obtained inexpensively or for free.

The results of Devanand et al.[3] raise important questions about the brain mechanisms underlying cognitive training. Hypotheses include compensatory neural scaffolding that supports networks during the acquisition of new skills,[4] activation of existing forms of cognitive reserve,[5] or cross-hemispheric recruitment.[6] At the level of large-scale networks, there is evidence that shows that visual speed of processing training results in greater central executive network connectivity in patients with amnestic MCI.[7]

Cognitive training can give patients and families a feeling of efficacy and empowerment in fighting the deleterious effects of early neurodegenerative disease in MCI, and this trial's demonstration of the efficacy of crossword puzzles can help patients right now.[3] Moreover, these results point the way to improved understanding of the underlying brain mechanisms to help develop precision interventions in the future.

Disclosures

Author disclosures are available at evidence.nejm.org.

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EDITORIAL

A 109-Year-Old Pastime Beats a High-Tech Teenager

Patrick Merrell[1]

Surprise! According to findings in the article entitled "Computerized Games versus Crosswords Training in Mild Cognitive Impairment," now published in *NEJM Evidence*,[1] solving crosswords had a more beneficial effect on older adults with mild cognitive impairment (MCI) than training with an array of Web-based brain games. The researchers had hypothesized just the opposite outcome, in part, on the basis of the findings of a 2015 study[2] involving cognitively intact participants of a greater age range (18–80 years of age in the earlier study vs. 55–95 years of age in the current study). Lumos Labs, creator of the Lumosity brain game website, funded the earlier research. It also provided the brain games and electronic crosswords for both studies.

The conclusion that crossword puzzles had a positive cognitive effect in the current report[1] is not a surprise to me. I know crosswords well. I've written 2000 of them over the past 22 years, the majority for the *New York Times* and *People* magazine (and one — so far — for *NEJM Evidence*) (Fig. 1). I've also created thousands of other word, visual, and logic puzzles, for both children and adults.

Puzzles are problems designed to be solved. They provide a bit of entertainment and make us feel smart in cracking them, although the level of challenge and engagement can vary widely. At the less taxing end are word search puzzles and mazes. Not much brainwork is needed to solve them. Crossword puzzles are at the opposite extreme.

I rate crosswords so highly because they offer such a rich experience. Vocabulary, lateral thinking, reading, spelling, recall, wordplay, humor, and a wide range of classic and current facts all come into play. Crossword solving also involves decoding skills, including being able to see word possibilities with only a few letters in place.

Lumosity's online brain games focus on specific skills, testing and training participants to complete narrowly defined tasks. Attractive graphics appear one after the other, or in continuous motion, and must be dealt with quickly. For example, "Train of Thought" has a series of tracks and switches, the goal being to route each train into a barn of the same color. Altogether, 18 game modules were used in the study,[1] offering a variety of challenges that reward greater accuracy and faster performance with higher scores.

So, what accounts for the success of crosswords in the current study[1] and for brain games previously?[2] I'll get to that in a moment but first a brief story.

The author affiliation is listed at the end of the article.

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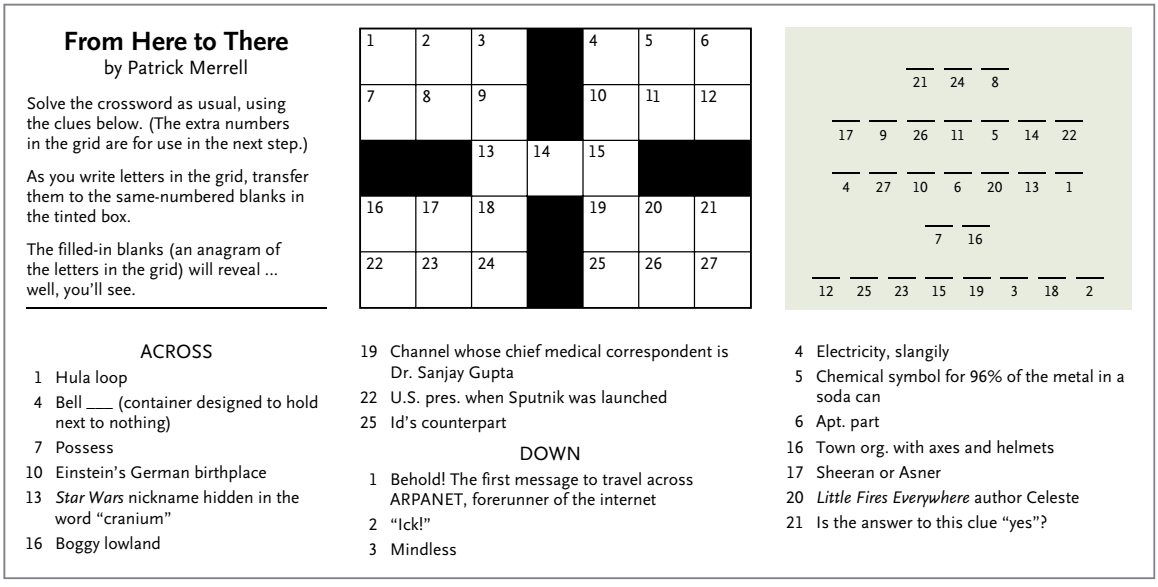

From Here to There
by Patrick Merrell

Solve the crossword as usual, using the clues below. (The extra numbers in the grid are for use in the next step.)

As you write letters in the grid, transfer them to the same-numbered blanks in the tinted box.

The filled-in blanks (an anagram of the letters in the grid) will reveal ... well, you'll see.

1	2	3	■	4	5	6
7	8	9	■	10	11	12
■	■	13	14	15	■	■
16	17	18	■	19	20	21
22	23	24	■	25	26	27

			21	24	8		
17	9	26	11	5	14	22	
4	27	10	6	20	13	1	
			7	16			
12	25	23	15	19	3	18	2

ACROSS

1 Hula loop
4 Bell ___ (container designed to hold next to nothing)
7 Possess
10 Einstein's German birthplace
13 *Star Wars* nickname hidden in the word "cranium"
16 Boggy lowland
19 Channel whose chief medical correspondent is Dr. Sanjay Gupta
22 U.S. pres. when Sputnik was launched
25 Id's counterpart

DOWN

1 Behold! The first message to travel across ARPANET, forerunner of the internet
2 "Ick!"
3 Mindless
4 Electricity, slangily
5 Chemical symbol for 96% of the metal in a soda can
6 Apt. part
16 Town org. with axes and helmets
17 Sheeran or Asner
20 *Little Fires Everywhere* author Celeste
21 Is the answer to this clue "yes"?

Figure 1. Crossword.

In 2001, I underwent intensive chemotherapy and, by the end of it, I'd developed a good case of what's called "chemo brain." I had trouble following telephone conversations, and multi-step tasks were challenging. A few months earlier, I'd been a strong crossword solver, but I found myself unable to finish anything beyond an easy puzzle.

Chemo brain is common, typically lasting 9 to 12 months, sometimes less, other times years. My approach in trying to reverse it was far from common, though. Determined to prove I still had it, I went into writing crosswords with a vengeance. Puzzle writing is a consuming mental workout, like puzzle solving on steroids — and it seemed to do the trick. Several months later, my brain fog had completely lifted and, as a bonus, I'd come up with four good crosswords, three of which I sold to the *New York Times*.

Did crosswords make a difference in my recovery or in speeding it along? Who knows, but it sure felt that way to me. And it's because of that that I'm particularly interested in what this latest research suggests.

Looking at the data from the current study,[1] crosswords had a beneficial effect by nearly every measure. And by every measure, crosswords performed better than the brain games. That's quite an outcome when you consider that crosswords were intended to be a baseline against which the brain games would be judged. The supporting actor upstaged the star!

I kept wishing a control group had been involved, receiving neither brain games nor crosswords. As there wasn't one, we can only compare the two activities against each other, and it can be a bit misleading. For example, at the end of the 78-week study, Alzheimer's Disease Assessment Scale–Cognitive subscale scores were 0.4 point worse for brain game players compared with baseline, and 0.98 point better for crossword solvers, a difference of 1.38. But how would a control group have scored? Let's say that group's score had worsened by one point, a modest prediction. Judged against that, brain games would have helped slightly in limiting cognitive decline, improving scores by 0.6 point. Crosswords would do even better, notching a gain of 1.98 points, three times that of brain games.

Finally, let's look at that 10-week 2015 study,[2] the results of which were reanalyzed in a 2021 peer-reviewed publication.[3] The age range was broad (participants were 18–80 years of age), and they were all cognitively intact. Either of those factors could be important, but there are two issues with the study that stand out. First is the risk of inadvertent experimenter or publication bias. Lumos Labs not only funded the project, but its stock-holding employees designed and implemented the study. Other employees offered input, including

with the published manuscript. Second, 52.5% of the original 9919 participants were not included in the final results; 49.1% of them dropped out along the way. Were those people who were lost to follow-up doing well with the brain games, or were they struggling and/or uninterested, which might have affected the results? We just don't know.

This is important work that could result in quality-of-life improvements for many people. Several intriguing questions have been raised by the current study,[1] and I wonder if additional research focusing solely on crosswords, as well as a few other types of word puzzles, might show that they can strengthen our minds.

Disclosures

Author disclosures are available at evidence.nejm.org.

Author Affiliation

[1] Patrick Merrell is a freelance puzzle maker, graphic artist, writer, illustrator, cartoonist (including as one of MAD magazine's "Usual Gang of Idiots"), and photographer — all in about equal doses.

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IN DEPTH

Climate Change and Extreme Heat Events: How Health Systems Should Prepare

Lisa Patel, MD, MESc, Kathryn C. Conlon, MPH, PhD, Cecilia Sorensen, MD, Samia McEachin, Kari Nadeau, MD, PhD, Khyati Kakkad, MD, Kenneth W. Kizer, MD, MPH

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Earth's warming climate is causing heat waves to become more frequent, longer lasting, and hotter, while occurring in locations unaccustomed to such weather events. Extreme heat events (EHEs), such as those in the western United States, India, Pakistan, Central Europe, and other locations in recent years, are one of the deadliest consequences of climate change. EHEs cause excess morbidity and mortality directly from heat illness, aggravation of comorbid conditions, and exacerbation of the damaging health effects of social factors as well as indirectly from corollary events such as wildfires and air pollution. Climate change–related EHEs are projected to worsen for at least the next 3 decades, necessitating that health systems be prepared to meet a growing burden of heat-related illnesses and become more heat resilient, as well as to reduce health care–related climate impacts. In this article, the authors discuss the health effects of EHEs and provide illustrative examples of what health systems can do to promote climate readiness and heat resiliency.

The United Nations Intergovernmental Panel on Climate Change (IPCC) reported in 2021 that human activity had increased Earth's temperature by 1.1°C since 1900, and warned that it will unalterably reach 1.5°C above 1900 levels in less than 20 years, causing devastating impacts on human health.[1] Without the rapid reduction of greenhouse gas emissions, global warming will rise more than 1.5°C and have catastrophic consequences for humanity.

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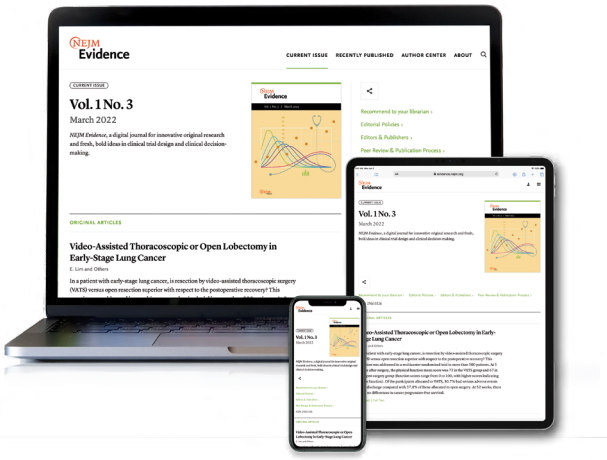

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