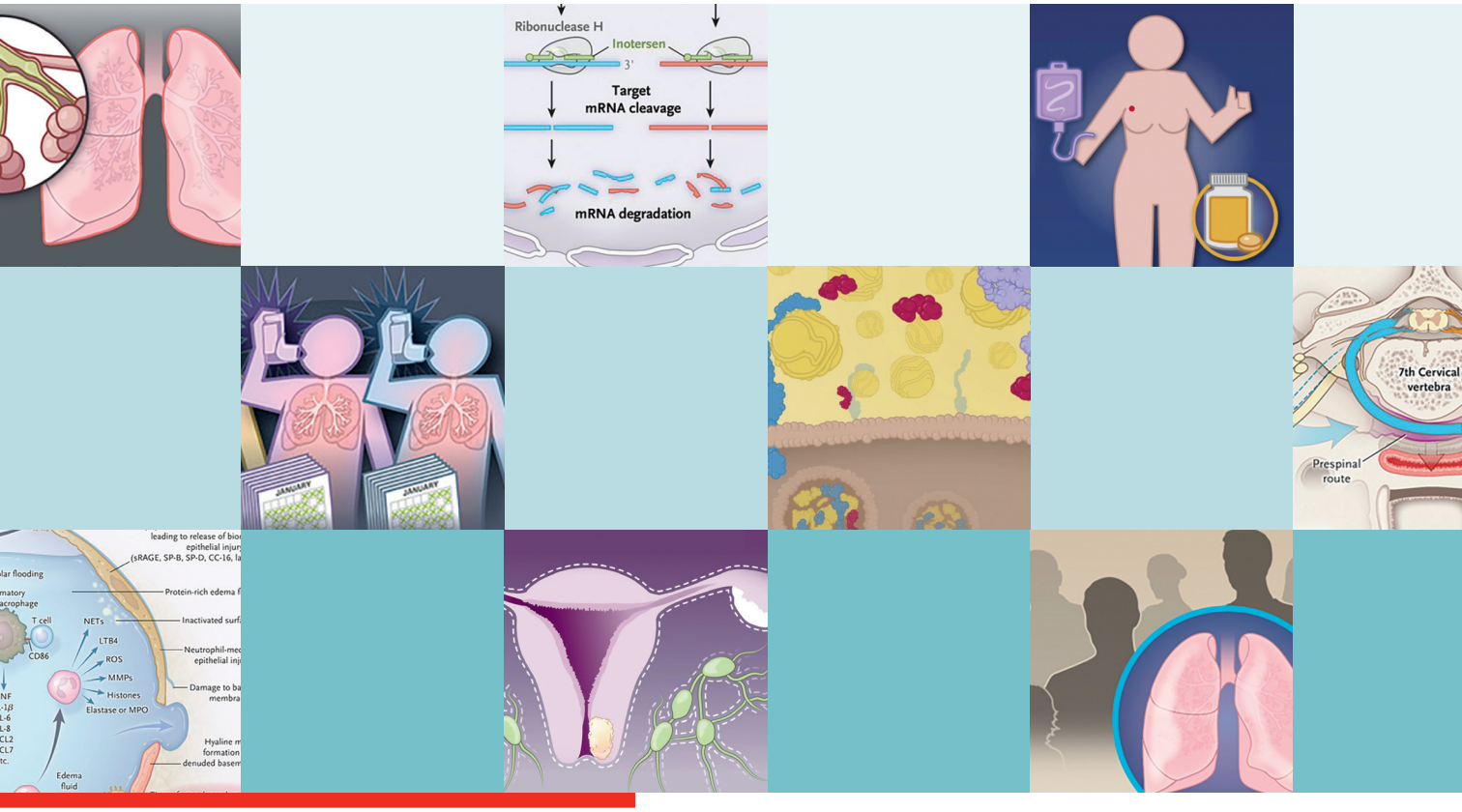
The NEW ENGLAND JOURNAL of MEDICINE



Notable Articles of 2018

A collection of articles selected by NEJM editors

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The NEW ENGLAND JOURNAL of MEDICINE

January 2019

Dear Reader,

Medicine is always changing and 2018 was no exception. Although many of the articles that were published in the *Journal* changed the way we *think* about certain things that we do, sometimes, when the evidence is strong enough, we even change what we do. Understanding these "game changers" is critical to staying at the cutting edge of medicine. Here are a few such pieces from 2018.

For a large fraction of our professional lives, we have been telling patients who suffered from a prior major cardiovascular event, such as myocardial infarction or stroke, that daily ingestion of about 82 mg of aspirin a day could help protect against further events. Since the intervention was perceived to have few side effects, many of us advised previously healthy older adults to take a daily low-dose aspirin to protect against cardiovascular disease. This daily regimen was inexpensive, low-risk — or so we thought — and appeared to provide a benefit. But a trio of studies published last September found that a daily aspirin doesn't do much good, and may even cause harm.

Peanut allergy is another diagnosis where we were compelled to shift our mindset. For decades, the advice, once the allergy was confirmed, was to stay away from peanuts for the rest of your life. It was possible to desensitize people, but the procedures are difficult and entail substantial risk. However, the PALISADE trial, published in November, described a new peanut oral immunotherapy that, when introduced to patients with peanut allergy, could desensitize children and adolescents who were highly allergic to peanuts. Although there were side effects, the use of a highly refined and standardized peanut allergen provided a reasonable margin of safety.

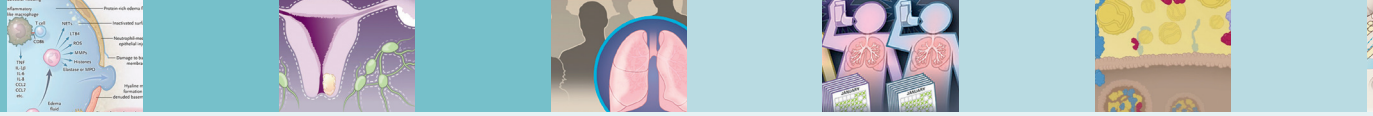
In this year's Notable Articles collection, we have gathered 12 articles that we believe had an impact on medicine. They include the studies on peanut allergy and aspirin, as well as a study on the first RNAi therapeutic for transthyretin amyloidosis, a disease where no therapy previously existed, and a trial on a new drug combination for cystic fibrosis that represents a major breakthrough, with the potential to improve quality of life and possibly survival in all patients who carry the most common CFTR mutation.

Among all papers published in 2018, this "most notable" collection was selected by the editors as being the most meaningful in improving medical practice and patient care. As always, we hope that you will take valuable insights from these articles.

Sincerely,

Jeffrey M. Drazen, M.D.
Editor-in-Chief, The New England Journal of Medicine

800.843.6356 | F: 781.891.1995 | NEJMGROUP@MMS.ORG
860 WINTER STREET, WALTHAM, MA 02451-1413
NEJMGROUP.ORG



Notable Articles of 2018

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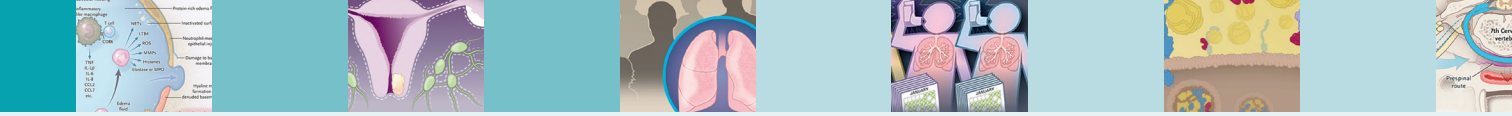

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ORIGINAL ARTICLE

Trial of Contralateral Seventh Cervical Nerve Transfer for Spastic Arm Paralysis

Mou-Xiong Zheng, M.D., Ph.D., Xu-Yun Hua, M.D., Ph.D., Jun-Tao Feng, M.D., Tie Li, M.D., Ph.D., Ye-Chen Lu, M.D., Yun-Dong Shen, M.D., Ph.D., Xiao-Hua Cao, Ph.D., Nai-Qing Zhao, M.S., Jia-Ying Lyu, B.S., Jian-Guang Xu, M.D., Ph.D., Yu-Dong Gu, M.D., and Wen-Dong Xu, M.D., Ph.D.

ABSTRACT

BACKGROUND

Spastic limb paralysis due to injury to a cerebral hemisphere can cause long-term disability. We investigated the effect of grafting the contralateral C7 nerve from the nonparalyzed side to the paralyzed side in patients with spastic arm paralysis due to chronic cerebral injury.

METHODS

We randomly assigned 36 patients who had had unilateral arm paralysis for more than 5 years to undergo C7 nerve transfer plus rehabilitation (18 patients) or to undergo rehabilitation alone (18 patients). The primary outcome was the change from baseline to month 12 in the total score on the Fugl–Meyer upper-extremity scale (scores range from 0 to 66, with higher scores indicating better function).

RESULTS

The mean increase in Fugl–Meyer score in the paralyzed arm was 17.7 in the surgery group and 2.6 in the control group (difference, 15.1; 95% confidence interval, 12.2 to 17.9; P<0.001). With regard to improvements in spasticity as measured on the Modified Ashworth Scale (an assessment of five joints, each scored from 0 to 5, with higher scores indicating more spasticity), the smallest between-group difference was in the thumb, with 6, 9, and 3 patients in the surgery group having a 2-unit improvement, a 1-unit improvement, or no change, respectively, as compared with 1, 6, and 7 patients in the control group (P=0.02). Transcranial magnetic stimulation and functional imaging showed connectivity between the ipsilateral hemisphere and the paralyzed arm. There were no significant differences from baseline to month 12 in power, tactile threshold, or two-point discrimination in the hand on the side of the donor graft.

CONCLUSIONS

In this single-center trial involving patients who had had unilateral arm paralysis due to chronic cerebral injury for more than 5 years, transfer of the C7 nerve from the nonparalyzed side to the side of the arm that was paralyzed was associated with a greater improvement in function and reduction of spasticity than rehabilitation alone over a period of 12 months. Physiological connectivity developed between the ipsilateral cerebral hemisphere and the paralyzed hand. (Funded by the National Natural Science Foundation of China and others; Chinese Clinical Trial Registry number, 13004466.)

From the Department of Hand Surgery, Huashan Hospital (M.-X.Z., X.-Y.H., J.-T.F., T.L., Y.-C.L., Y.-D.S., J.-G.X., Y.-D.G., W.-D.X.), the National Clinical Research Center for Aging and Medicine (M.-X.Z., X.-Y.H., J.-T.F., T.L., Y.-C.L., Y.-D.S., J.-G.X., Y.-D.G., W.-D.X.), Department of Biostatistics, School of Public Health (N.-Q.Z., J.-Y.L.), and State Key Laboratory of Medical Neurobiology (W.-D.X.), Fudan University, the Key Laboratory of Hand Reconstruction, Ministry of Health (M.-X.Z., X.-Y.H., J.-T.F., T.L., Y.-C.L., Y.-D.S., J.-G.X., Y.-D.G., W.-D.X.), the Shanghai Key Laboratory of Peripheral Nerve and Microsurgery (M.-X.Z., X.-Y.H., J.-T.F., T.L., Y.-C.L., Y.-D.S., J.-G.X., Y.-D.G., W.-D.X.), the Department of Hand and Upper Extremity Surgery, Jing'an District Central Hospital (M.-X.Z., X.-Y.H., J.-T.F., T.L., Y.-C.L., Y.-D.S., W.-D.X.), and the Key Laboratory of Brain Functional Genomics (Ministry of Education) and Shanghai Key Laboratory of Brain Functional Genomics, East China Normal University (X.-H.C.) — all in Shanghai, China. Address reprint requests to Dr. Xu at the Department of Hand Surgery, Huashan Hospital, Fudan University, No. 12 Middle Wulumuqi Rd., Shanghai 200040, China, or at wendongxu@fudan.edu.cn.

Drs. Zheng, Hua, Feng, Li, and Lu contributed equally to this article.

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EDITORIAL

Rewiring to Regain Function in Patients with Spastic Hemiplegia

Robert J. Spinner, M.D., Alexander Y. Shin, M.D., and Allen T. Bishop, M.D.

Spastic hemiplegia results from several relatively common disorders, including stroke, traumatic brain injury, and cerebral palsy. Frequently, upper-limb function is impaired. In this issue of the *Journal*, Zheng et al.[1] report a new approach to the treatment of this condition: the use of a contralateral C7 nerve transfer from the nonparalyzed side to the paralyzed side in order to engage the unimpaired cerebral hemisphere.

Nerve transfers have long been performed as treatment for lesions affecting the lower motor neurons, mostly involving the brachial plexus. Gu and colleagues at Huashan Hospital, Fudan University, in Shanghai have pioneered nerve transfers, particularly those in which contralateral C7 and phrenic nerves are used as donor nerves for injuries to the brachial plexus.[2,3] They showed that the contralateral C7 nerve could be sacrificed with few if any long-term adverse effects and that the procedure could result in useful recovery of distal hand function.[4,5] The distance for nerve regeneration from the contralateral side of the neck to the opposite distal limb has been shortened by modifications in transposition techniques. Studies of brain plasticity in patients who have undergone surgery led to observations of cortical reorganization and bilateral motor-cortex control.[6,7] Despite these advances, contralateral C7 nerve transfer in adults with injuries to the brachial plexus remains controversial because of the risk–benefit ratio and the inherent challenges of the long distance and time needed for regeneration (estimated to occur at a rate of an inch per month) and the degree of cortical reorganization required.

Nerve transfers are now being introduced for patients with upper-limb paralysis resulting from injuries to the upper motor neurons — most often injuries to the spinal cord but also cerebral injuries. For example, a 4-year-old with cerebral palsy who was treated by the Huashan group with contralateral C7 nerve transfer to the middle trunk of the brachial plexus had some alleviation of spasticity and increased strength.[8] This technique was then demonstrated in a small trial involving six adult patients with hemiplegia,[9] which set the stage for the current, larger trial.

Zheng et al. report a prospective, randomized, controlled trial involving patients with severe spastic hemiparesis (but not hemiplegia) whose neurologic condition had plateaued after 5 years of rehabilitation. Magnetic resonance imaging (MRI) of the head revealed isolated injury to the brain hemisphere contralateral to the paralyzed hand, and transcranial magnetic stimulation was used to document exclusive control of the affected limb by the ipsilesional (contralateral) hemisphere. The 18 patients in the surgery group underwent a direct neurorrhaphy (i.e., suturing of cut nerves) of the contralateral C7 nerve to the C7 nerve on the paralyzed side through a prespinal route and then received rehabilitation therapy. A group of 18 matched control patients received rehabilitation therapy only.

Patients who underwent the surgery had only transient neurologic sequelae from the sectioning of the C7 nerve contralateral to the paralysis and had significantly greater improvement in the paralyzed limb, as measured on the Fugl–Meyer (motor recovery) and Modified Ashworth Scale (spasticity) scales at 12 months as compared

with baseline, than did patients in the control group. Physiological connectivity was shown between the ipsilateral cerebral hemisphere and the paralyzed hand in the surgery group by means of electrophysiological testing, transcranial magnetic stimulation of the cortex, and functional MRI.

In our opinion, the results of the trial are exciting but need clarification and confirmation. The time frame for improvement is the major question: that distal muscles are functionally reinnervated in such a short time seems unlikely to us. An alternative hypothesis to explain the functional improvement is that there was reduction in spasticity caused by the C7 neurotomy on the paralyzed side: the neurotomy may have led to a reduction in limb spasticity and improved function through the normal motor pathways of the C5, C6, C8, and T1 nerves, and the effect may have been augmented by rehabilitation. The C7 neurotomy itself, associated with an immediate reduction in spasticity, represents a major advance for some patients with brain injury who have poor function and spasticity. A reduction in spasticity may also result in improved efficacy of the damaged motor cortex, an effect that may be enhanced by ongoing physical therapy. An improvement in function at 10 months cannot be readily explained as being predominantly a result of the contralateral nerve transfer, because nerves do not regenerate that quickly, fully, or consistently. Another trial from these investigators involving patients with brachial plexus injury with 6.9 years of follow-up showed that 49% of patients had motor recovery.[10] The presence of physiological connectivity observed in the trials does not necessarily equate with functional recovery.

Future studies of contralateral C7 nerve transposition in hemiplegic patients should include a group in which the patients undergo C7 neurotomy alone (i.e., without the nerve transfer) along with rehabilitation. Because of the high volume for this type of procedure at Huashan Hospital, the results obtained by these surgeons may not be easy to reproduce elsewhere. These surgeons are currently hosting workshops to train others in their techniques. Factors other than technical ones, including differences in body-mass index and limb length across different populations, may lead to different surgical outcomes.

The creative use of a strategy involving the peripheral nervous system, whether a nerve transfer or a neurotomy, for problems with the central nervous system represents a fresh approach and provides opportunities for insights into basic neuroanatomy and neurophysiology. Future research will need to address other ways to optimize physiological change — to enhance or speed up nerve regeneration, improve plasticity, and maximize rehabilitation.

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

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From the Mayo Clinic, Departments of Neurologic Surgery and Orthopedics, Division of Hand Surgery, Rochester, MN.

1. Zheng M-X, Hua X-Y, Feng J-T, et al. Trial of contralateral seventh cervical nerve transfer for spastic arm paralysis. N Engl J Med 2018;378:22-34.
2. Chen L, Gu YD. An experimental study of the treatment of root avulsion of brachial plexus using contralateral C7 nerve neurotization (nerve transfer). Zhonghua Wai Ke Za Zhi 1992;30:525-527, 570-1. (In Chinese.)
3. Gu YD, Zhang GM, Chen DS, Yan JG, Cheng XM, Chen L. Seventh cervical nerve root transfer from the contralateral healthy side for treatment of brachial plexus root avulsion. J Hand Surg Br 1992;17:518-21.
4. Gu YD, Chen DS, Zhang GM, et al. Long-term functional results of contralateral C7 transfer. J Reconstr Microsurg 1998;14:57-9.
5. Gu YD. Contralateral C7 root transfer over the last 20 years in China. Chin Med J (Engl) 2007;120:1123-6.
6. Jiang S, Li ZY, Hua XY, Xu WD, Xu JG, Gu YD. Reorganization in motor cortex after brachial plexus avulsion injury and repair with the contralateral C7 root transfer in rats. Microsurgery 2010;30:314-20.
7. Hua XY, Zuo CT, Xu WD, et al. Reversion of transcallosal interhemispheric neuronal inhibition on motor cortex after contralateral C7 neurotization. Clin Neurol Neurosurg 2012;114:1035-8.
8. Xu WD, Hua XY, Zheng MX, Xu JG, Gu YD. Contralateral C7 nerve root transfer in treatment of cerebral palsy in a child: case report. Microsurgery 2011;31:404-8.
9. Hua XY, Qiu YQ, Li T, et al. Contralateral peripheral neurotization for hemiplegic upper extremity after central neurologic injury. Neurosurgery 2015;76:187-95.
10. Gao KM, Lao J, Zhao X, Gu YD. Outcome of contralateral C7 nerve transferring to median nerve. Chin Med J (Engl) 2013;126:3865-8.

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ORIGINAL ARTICLE

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot, M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes, K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*

ABSTRACT

BACKGROUND

Whether hydrocortisone reduces mortality among patients with septic shock is unclear.

METHODS

We randomly assigned patients with septic shock who were undergoing mechanical ventilation to receive hydrocortisone (at a dose of 200 mg per day) or placebo for 7 days or until death or discharge from the intensive care unit (ICU), whichever came first. The primary outcome was death from any cause at 90 days.

RESULTS

From March 2013 through April 2017, a total of 3800 patients underwent randomization. Status with respect to the primary outcome was ascertained in 3658 patients (1832 of whom had been assigned to the hydrocortisone group and 1826 to the placebo group). At 90 days, 511 patients (27.9%) in the hydrocortisone group and 526 (28.8%) in the placebo group had died (odds ratio, 0.95; 95% confidence interval [CI], 0.82 to 1.10; P=0.50). The effect of the trial regimen was similar in six prespecified subgroups. Patients who had been assigned to receive hydrocortisone had faster resolution of shock than those assigned to the placebo group (median duration, 3 days [interquartile range, 2 to 5] vs. 4 days [interquartile range, 2 to 9]; hazard ratio, 1.32; 95% CI, 1.23 to 1.41; P<0.001). Patients in the hydrocortisone group had a shorter duration of the initial episode of mechanical ventilation than those in the placebo group (median, 6 days [interquartile range, 3 to 18] vs. 7 days [interquartile range, 3 to 24]; hazard ratio, 1.13; 95% CI, 1.05 to 1.22; P<0.001), but taking into account episodes of recurrence of ventilation, there were no significant differences in the number of days alive and free from mechanical ventilation. Fewer patients in the hydrocortisone group than in the placebo group received a blood transfusion (37.0% vs. 41.7%; odds ratio, 0.82; 95% CI, 0.72 to 0.94; P=0.004). There were no significant between-group differences with respect to mortality at 28 days, the rate of recurrence of shock, the number of days alive and out of the ICU, the number of days alive and out of the hospital, the recurrence of mechanical ventilation, the rate of renal-replacement therapy, and the incidence of new-onset bacteremia or fungemia.

CONCLUSIONS

Among patients with septic shock undergoing mechanical ventilation, a continuous infusion of hydrocortisone did not result in lower 90-day mortality than placebo. (Funded by the National Health and Medical Research Council of Australia and others; ADRENAL ClinicalTrials.gov number, NCT01448109.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Venkatesh at the Department of Intensive Care, Wesley Hospital, 451 Coronation Dr., Auchenflower, Brisbane, QLD 4066, Australia, or at bvenkatesh@georgeinstitute.org.au.

*A full list of investigators in the ADRENAL Trial is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIAL

A Role for Hydrocortisone Therapy in Septic Shock?

Anthony F. Suffredini, M.D.

One of the first double-blind, multicenter trials of hydrocortisone in the management of severe infections involved 194 patients and was reported in 1963.[1] The authors noted that "the role of adrenocorticosteroids in the management of infectious diseases has been a subject of much controversy."[1] Although "corticosteroids depress resistance to infection by reducing inflammation . . . corticosteroids have been shown . . . to be antiendotoxic and antipyretic, and to influence vascular reactivity in a manner that might conceivably be beneficial to the infected individual." Nevertheless, the authors found that low-dose hydrocortisone did not improve the 44% overall mortality among these patients.

During the past half century, the manifestations of serious infections that result in syndromes of sepsis and septic shock have become well defined. Multiple randomized, controlled trials of varying rigor have assessed the benefits and risks of corticosteroid therapy in sepsis and septic shock, with doses that ranged from stress doses (200 to 300 mg of hydrocortisone per day for 5 to 7 days) to pharmacologic doses that were 10 to 40 times as great as stress doses and were given over a period of 1 or 2 days. The high-dose regimens were abandoned because of worse outcomes.[2]

Meta-analyses and systematic reviews have reached conflicting conclusions from the small trials conducted during the past five decades. One systematic review summarized the effects of corticosteroids in 33 randomized, controlled trials in sepsis (involving 4268 total participants) and concluded that low-dose corticosteroids (22 trials) reduced 28-day mortality, increased shock reversal, and reduced organ injury scores.[3] In contrast, another systematic review (35 trials of sepsis and septic shock, involving 4682 patients) concluded that the majority of trials had a high risk of bias and were underpowered and overall did not detect a beneficial effect of high-dose or low-dose corticosteroids in septic shock.[4]

Thus, the recent completion of two large, randomized, blinded, multicenter, controlled trials of low-dose corticosteroids in gravely ill patients with septic shock has been eagerly anticipated to confirm or refute the effects described in previous studies. Reported in this issue of the *Journal*, the Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial[5] and the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial[6] are landmark studies describing the largest comprehensive analyses of hydrocortisone effects in critically ill medical and surgical patients with septic shock. The size of the trials (>5000 combined patients) dwarfs all the previous controlled trials. Entry criteria for both studies had clear definitions of vasopressor-dependent shock and respiratory failure leading to the use of mechanical ventilation, details of antimicrobial therapy, assessment of survival at 90 days, and well-defined secondary outcomes and analyses of adverse events.

The thoughtful reader may ask, How can the 90-day mortality in these two studies differ so dramatically (ADRENAL trial, 27.9% with hydrocortisone and 28.8% with placebo [$P=0.50$]; APROCCHSS trial, 43.0% with hydrocortisone plus fludrocortisone vs. 49.1% with placebo [$P=0.03$])? The severity-of-illness scores that were

used at entry in the ADRENAL trial (score on the Acute Physiology and Chronic Health Evaluation II) and the APROCCHSS trial (score on the Sequential Organ Failure Assessment and the Simplified Acute Physiology Score II) highlight the high-risk populations studied but are not directly comparable. The mortality in the control group in the APROCCHSS trial suggests a more seriously ill patient population. What other differences might contribute to these divergent outcomes? Oral fludrocortisone was used in the APROCCHSS trial, yet a previous study had shown that its effects in septic shock were not different from those of hydrocortisone alone.[7] As compared with the participants in the APROCCHSS trial, the participants in the ADRENAL trial had a higher rate of surgical admissions (31.5% vs. 18.3%); a lower rate of renal-replacement therapy (12.7% vs 27.6%); lower rates of blood infection (17.3% vs. 36.6%), pulmonary infection (35.2% vs. 59.4%), and urinary tract infection (7.5% vs. 17.7%); and a higher rate of abdominal infection (25.5% vs. 11.5%). For secondary outcomes, both trials showed improved resolution of shock and more rapid cessation of mechanical ventilation. Rates of serious adverse events, beyond hyperglycemia with bolus glucocorticoid doses, were low.

Previous experimental and clinical studies of antiinflammatory therapies have suggested that their benefit may be dependent on the risk of death that exists at the time of treatment initiation.[8] Similarly, an earlier analysis of low-dose corticosteroids in sepsis and septic shock suggested that their benefit may be dependent on the risk of death, and this was apparent only in more severely ill patients.[2] A patient-level analysis of outcome that was adjusted for illness severity and other potential confounders across both the ADRENAL and APROCCHSS trials may provide further insight into the relevance of this relationship.

Will these two trials change clinical practice? Although 90-day survival differed between the studies, both showed the beneficial effects of hydrocortisone on secondary outcomes of shock reversal and the duration of mechanical ventilation. It is unlikely that in the near future sufficiently powered trials will provide us with better data. Thus, clinicians will have to use these data and subsequent meta-analyses to decide how best to treat patients with septic shock. Estimating 90-day mortality at the bedside is not practical. It is likely that some practitioners caring for a patient with a deteriorating condition who is receiving escalating doses of vasopressors, in whom other core interventions have been instituted (i.e., appropriate antibiotics and adequate volume resuscitation and source control), will consider that the short-term benefits of low-dose hydrocortisone may exceed any risks (e.g., antiinflammatory effects) as an added therapy in selected patients.

The opinions expressed in this editorial are those of the author and do not represent any position or policy of the National Institutes of Health, the U.S. Department of Health and Human Services, or the U.S. government.

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

From the Critical Care Medicine Department, Clinical Center, National Institutes of Health, Bethesda, MD.

1. The Cooperative Study Group. The effectiveness of hydrocortisone in the management of severe infections. JAMA 1963;183:462-5.
2. Minneci PC, Deans KJ, Eichacker PQ, Natanson C. The effects of steroids during sepsis depend on dose and severity of illness: an updated meta-analysis. Clin Microbiol Infect 2009;15:308-18.
3. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for treating sepsis. Cochrane Database Syst Rev 2015;12:CD002243.
4. Volbeda M, Wetterslev J, Gluud C, Zijlstra JG, van der Horst IC, Keus F. Glucocorticosteroids for sepsis: systematic review with meta-analysis and trial sequential analysis. Intensive Care Med 2015;41:1220-34.
5. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med 2018;378:797-808.
6. Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med 2018;378:809-18.
7. The COIITSS Study Investigators. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. JAMA 2010;303:341-8.
8. Eichacker PQ, Parent C, Kalil A, et al. Risk and the efficacy of antiinflammatory agents: retrospective and confirmatory studies of sepsis. Am J Respir Crit Care Med 2002;166:1197-205.

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ORIGINAL ARTICLE

As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma

Eric D. Bateman, M.D., Helen K. Reddel, M.B., B.S., Ph.D., Paul M. O'Byrne, M.B., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Agnieszka Siwek-Posluszna, M.D., and J. Mark FitzGerald, M.D.

ABSTRACT

BACKGROUND

Patients with mild asthma often rely on inhaled short-acting β_2-agonists for symptom relief and have poor adherence to maintenance therapy. Another approach might be for patients to receive a fast-acting reliever plus an inhaled glucocorticoid component on an as-needed basis to address symptoms and exacerbation risk.

METHODS

We conducted a 52-week, double-blind, multicenter trial involving patients 12 years of age or older who had mild asthma and were eligible for treatment with regular inhaled glucocorticoids. Patients were randomly assigned to receive twice-daily placebo plus budesonide–formoterol (200 μg of budesonide and 6 μg of formoterol) used as needed or budesonide maintenance therapy with twice-daily budesonide (200 μg) plus terbutaline (0.5 mg) used as needed. The primary analysis compared budesonide–formoterol used as needed with budesonide maintenance therapy with regard to the annualized rate of severe exacerbations, with a prespecified noninferiority limit of 1.2. Symptoms were assessed according to scores on the Asthma Control Questionnaire–5 (ACQ-5) on a scale from 0 (no impairment) to 6 (maximum impairment).

RESULTS

A total of 4215 patients underwent randomization, and 4176 (2089 in the budesonide–formoterol group and 2087 in the budesonide maintenance group) were included in the full analysis set. Budesonide–formoterol used as needed was noninferior to budesonide maintenance therapy for severe exacerbations; the annualized rate of severe exacerbations was 0.11 (95% confidence interval [CI], 0.10 to 0.13) and 0.12 (95% CI, 0.10 to 0.14), respectively (rate ratio, 0.97; upper one-sided 95% confidence limit, 1.16). The median daily metered dose of inhaled glucocorticoid was lower in the budesonide–formoterol group (66 μg) than in the budesonide maintenance group (267 μg). The time to the first exacerbation was similar in the two groups (hazard ratio, 0.96; 95% CI, 0.78 to 1.17). The change in ACQ-5 score showed a difference of 0.11 units (95% CI, 0.07 to 0.15) in favor of budesonide maintenance therapy.

CONCLUSIONS

In patients with mild asthma, budesonide–formoterol used as needed was noninferior to twice-daily budesonide with respect to the rate of severe asthma exacerbations during 52 weeks of treatment but was inferior in controlling symptoms. Patients in the budesonide–formoterol group had approximately one quarter of the inhaled glucocorticoid exposure of those in the budesonide maintenance group. (Funded by AstraZeneca; SYGMA 2 ClinicalTrials.gov number, NCT02224157.)

From the Division of Pulmonology, Department of Medicine, University of Cape Town, Cape Town, South Africa (E.D.B.); Woolcock Institute of Medical Research, University of Sydney, Sydney (H.K.R.); Firestone Institute for Respiratory Health, St. Joseph's Healthcare and Department of Medicine, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, ON (P.M.O.), and the Institute for Heart and Lung Health, University of British Columbia, Vancouver (J.M.F.) — both in Canada; Airway Disease Section, National Heart and Lung Institute, Imperial College, London (P.J.B.); State Key Laboratory of Respiratory Diseases, First Affiliated Hospital, Guangzhou Medical University, Guangzhou, China (N.Z.); AstraZeneca Research and Development, Gothenburg, Sweden (C.K., C.J.); AstraZeneca Research and Development, Barcelona (R.L.); and AstraZeneca Research and Development, Warsaw, Poland (A.S.-P.). Address reprint requests to Dr. Bateman at the University of Cape Town Lung Institute, George St., Cape Town 7700, South Africa, or at eric.bateman@uct.ac.za.

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ORIGINAL ARTICLE

Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome

A. Combes, D. Hajage, G. Capellier, A. Demoule, S. Lavoué, C. Guervilly, D. Da Silva, L. Zafrani, P. Tirot, B. Veber, E. Maury, B. Levy, Y. Cohen, C. Richard, P. Kalfon, L. Bouadma, H. Mehdaoui, G. Beduneau, G. Lebreton, L. Brochard, N.D. Ferguson, E. Fan, A.S. Slutsky, D. Brodie, and A. Mercat, for the EOLIA Trial Group, REVA, and ECMONet*

ABSTRACT

BACKGROUND

The efficacy of venovenous extracorporeal membrane oxygenation (ECMO) in patients with severe acute respiratory distress syndrome (ARDS) remains controversial.

METHODS

In an international clinical trial, we randomly assigned patients with very severe ARDS, as indicated by one of three criteria — a ratio of partial pressure of arterial oxygen (Pao_2) to the fraction of inspired oxygen (Fio_2) of less than 50 mm Hg for more than 3 hours; a Pao_2:Fio_2 of less than 80 mm Hg for more than 6 hours; or an arterial blood pH of less than 7.25 with a partial pressure of arterial carbon dioxide of at least 60 mm Hg for more than 6 hours — to receive immediate venovenous ECMO (ECMO group) or continued conventional treatment (control group). Crossover to ECMO was possible for patients in the control group who had refractory hypoxemia. The primary end point was mortality at 60 days.

RESULTS

At 60 days, 44 of 124 patients (35%) in the ECMO group and 57 of 125 (46%) in the control group had died (relative risk, 0.76; 95% confidence interval [CI], 0.55 to 1.04; P=0.09). Crossover to ECMO occurred a mean (±SD) of 6.5±9.7 days after randomization in 35 patients (28%) in the control group, with 20 of these patients (57%) dying. The frequency of complications did not differ significantly between groups, except that there were more bleeding events leading to transfusion in the ECMO group than in the control group (in 46% vs. 28% of patients; absolute risk difference, 18 percentage points; 95% CI, 6 to 30) as well as more cases of severe thrombocytopenia (in 27% vs. 16%; absolute risk difference, 11 percentage points; 95% CI, 0 to 21) and fewer cases of ischemic stroke (in no patients vs. 5%; absolute risk difference, –5 percentage points; 95% CI, –10 to –2).

CONCLUSIONS

Among patients with very severe ARDS, 60-day mortality was not significantly lower with ECMO than with a strategy of conventional mechanical ventilation that included ECMO as rescue therapy. (Funded by the Direction de la Recherche Clinique et du Développement and the French Ministry of Health; EOLIA ClinicalTrials.gov number, NCT01470703.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Combes at Service de Médecine Intensive–Réanimation, Hôpital Pitié–Salpêtrière, Assistance Publique–Hôpitaux de Paris, Sorbonne Université INSERM, UMRS 1166-ICAN, Institute of Cardiometabolism and Nutrition 47, Boulevard de l'Hôpital, F-75013 Paris, France, or at alain.combes@aphp.fr.

*A list of the investigators in the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) Trial Group, the Réseau Européen en Ventilation Artificielle (REVA), and the International ECMO Network (ECMONet) is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Brodie and Mercat contributed equally to this article.

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EDITORIAL

ECMO for Severe ARDS

C. Corey Hardin, M.D., Ph.D., and Kathryn Hibbert, M.D.

The acute respiratory distress syndrome (ARDS), which is characterized by severe hypoxemic respiratory failure, affects as many as 10% of patients in the intensive care unit and is a common reason for the use of therapeutic mechanical ventilation.[1] On the basis of results of landmark clinical trials, there is substantial consensus around an initial approach to ARDS that combines invasive mechanical ventilation with limited tidal volumes,[2] the use of positive end-expiratory pressure (PEEP) to prevent derecruitment (the collapse of small airways and alveoli),[3] and conservative fluid management.[4] In patients with severe ARDS, defined as a ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao_2:Fio_2) of less than 150 mm Hg, heavy sedation with neuromuscular blockade[5] and ventilation in the prone position[6] have been associated with lower mortality. Even so, severe ARDS is associated with mortality that can exceed 40%.[1] Part of the treatment challenge is that mechanical ventilation, which may be lifesaving, may also perpetuate lung injury because of overdistention of ventilated lung units and repetitive opening and closing of other lung units.[1] One approach that is used to avoid the potentially injurious aspects of mechanical ventilation is extracorporeal membrane oxygenation (ECMO), in which gas exchange occurs by means of an extracorporeal membrane perfused with venous blood.[6]

Although ECMO has been used for decades to support patients with respiratory failure, advances in its technical delivery have been associated with an increase in the number of centers and cases using this approach, particularly since the 2009 H1N1 influenza pandemic.[7] This has occurred despite limited data from high-quality, randomized trials showing convincing evidence of benefit. Until now, the best available evidence to support the use of ECMO was the Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial.[8] Although this trial aimed to compare ECMO with standard of care in patients with severe ARDS, it was weakened by heterogeneous ventilation strategies in the control group (including the use of larger-than-recommended tidal volumes in the control group) and a large percentage of patients in the ECMO group who were transferred to expert centers but never received ECMO. Thus, most practitioners have agreed that there is a need for a large, randomized trial to test the efficacy of ECMO for the treatment of severe ARDS.

In this issue of the *Journal*, Combes et al.[9] present the highly anticipated results of the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial of venovenous ECMO in patients with severe ARDS. The trial design specifically addresses weaknesses of previous trials. Patients who were enrolled in this trial were very sick (Pao_2:Fio_2, <80 mm Hg; respiratory-system compliance, <30 ml per centimeter of water; driving pressure, >16 cm of water; and Sequential Organ Failure Assessment score [on a scale from 0 to 24, with higher scores indicating more severe organ failure], >10 at randomization) and were enrolled within 7 days after the diagnosis of severe ARDS. In addition, unlike in the CESAR trial, patients in the EOLIA trial who had been randomly assigned to ECMO almost universally received it (121 of 124 patients). Lastly, the ECMO approach was highly standardized, and the protocol for ventilator management in the control group reflected

the current standard of care. This included ventilation with low tidal volumes, recruitment maneuvers with PEEP, prone positioning (used in 90% of the patients in the control group), and neuromuscular blockade (used in 100%). A large percentage of patients also received inhaled nitric oxide or other adjuvant therapies.

Overall, there was no significant difference in mortality, the primary end point, between the ECMO group and the control group. The interpretation of this end point is complicated by a high percentage of patients (28%) in the control group who crossed over to ECMO in the context of refractory respiratory failure and deteriorating hemodynamics. It is worth noting that the patients who crossed over were identifiably sicker at the time of enrollment than other patients in the control group: they had lower respiratory-system compliance, higher driving pressures, and more extensive infiltrates.[9] Ultimately, they had higher mortality (57%) than patients in the control group who did not cross over to ECMO (41%) and than patients in the ECMO group (35%). Given that the patients who crossed over were potentially identifiable at enrollment, an interesting, but unanswered, question is how their outcomes compared with those in patients in the ECMO group who were comparably sick at the time of enrollment. These data are not presented. In addition, the trial was, controversially,[10] halted before full enrollment after it was determined that the futility threshold had been crossed. Although it is tempting to speculate what the effect of continued enrollment may have been, this is ultimately not knowable.

Nevertheless, at least one important conclusion can be drawn — the routine use of ECMO in patients with severe ARDS is not superior to the use of ECMO as a rescue maneuver in patients whose condition has deteriorated further. This conclusion comes with the important caveat that, to achieve similar results, clinicians ought to use all other evidence-based interventions, including paralysis and prone positioning, and can consider additional rescue maneuvers, including the use of inhaled pulmonary vasodilators. Given the complexity of such a trial and the slow enrollment that occurred in this cohort (249 patients over a period of 6 years), it is unlikely that another trial will be performed in the near future. For now, clinicians may feel secure with an approach to severe ARDS that combines the above evidence-based interventions while reserving ECMO for patients whose life-threatening hypoxemia persists despite these efforts.

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

From the Department of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Boston.

1. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med 2017;377:562-72.
2. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
3. Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 2006;354:1775-86.
4. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354:2564-75.
5. Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107-16.
6. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159-68.
7. Davies A, Jones D, Bailey M, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. JAMA 2009;302:1888-95.
8. Peek GJ, Clemens F, Elbourne D, et al. CESAR: conventional ventilatory support vs extracorporeal membrane oxygenation for severe adult respiratory failure. BMC Health Serv Res 2006;6:163.
9. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378:1965-75.
10. Harrington D, Drazen JM. Learning from a trial stopped by a data and safety monitoring board. N Engl J Med 2018;378:2031-2.

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ORIGINAL ARTICLE

Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

D. Adams, A. Gonzalez-Duarte, W.D. O'Riordan, C.-C. Yang, M. Ueda, A.V. Kristen, I. Tournev, H.H. Schmidt, T. Coelho, J.L. Berk, K.-P. Lin, G. Vita, S. Attarian, V. Planté-Bordeneuve, M.M. Mezei, J.M. Campistol, J. Buades, T.H. Brannagan III, B.J. Kim, J. Oh, Y. Parman, Y. Sekijima, P.N. Hawkins, S.D. Solomon, M. Polydefkis, P.J. Dyck, P.J. Gandhi, S. Goyal, J. Chen, A.L. Strahs, S.V. Nochur, M.T. Sweetser, P.P. Garg, A.K. Vaishnaw, J.A. Gollob, and O.B. Suhr

ABSTRACT

BACKGROUND

Patisiran, an investigational RNA interference therapeutic agent, specifically inhibits hepatic synthesis of transthyretin.

METHODS

In this phase 3 trial, we randomly assigned patients with hereditary transthyretin amyloidosis with polyneuropathy, in a 2:1 ratio, to receive intravenous patisiran (0.3 mg per kilogram of body weight) or placebo once every 3 weeks. The primary end point was the change from baseline in the modified Neuropathy Impairment Score+7 (mNIS+7; range, 0 to 304, with higher scores indicating more impairment) at 18 months. Other assessments included the Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QOL-DN) questionnaire (range, −4 to 136, with higher scores indicating worse quality of life), 10-m walk test (with gait speed measured in meters per second), and modified body-mass index (modified BMI, defined as [weight in kilograms divided by square of height in meters] × albumin level in grams per liter; lower values indicated worse nutritional status).

RESULTS

A total of 225 patients underwent randomization (148 to the patisiran group and 77 to the placebo group). The mean (±SD) mNIS+7 at baseline was 80.9±41.5 in the patisiran group and 74.6±37.0 in the placebo group; the least-squares mean (±SE) change from baseline was −6.0±1.7 versus 28.0±2.6 (difference, −34.0 points; P<0.001) at 18 months. The mean (±SD) baseline Norfolk QOL-DN score was 59.6±28.2 in the patisiran group and 55.5±24.3 in the placebo group; the least-squares mean (±SE) change from baseline was −6.7±1.8 versus 14.4±2.7 (difference, −21.1 points; P<0.001) at 18 months. Patisiran also showed an effect on gait speed and modified BMI. At 18 months, the least-squares mean change from baseline in gait speed was 0.08±0.02 m per second with patisiran versus −0.24±0.04 m per second with placebo (difference, 0.31 m per second; P<0.001), and the least-squares mean change from baseline in the modified BMI was −3.7±9.6 versus −119.4±14.5 (difference, 115.7; P<0.001). Approximately 20% of the patients who received patisiran and 10% of those who received placebo had mild or moderate infusion-related reactions; the overall incidence and types of adverse events were similar in the two groups.

CONCLUSIONS

In this trial, patisiran improved multiple clinical manifestations of hereditary transthyretin amyloidosis. (Funded by Alnylam Pharmaceuticals; APOLLO ClinicalTrials.gov number, NCT01960348.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Adams at the Department of Neurology, CHU Bicêtre, 78 rue du Général Leclerc, 94275 Le Kremlin-Bicêtre CEDEX, France, or at david.adams@aphp.fr.

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EDITORIAL

Oligonucleotide Drugs for Transthyretin Amyloidosis

Joel N. Buxbaum, M.D.

In this issue of the *Journal*, Adams et al.[1] and Benson et al.[2] report the results of two randomized, double-blind, controlled trials testing the therapeutic efficacy of two different chemically modified oligonucleotides to treat transthyretin amyloidosis, which is an autosomal dominant hereditary polyneuropathy related to the organ deposition of mutant forms of the transthyretin protein (encoded by mutated *TTR*) over time. The circulating protein is synthesized predominantly in the liver, but there is also important local production in the eye by retinal pigment epithelial cells and by the choroid plexus epithelium. Transthyretin proteins form a homotetramer; tetramers containing at least one mutant subunit are kinetically or thermodynamically unstable and dissociate under physiologic conditions to release monomers. Once released, the monomers are no longer constrained by the tetrameric structure and misfold into aggregation-prone polypeptides that form toxic oligomers and amyloid fibrils (Fig. 1).[3]

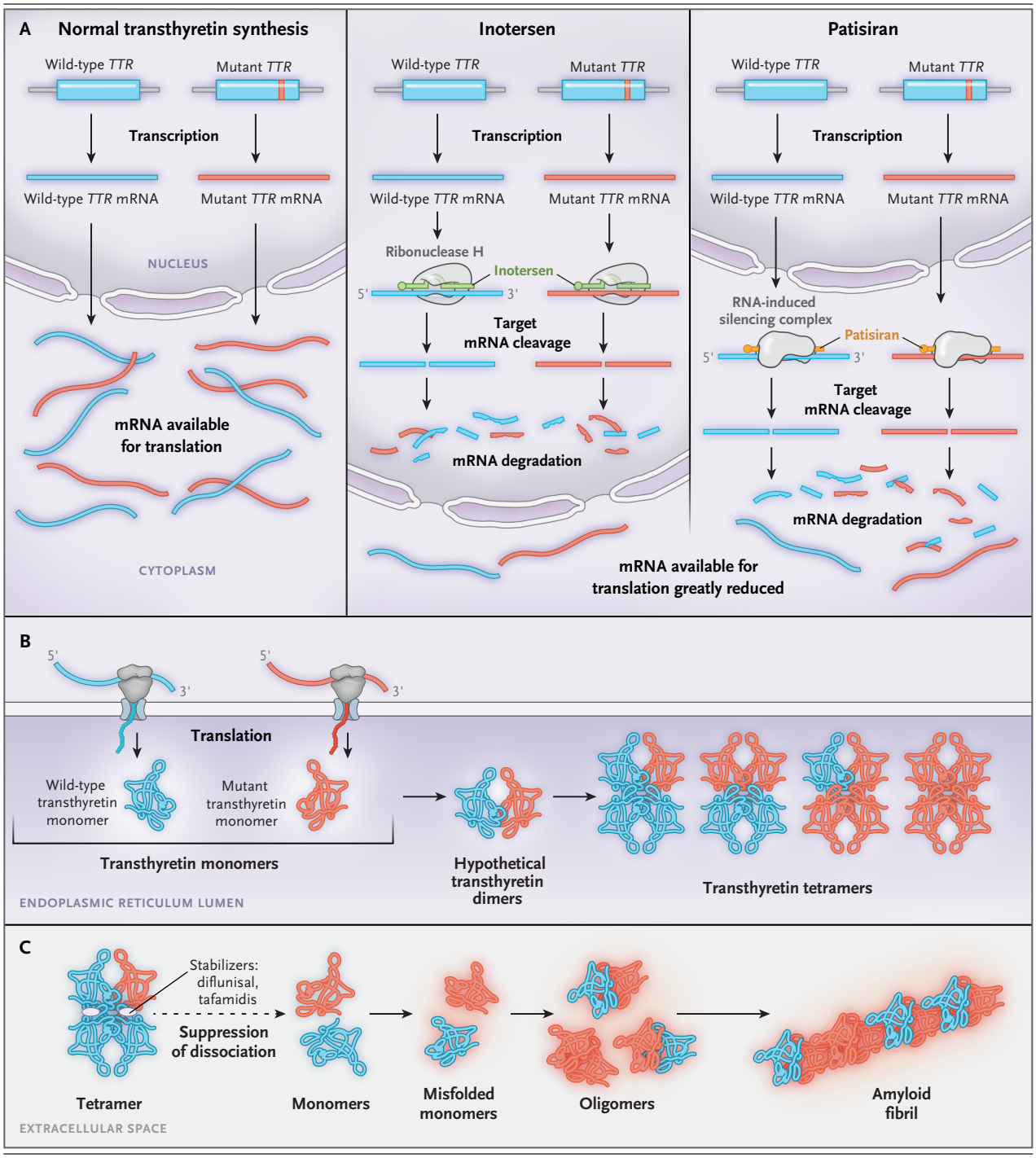
This proposed mechanism appears to apply to the mutant proteins encoded by all known amyloidogenic *TTR* mutations and has led to the notion that disease can be treated and perhaps prevented by approaches that reduce the availability of misfolded monomer. An assumption inherent in each approach is that the "off-rate" of established amyloid deposits (in target tissues such as nerves or cardiac muscle) would exceed the (therapeutically reduced) rate of deposition. The amyloid deposits would gradually diminish, resulting in improved organ function.

The first approach (on which the trials by Adams et al. and Benson et al. are based) is to reduce or halt the amount of mutant transthyretin

Figure 1 (facing page). Current Therapies for Autosomal Dominant Hereditary Amyloidotic Polyneuropathy Caused by Mutations in the Gene Encoding Transthyretin (*TTR*).

As shown in Panel A, the genome of patients with hereditary amyloidotic polyneuropathy contains one copy of wild-type *TTR* and one copy containing a base substitution resulting in a change in the amino acid sequence. In hepatocytes, both copies appear to be equally transcribed and translated. Patisiran and inotersen bind to wild-type and mutant transthyretin RNA transcripts, resulting in their degradation either in the nucleus by ribonuclease H (inotersen) or by the cytoplasmic Dicer small interfering RNA mechanism (patisiran), both of which substantially reduce the amount available for translation. As shown in Panel B, in the presence of adequate wild-type or mutant transthyretin messenger RNA (mRNA) transcripts, transthyretin is synthesized on membrane-bound polyribosomes and transported into the endoplasmic reticulum. Noncovalent tetramer formation appears to occur either in the endoplasmic reticulum or the Golgi apparatus, probably through a transient dimer intermediate, close to the time of secretion. Tetramerization stabilizes even mutant monomers; however, it is possible that the translated mutant transthyretin monomer is less stable than the wild-type monomer and a greater proportion is directed to the endoplasmic reticulum–associated degradation pathway. Tetramers may contain one to four mutant monomers. As shown in Panel C, circulating transthyretin is predominantly tetrameric, but mutant or wild-type monomers may also be found in the circulation as a consequence of tetramer dissociation, which is enhanced by the presence of one or more mutant monomers. The dissociation is suppressed by the natural ligand thyroxine or more effectively by the small molecules tafamidis and diflunisal, which bind in the thyroxine-binding site of the tetramer and reduce the amount of dissociated monomer available to misfold and aggregate at distal tissue sites. In all panels, wild-type molecules (DNA, RNA, and protein) are shown in blue and mutant molecules are shown in red.

that is synthesized by the liver (Fig. 1A). The results in approximately 2000 liver-transplant recipients in whom a liver producing mutant transthyretin was replaced by one synthesizing only the wild-type protein indicate a slowing of disease: 80% of the patients survived for at least 10 years, and arrest of progression of the neuropathy was achieved in the majority. However, recovery of organ function did not seem to occur.[4] The second strategy is to stabilize the mutant tetramers so that amyloidogenic monomers are not released (Fig. 1C).[4] Randomized, controlled trials of small-molecule



transthyretin tetramer stabilizers (tafamidis and diflunisal) have shown clinical efficacy.[5,6]

The placebo-controlled trials by Adams et al. and Benson et al. build on earlier studies from the same groups showing that *TTR*-specific oligonucleotides, as either small interfering RNA (patisiran) or "antisense" (inotersen) constructs, can reduce levels of *TTR* messenger RNA, the amount of transthyretin synthesized, the serum concentrations of transthyretin, and presumably the amount of misfolded monomer available to aggregate and form deposits.[7,8] The two trials were similar in design, demographic variables, and outcome measures. However, there were differences in addition to oligonucleotide formulations, notably treatment duration and mode of administration — that is, subcutaneous[2] and intravenous.[1]

In both trials, the patients who received the active drug had a lower mean rate of progression of the manifestations of the neuropathy (as determined by the modified Neuropathy Impairment Score+7 [NIS+7]) than did the patients who received placebo. The frequency of adverse events was similar among patients who received patisiran and those who received placebo. However, inotersen appeared to systematically reduce circulating platelet levels, with mean platelet counts being significantly lower in the drug-recipient cohort than in the placebo group; one patient who received inotersen had a fatal intracranial hemorrhage. The mechanism of the thrombocytopenia, for which patients were monitored once its association with inotersen became apparent, is not known. A review of all the clinical trials of antisense oligonucleotides that were performed by the sponsor (Ionis Pharmaceuticals) suggests that the effect may be specific to inotersen, despite the fact that transthyretin has no known function in platelets and is not known to interact with other clotting factors.[9]

The results of the trials by Adams et al. and Benson et al., as well as observations of patients receiving liver transplants and small-molecule interventions, showed that at best only 56% of participants had a response to any treatment. It may be that the mNIS+7, while quantitative, was too blunt an instrument for these analyses, although it did reflect a relevant tissue response. It is also possible that the most profound improvement in clinical status requires a period of administration of more than 18 months (the longer of the two intervention periods). The most effective dose of a drug to lower serum levels of transthyretin may not be adequate to achieve a more robust tissue response. A mean reduction of 81% was achieved with patisiran, whereas inotersen lowered the serum concentration by 71%. Furthermore, when the relationship between the mNIS+7 response in individual participants was analyzed with respect to their serum transthyretin response, a correlation was clear in the patients receiving patisiran but not in those receiving inotersen, findings that suggest a qualitative as well as quantitative difference between the two compounds. With respect to the small molecules tafamidis and diflunisal, there is still the potential to increase the dose to achieve greater in vivo tetramer stabilization or to identify other molecules with even better stabilizing capacities.

It seems likely that, over the course of 18 months and given the clinical metrics available, a response in 60% of patients is the best that can be obtained with current interventions. The development of more sensitive, dynamic measures to serve as predictors of response seems feasible and desirable, preferably in the form of a noninvasive biomarker related to the pathophysiology of the disease that reflects the effect of an intervention of short duration on both transthyretin availability and tissue deposition. Measuring the reduction in total transthyretin level or the stabilization of the tetramer, although adequate to compare treated with untreated populations, may not be sufficient to define the therapeutic response in a single patient. Perhaps a better approach could be established by carefully examining the features of the disease or physiological or molecular characteristics of the patients who have the best response in comparison with those who do not have a response to define potentially predictive indicator molecules.

Although each of the trials unequivocally shows a therapeutic effect, there remain questions. Would a single patient have a response to each of the therapeutics to the same degree? If so, it is in the patient's interest to use the least expensive therapy. If not, N-of-1 trials of sequential treatments, although cumbersome, would be required to identify the best treatment for each patient, conditional on the availability of a rapidly responsive, validated surrogate marker of disease.[10] It is also possible that a combination of interventions would elicit a more pronounced, durable therapeutic effect. Although there remains much work to be done, the

trials by Adams et al. and Benson et al. represent a landmark: together, they show that the rate of progression of a peripheral neurologic disease can be slowed, and perhaps ameliorated, through the use of oligonucleotide drugs that are administered systemically.

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

From the Scripps Research Institute, La Jolla, CA.

1. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med 2018;379:11-21.
2. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. N Engl J Med 2018;379:22-31.
3. Johnson SM, Connelly S, Fearns C, Powers ET, Kelly JW. The transthyretin amyloidoses: from delineating the molecular mechanism of aggregation linked to pathology to a regulatory-agency-approved drug. J Mol Biol 2012;421:185-203.
4. Ericzon BG, Wilczek HE, Larsson M, et al. Liver transplantation for hereditary transthyretin amyloidosis: after 20 years still the best therapeutic alternative? Transplantation 2015;99:1847-54.
5. Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology 2012;79:785-92.
6. Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. JAMA 2013;310:2658-67.
7. Coelho T, Adams D, Silva A, et al. Safety and efficacy of RNAi therapy for transthyretin amyloidosis. N Engl J Med 2013;369:819-29.
8. Ackermann EJ, Guo S, Benson MD, et al. Suppressing transthyretin production in mice, monkeys and humans using 2nd-Generation antisense oligonucleotides. Amyloid 2016;23:148-57.
9. Crooke ST, Baker BF, Witztum JL, et al. The effects of 2′-O-methoxyethyl containing antisense oligonucleotides on platelets in human clinical trials. Nucleic Acid Ther 2017;27:121-9.
10. Schork NJ. Personalized medicine: time for one-person trials. Nature 2015;520:609-11.

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ORIGINAL ARTICLE

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P.M. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.

ABSTRACT

BACKGROUND

The recurrence score based on the 21-gene breast cancer assay predicts chemotherapy benefit if it is high and a low risk of recurrence in the absence of chemotherapy if it is low; however, there is uncertainty about the benefit of chemotherapy for most patients, who have a midrange score.

METHODS

We performed a prospective trial involving 10,273 women with hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative, axillary node–negative breast cancer. Of the 9719 eligible patients with follow-up information, 6711 (69%) had a midrange recurrence score of 11 to 25 and were randomly assigned to receive either chemoendocrine therapy or endocrine therapy alone. The trial was designed to show noninferiority of endocrine therapy alone for invasive disease–free survival (defined as freedom from invasive disease recurrence, second primary cancer, or death).

RESULTS

Endocrine therapy was noninferior to chemoendocrine therapy in the analysis of invasive disease–free survival (hazard ratio for invasive disease recurrence, second primary cancer, or death [endocrine vs. chemoendocrine therapy], 1.08; 95% confidence interval, 0.94 to 1.24; P=0.26). At 9 years, the two treatment groups had similar rates of invasive disease–free survival (83.3% in the endocrine-therapy group and 84.3% in the chemoendocrine-therapy group), freedom from disease recurrence at a distant site (94.5% and 95.0%) or at a distant or local–regional site (92.2% and 92.9%), and overall survival (93.9% and 93.8%). The chemotherapy benefit for invasive disease–free survival varied with the combination of recurrence score and age (P=0.004), with some benefit of chemotherapy found in women 50 years of age or younger with a recurrence score of 16 to 25.

CONCLUSIONS

Adjuvant endocrine therapy and chemoendocrine therapy had similar efficacy in women with hormone-receptor–positive, HER2-negative, axillary node–negative breast cancer who had a midrange 21-gene recurrence score, although some benefit of chemotherapy was found in some women 50 years of age or younger. (Funded by the National Cancer Institute and others; TAILORx ClinicalTrials.gov number, NCT00310180.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Sparano at Montefiore Medical Center, 1695 Eastchester Rd., Bronx, NY 10461, or at jsparano@montefiore.org.

A full list of the investigators in this trial is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIAL

TAILORing Adjuvant Systemic Therapy for Breast Cancer

Vered Stearns, M.D.

Five to ten years of adjuvant endocrine therapy provides a substantial benefit in terms of survival outcomes among women with early-stage hormone receptor–positive breast cancer, the most common subtype of breast cancer diagnosed in Western society.[1-3] Several tools are available to help select women who will benefit from the addition of chemotherapy to adjuvant endocrine therapy.[4,5] The 21-gene recurrence assay is one such tool. It was developed and validated in retrospective analyses of samples obtained from women with node-negative, hormone receptor–positive breast cancer who were enrolled in large, prospective, randomized clinical trials. Recurrence scores based on this assay range from 0 to 100, with higher scores indicating a worse prognosis and a greater potential benefit from chemotherapy.[6,7]

The Trial Assigning Individualized Options for Treatment (TAILORx) investigators sought to prospectively demonstrate the noninferiority of endocrine therapy alone to chemoendocrine therapy for invasive disease–free survival — defined as freedom from invasive disease recurrence, second primary cancer, or death — in a group of women with intermediate recurrence scores (11 to 25) (with noninferiority defined as a hazard ratio [endocrine vs. chemoendocrine] <1.322). These investigators now report in the *Journal* that among the 6711 women with recurrence scores of 11 to 25 who underwent randomization, endocrine therapy was indeed noninferior to chemoendocrine therapy with respect to invasive disease–free survival (hazard ratio, 1.08; 95% confidence interval, 0.94 to 1.24; P=0.26).[8] Endocrine therapy was also noninferior to chemoendocrine therapy for secondary survival outcomes at 9 years. An exploratory subgroup analysis revealed an interaction between chemotherapy use and age for both invasive disease–free survival and freedom from recurrence of breast cancer at a distant or local–regional site. Chemotherapy provided small benefits to women who were 50 years of age or younger and had recurrence scores of 16 to 25.

In a cohort of 1626 women with a low recurrence score (0 to 10) who received endocrine therapy alone, the authors had previously reported excellent survival benefits regardless of age or menopausal status.[9] In this 9-year update, the rate of invasive disease–free survival among women with low recurrence scores was similar to that among women with scores of 11 to 25.[8]

The results of TAILORx clearly will aid clinicians in providing treatment recommendations to women with intermediate recurrence scores. The participants in the trial received fairly modern chemoendocrine therapy. Approximately 35% of the participants received extended adjuvant endocrine therapy, but such therapy is associated with only small additional benefits, if any, as compared with 5-year therapy.

In women older than 50 years with recurrence scores of 0 to 25, chemoendocrine therapy is unlikely to be superior to endocrine therapy alone. In women 50 years of age or younger, the threshold may be lower: those with recurrence scores of 16 or higher may benefit from chemoendocrine therapy. Younger women are indeed at a relatively higher risk for relapse than older women. The majority of premenopausal women in the TAILORx trial received tamoxifen or tamoxifen followed by an aromatase inhibitor, and only 13% received ovarian function suppression. Some younger women with intermediate recurrence scores may have benefited more from chemoendocrine ther-

apy than they would have from endocrine therapy alone because of chemotherapy-induced menopause. Endocrine therapy combined with ovarian function suppression and tamoxifen or an aromatase inhibitor should be considered instead of tamoxifen alone in this population.[2] However, chemotherapy should also be considered for younger women with recurrence scores of 16 or higher, regardless of whether ovarian function suppression is used in their treatment.

Yet women with early-stage hormone receptor–positive breast cancer remain at risk for being undertreated or overtreated with endocrine therapy and chemotherapy. At 9 years, women with low or intermediate recurrence scores had a greater than 15% risk of invasive disease recurrence, second primary cancer, or death and a 3 to 5% risk of breast cancer recurrence at a distant site. Among women with recurrence scores of 26 or higher, at 9 years, the rate of invasive disease recurrence, second primary cancer, or death was approximately 24% and the rate of recurrence of breast cancer at a distant site was approximately 13%. Despite having received effective local and adjuvant systemic therapy, women can have recurrence of breast cancer years or decades after their original diagnosis.[10]

Can we further improve outcomes among women with early-stage hormone receptor–positive breast cancer? New agents, such as inhibitors of the phosphatidylinositol 3-kinase–Akt–mammalian target of rapamycin (PI3K–Akt–mTOR) pathway or cyclin-dependent kinase (CDK) 4 and 6 inhibitors, benefit women who have metastatic hormone receptor–positive breast cancer. These agents may reverse de novo or acquired resistance to endocrine therapy and are under investigation for the treatment of early-stage disease. If these or other new agents provide survival benefits for such women, it will be valuable to develop tools for selecting only the women who need more than endocrine or chemoendocrine therapy, thereby reducing treatment-related toxic effects and costs.

Perhaps most importantly, TAILORx provides a wealth of well-annotated clinicopathological data and a rich biospecimen repository that can be used to investigate emerging tissue-based and circulating biomarkers. Circulating biomarkers have the potential to more precisely identify women with micrometastatic disease for whom adjuvant systemic therapy would be indicated, as well as perhaps to identify those in whom resistance to treatment is developing and for whom an alternate therapy could improve survival outcomes. The challenge ahead is to carefully study the exciting new assays, agents, and emerging technologies to better tailor treatments to women with early-stage breast cancer.

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From the Department of Oncology, Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center, Baltimore.

1. Burstein HJ, Prestrud AA, Seidenfeld J, et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Clin Oncol 2010;28:3784-96.
2. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline update on ovarian suppression. J Clin Oncol 2016;34:1689-701.
3. Gradishar WJ, Anderson BO, Balassanian R, et al. NCCN guidelines insights: breast cancer, version 1.2017. J Natl Compr Canc Netw 2017;15:433-51.
4. Harris LN, Ismaila N, McShane LM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2016;34:1134-50.
5. Krop I, Ismaila N, Andre F, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. J Clin Oncol 2017;35:2838-47.
6. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351:2817-26.
7. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006;24:3726-34.
8. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 2018;379:111-21.
9. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med 2015;373:2005-14.
10. Pan H, Gray R, Braybrooke J, et al. 20-Year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med 2017;377:1836-46.

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ORIGINAL ARTICLE

AR101 Oral Immunotherapy for Peanut Allergy

The PALISADE Group of Clinical Investigators*

ABSTRACT

BACKGROUND

Peanut allergy, for which there are no approved treatment options, affects patients who are at risk for unpredictable and occasionally life-threatening allergic reactions.

METHODS

In a phase 3 trial, we screened participants 4 to 55 years of age with peanut allergy for allergic dose-limiting symptoms at a challenge dose of 100 mg or less of peanut protein (approximately one third of a peanut kernel) in a double-blind, placebo-controlled food challenge. Participants with an allergic response were randomly assigned, in a 3:1 ratio, to receive AR101 (a peanut-derived investigational biologic oral immunotherapy drug) or placebo in an escalating-dose program. Participants who completed the regimen (i.e., received 300 mg per day of the maintenance regimen for approximately 24 weeks) underwent a double-blind, placebo-controlled food challenge at trial exit. The primary efficacy end point was the proportion of participants 4 to 17 years of age who could ingest a challenge dose of 600 mg or more, without dose-limiting symptoms.

RESULTS

Of the 551 participants who received AR101 or placebo, 496 were 4 to 17 years of age; of these, 250 of 372 participants (67.2%) who received active treatment, as compared with 5 of 124 participants (4.0%) who received placebo, were able to ingest a dose of 600 mg or more of peanut protein, without dose-limiting symptoms, at the exit food challenge (difference, 63.2 percentage points; 95% confidence interval, 53.0 to 73.3; P<0.001). During the exit food challenge, the maximum severity of symptoms was moderate in 25% of the participants in the active-drug group and 59% of those in the placebo group and severe in 5% and 11%, respectively. Adverse events during the intervention period affected more than 95% of the participants 4 to 17 years of age. A total of 34.7% of the participants in the active-drug group had mild events, as compared with 50.0% of those in the placebo group; 59.7% and 44.4% of the participants, respectively, had events that were graded as moderate, and 4.3% and 0.8%, respectively, had events that were graded as severe. Efficacy was not shown in the participants 18 years of age or older.

CONCLUSIONS

In this phase 3 trial of oral immunotherapy in children and adolescents who were highly allergic to peanut, treatment with AR101 resulted in higher doses of peanut protein that could be ingested without dose-limiting symptoms and in lower symptom severity during peanut exposure at the exit food challenge than placebo. (Funded by Aimmune Therapeutics; PALISADE ClinicalTrials.gov number, NCT02635776.)

The members of the writing committee (Brian P. Vickery, M.D., Andrea Vereda, M.D., Ph.D., Thomas B. Casale, M.D., Kirsten Beyer, M.D., George Du Toit, M.B., B.Ch., Jonathan O. Hourihane, M.D., Stacie M. Jones, M.D., Wayne G. Shreffler, M.D., Annette Marcantonio, M.B.A., Rezi Zawadzki, Dr.P.H., Stephen G. Dilly, M.B., B.S., Ph.D., Daniel C. Adelman, M.D., and A. Wesley Burks, M.D.) assume responsibility for the overall content and integrity of the article. The affiliations of the members of the writing committee and the full names and degrees of all the authors are provided in the Appendix.

Address reprint requests to Dr. Adelman at Aimmune Therapeutics, 8000 Marina Blvd., Suite 300, Brisbane, CA 94005.

*A complete list of the members of the PALISADE Group of Clinical Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIAL

Oral Desensitization to Peanuts

Michael R. Perkin, Ph.D.

Once a peanut allergy develops, advice has historically been simple: lifelong complete avoidance is needed to prevent systemic allergic reactions, some of which could be fatal. However, over the past decade, a series of case reports and small studies have shown that the systematic introduction of tiny amounts of peanut allergen, followed by gradual increases in dose, could prevent or attenuate systemic reactions.[1-4] The concept gained traction when a group in Cambridge, United Kingdom, found that 12% defatted peanut flour could induce desensitization in children.[5]

Vickery and colleagues now present in the *Journal*[6] the results of a randomized, controlled trial involving approximately 550 participants with peanut allergy. The trial used a Good Manufacturing Process–produced 12% defatted peanut flour preparation, known as AR101, as the allergen. For the peanut challenges at screening and trial exit, the authors chose to focus on the final tolerated dose (i.e., the dose that could be ingested without dose-limiting symptoms). In reality, families are interested in how much peanut their child can be exposed to in one meal without it inducing symptoms, not the final dose. Furthermore, peanuts vary in size and therefore in protein content, so translating the doses of peanut protein that were used in the trial to the equivalent in actual peanuts is difficult. In this editorial, I have used the conversion factor that was used by Vickery and colleagues — that is, that one peanut kernel contains 300 mg of peanut protein (in contrast to the Cambridge group, which estimated that one peanut kernel contains 160 mg of peanut protein). In the primary analysis population of children and adolescents 4 to 17 years of age, after 1 year of treatment with AR101, before which they could consume less than half a peanut, two thirds of them could consume a cumulative dose of approximately four peanuts, whereas in the control group only 1 in 25 participants could consume this amount. In the 56 participants older than 17 years of age, no effect of AR101 treatment was shown.

Desensitization was not easy on the patients. Side effects during the intervention period that led to withdrawal from the trial occurred in 11.6% of the participants in the active-drug group and in 2.4% of those in the control group. This is not something to start at home. Epinephrine was used by 14.0% of the participants in the active-drug group as a result of reactions to treatment. The longer-term side effects of sustained consumption of an allergen to which the body has produced IgE antibodies remain unknown. Current thinking has focused on eosinophilic disease, such as eosinophilic esophagitis, but surveillance and follow-up will be crucial.

The major concern regarding immunotherapy is that the allergen tolerance that is induced will be temporary and lost if regular consumption ceases. Neither the Cambridge group, nor the investigators in this trial, have attempted to establish the duration for which allergen tolerance is maintained in the absence of ongoing consumption. Sustained unresponsiveness was claimed in an immunotherapy trial conducted by Tang et al.,[7] which also used peanut flour, but the median duration of cessation of consumption was only

2.3 weeks — a period that would be better described as a brief interruption in therapy rather than as sustained cessation. Hence, sustained, potentially lifelong, regular consumption may be needed to maintain allergen tolerance. Most parents would see the regular consumption of a few peanuts by their child as a very small price to pay to keep the potential threat of systemic anaphylaxis at bay.

For the one third of participants who did not tolerate the cumulative dose of approximately four peanuts during the exit challenge, questions remain as to what role, if any, adjunctive therapy with, for example, anti-IgE therapy, epicutaneous immunotherapy, or probiotics might have in helping these persons benefit from oral desensitization. Once the increasing-dose phase is complete, maintenance treatment should continue with actual peanuts, as was offered by the Cambridge group when they initially investigated the efficacy and safety of their then-new oral immunotherapy protocol, which allowed participants the choice of receiving their maintenance immunotherapy as actual peanuts instead of as peanut flour.[8]

The clinical value of AR101 will be to allow the initiation of peanut immunotherapy with a product that reliably contains the tiny initial quantities of peanut that are required to safely launch oral desensitization. The lowest-dose capsules of AR101 contain 0.5 mg and 1 mg of peanut protein. In the absence of a product such as AR101, it is extremely difficult to administer such a small amount of allergen to a patient on a consistent basis. The Cambridge group used microscales and issued the doses of peanut flour in vials. However, errors regarding the initial doses during the increasing-dose phase would seem to be a more likely occurrence if allergy treatment centers all measured their own doses of peanut flour rather than using a carefully manufactured product. Furthermore, the issuing of peanut flour to a patient with peanut allergy may result in the peanut being deemed an unlicensed medicinal product by regulatory organizations in some countries.[9] Once a product such as AR101 appears, such regulators will insist that a licensed product be used when it is available, thus preventing the ongoing use of peanut flour itself.

AR101 and other, similar products such as CA002, which is being developed by the Cambridge group, would therefore appear to have a role in initial dose escalation. The potential market for these products is believed to be billions of dollars.[10] It is perhaps salutary to consider that in the study conducted by the Cambridge group, children underwent desensitization with a bag of peanut flour costing peanuts.

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

From the Population Health Research Institute, St. George's, University of London, London.

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1. Mansfield L. Successful oral desensitization for systemic peanut allergy. Ann Allergy Asthma Immunol 2006;97:266-7.
2. Patriarca G, Nucera E, Pollastrini E, et al. Oral rush desensitization in peanut allergy: a case report. Dig Dis Sci 2006;51:471-3.
3. Jones SM, Pons L, Roberts JL, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol 2009;124(2):292-300, 300.e1.
4. Clark AT, Islam S, King Y, Deighton J, Anagnostou K, Ewan PW. Successful oral tolerance induction in severe peanut allergy. Allergy 2009;64:1218-20.
5. Anagnostou K, Islam S, King Y, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet 2014;383:1297-304.
6. The PALISADE Group of Clinical Investigators. AR101 oral immunotherapy for peanut allergy. N Engl J Med 2018;379:1991-2001.
7. Tang ML, Ponsonby AL, Orsini F, et al. Administration of a probiotic with peanut oral immunotherapy: a randomized trial. J Allergy Clin Immunol 2015;135(3):737-44.e8.
8. Anagnostou K, Clark A, King Y, Islam S, Deighton J, Ewan P. Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. Clin Exp Allergy 2011;41:1273-81.
9. The human medicines regulations 2012: regulation 2. Norwich, United Kingdom: The Stationery Office (http://www.legislation.gov.uk/uksi/2012/1916/regulation/2/made).
10. GlobalData Healthcare. Peanut allergy market set for remarkable growth to 2027. Pharmaceutical Technology. July 4, 2018 (https://www.pharmaceutical-technology.com/comment/peanut-allergy-market-set-remarkable-growth-2027/).

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ORIGINAL ARTICLE

Effect of Aspirin on Disability-free Survival in the Healthy Elderly

J.J. McNeil, R.L. Woods, M.R. Nelson, C.M. Reid, B. Kirpach, R. Wolfe, E. Storey, R.C. Shah, J.E. Lockery, A.M. Tonkin, A.B. Newman, J.D. Williamson, K.L. Margolis, M.E. Ernst, W.P. Abhayaratna, N. Stocks, S.M. Fitzgerald, S.G. Orchard, R.E. Trevaks, L.J. Beilin, G.A. Donnan, P. Gibbs, C.I. Johnston, J. Ryan, B. Radziszewska, R. Grimm, and A.M. Murray, for the ASPREE Investigator Group*

ABSTRACT

BACKGROUND

Information on the use of aspirin to increase healthy independent life span in older persons is limited. Whether 5 years of daily low-dose aspirin therapy would extend disability-free life in healthy seniors is unclear.

METHODS

From 2010 through 2014, we enrolled community-dwelling persons in Australia and the United States who were 70 years of age or older (or ≥65 years of age among blacks and Hispanics in the United States) and did not have cardiovascular disease, dementia, or physical disability. Participants were randomly assigned to receive 100 mg per day of enteric-coated aspirin or placebo orally. The primary end point was a composite of death, dementia, or persistent physical disability. Secondary end points reported in this article included the individual components of the primary end point and major hemorrhage.

RESULTS

A total of 19,114 persons with a median age of 74 years were enrolled, of whom 9525 were randomly assigned to receive aspirin and 9589 to receive placebo. A total of 56.4% of the participants were women, 8.7% were nonwhite, and 11.0% reported previous regular aspirin use. The trial was terminated at a median of 4.7 years of follow-up after a determination was made that there would be no benefit with continued aspirin use with regard to the primary end point. The rate of the composite of death, dementia, or persistent physical disability was 21.5 events per 1000 person-years in the aspirin group and 21.2 per 1000 person-years in the placebo group (hazard ratio, 1.01; 95% confidence interval [CI], 0.92 to 1.11; P=0.79). The rate of adherence to the assigned intervention was 62.1% in the aspirin group and 64.1% in the placebo group in the final year of trial participation. Differences between the aspirin group and the placebo group were not substantial with regard to the secondary individual end points of death from any cause (12.7 events per 1000 person-years in the aspirin group and 11.1 events per 1000 person-years in the placebo group), dementia, or persistent physical disability. The rate of major hemorrhage was higher in the aspirin group than in the placebo group (3.8% vs. 2.8%; hazard ratio, 1.38; 95% CI, 1.18 to 1.62; P<0.001).

CONCLUSIONS

Aspirin use in healthy elderly persons did not prolong disability-free survival over a period of 5 years but led to a higher rate of major hemorrhage than placebo. (Funded by the National Institute on Aging and others; ASPREE ClinicalTrials.gov number, NCT01038583.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. McNeil at the Department of Epidemiology and Preventive Medicine, Monash University, 553 St. Kilda Rd., Melbourne, VIC 3004, Australia, or at john.mcneil@monash.edu.

*A complete list of the ASPREE trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. McNeil and Woods contributed equally to this article.

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EDITORIAL

Should Aspirin Be Used for Primary Prevention in the Post-Statin Era?

Paul M Ridker, M.D., M.P.H.

Between 1853 and 1897, German chemists learned to efficiently combine sodium salicylate with acetyl chloride to produce acetylsalicylic acid. That compound, trademarked as aspirin, proved to be a remarkable antiinflammatory and antithrombotic agent and one of the most widely used drugs in pharmaceutical history.

As the medical community's understanding of platelet biology and atherothrombosis evolved, it became clear that aspirin was highly effective in the secondary prevention of cardiovascular events. Subsequent large-scale primary prevention trials, including the Physicians' Health Study and the Women's Health Study, provided evidence of small-to-modest cardiovascular benefits in high-risk patients, albeit with an increased risk of bleeding.[1,2] Yet these and other early prevention trials of aspirin were conducted at a time when smoking was common, blood pressure control suboptimal, and aggressive lipid lowering rare. Thus, the risks and benefits of prophylactic aspirin in current preventive practice remain uncertain, as do standards for dose and duration.[3] This calculus is further complicated by data suggesting that the use of aspirin may lower the incidence of colorectal cancers.[4]

In this issue of the *Journal* and in a recent issue of the *Lancet*, results are reported for three primary prevention trials of aspirin: the ASCEND (A Study of Cardiovascular Events in Diabetes) trial,[5] which involved participants with diabetes; the ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events) trial,[6] which was intended to involve high-risk participants without diabetes; and the ASPREE (Aspirin in Reducing Events in the Elderly) trial,[7-9] which involved older participants. These new trials share a common theme in that they address the level of risk, if any, that justifies the use of aspirin for primary prevention in current practice.

In the ASCEND trial, 15,480 participants with diabetes were randomly assigned to receive aspirin at a dose of 100 mg daily or matching placebo. During a mean follow-up of 7.4 years, the rate of serious vascular events was 8.5% with aspirin as compared with 9.6% with placebo (rate ratio, 0.88; 95% confidence interval [CI], 0.79 to 0.97; P=0.01); thus, the use of aspirin was associated with a 12% decrease in the rate of serious vascular events. This benefit, however, came at the cost of a 29% increase in the rate of major bleeding events (4.1% with aspirin vs. 3.2% with placebo; rate ratio, 1.29; 95% CI, 1.09 to 1.52, P=0.003). When weighing the vascular benefit against the bleeding risk, it is important to recognize that the definition of myocardial infarction in contemporary trials often includes small ischemic events that can be detected only on high-sensitivity cardiac-enzyme testing. If such small myocardial events and episodes of transient ischemic attack are excluded from the primary end point of serious vascular events, the net benefit–risk ratio for aspirin among high-risk participants with diabetes becomes smaller still. In the ASCEND trial, all-cause mortality was neutral between the trial groups (rate ratio, 0.94; 95% CI, 0.85 to 1.04).

The ARRIVE trial was intended to investigate the role of aspirin at a dose of 100 mg daily as compared with placebo for the primary prevention of cardiovascular events among high-risk participants without diabetes. However, during 5 years of follow-up among 12,546 participants,

the observed 10-year risk estimates were substantially lower than predicted. Thus, in interpreting the results of the ARRIVE trial, the participants should be considered to have low to moderate risk. In this context, the results are consistent with the results of previous trials, in which the use of aspirin conferred no vascular benefit but resulted in a significant increase in the risk of bleeding complications. In the intention-to-treat analysis of the ARRIVE trial, the incidence of the composite primary outcome of myocardial infarction, stroke, unstable angina, transient ischemic attack, or death from cardiovascular causes was 4.3% with aspirin and 4.5% with placebo (hazard ratio, 0.96; 95% CI, 0.81 to 1.13; P=0.60), whereas the incidence of gastrointestinal bleeding events with aspirin was twice the incidence with placebo (hazard ratio, 2.1; 95% CI, 1.36 to 3.28; P<0.001). In a per-protocol analysis that partially addressed differences between the trial groups in adherence to the trial regimen (but may have introduced bias), the results were more optimistic with respect to a benefit of aspirin. In the ARRIVE trial, there was no significant difference between the trial groups in the rate of fatal bleeding events, and all-cause mortality was again neutral between the two groups (hazard ratio, 0.99; 95% CI, 0.80 to 1.24; P=0.95).

The results of the ASPREE trial were published in three separate articles. The trial involved 19,114 participants in Australia and the United States who were 70 years of age or older and were free from cardiovascular disease, dementia, and disability at trial entry. The participants were randomly assigned to receive 100 mg per day of enteric-coated aspirin or placebo and were followed for up to 5 years. In the ASPREE trial, the use of aspirin conferred no benefit with respect to the prespecified composite primary end point of death, dementia, or persistent physical disability, an issue of considerable importance in the elderly (hazard ratio with aspirin vs. placebo, 1.01; 95% CI, 0.92 to 1.11; P=0.79). Of the primary end-point events that occurred, half were death, 30% dementia, and 20% persistent physical disability. Similar to the ARRIVE trial, the ASPREE trial showed no evidence of a cardiovascular benefit of aspirin (hazard ratio for cardiovascular disease with aspirin vs. placebo, 0.95; 95% CI, 0.83 to 1.08), yet the risk of major bleeding was again higher with aspirin than with placebo (hazard ratio, 1.39; 95% CI, 1.18 to 1.62; P<0.001).

With regard to other outcomes in the ASPREE trial, the investigators report that the rate of the secondary end point of death from any cause was potentially higher with aspirin than with placebo (hazard ratio, 1.14; 95% CI, 1.01 to 1.29). This finding is at odds with the results of previous primary prevention trials of aspirin and with the results of the ASCEND and ARRIVE trials (Fig. 1). The potentially higher mortality with aspirin was limited to the Australian cohort and was driven by an unexpectedly higher risk of cancer-related death with aspirin than with placebo (hazard ratio, 1.31; 95% CI, 1.10 to 1.56). These latter data should be interpreted with caution. In the ASPREE trial, the observed higher cancer-related mortality with aspirin was not specific to cancer site or pathologic type, and the potential adverse effect of aspirin on the incidence of cancer was of smaller magnitude than the effect on the incidence of fatal cancer; in contrast, in the ASCEND trial, which had a longer average follow-up time than the ASPREE trial, no increase or decrease in the rate of cancer was observed with the use of aspirin. Data on cancer from the ARRIVE trial have not yet been reported. Given such uncertainty and given the long latencies for cancer, continued follow-up from all three trials would help to robustly address hypotheses regarding benefits or harms of aspirin on the occurrence of site-specific cancer.

With regard to patient care, the results of these contemporary aspirin trials, which showed minimal benefits and consistent bleeding risks, should be considered alongside the results of contemporary statin trials. In primary prevention trials, the use of statins was associated with a 25% decrease in the risk of major vascular events for every 1 mmol per liter decrease in the low-density lipoprotein cholesterol level (rate ratio with statin vs. placebo, 0.75; 95% CI, 0.69 to 0.82).[10] This statistically certain benefit was associated with an enviable safety profile and was not associated with the bleeding complications seen with aspirin. The percentage of participants who were taking statins in the ASPREE, ARRIVE, and ASCEND trials was 34%, 43%, and 75%, respectively.

What can we conclude about the use of aspirin for prophylaxis 150 years after its chemical synthesis? For secondary prevention, in which risk is determined largely by the extent of atherosclerotic disease, the benefits of aspirin outweigh

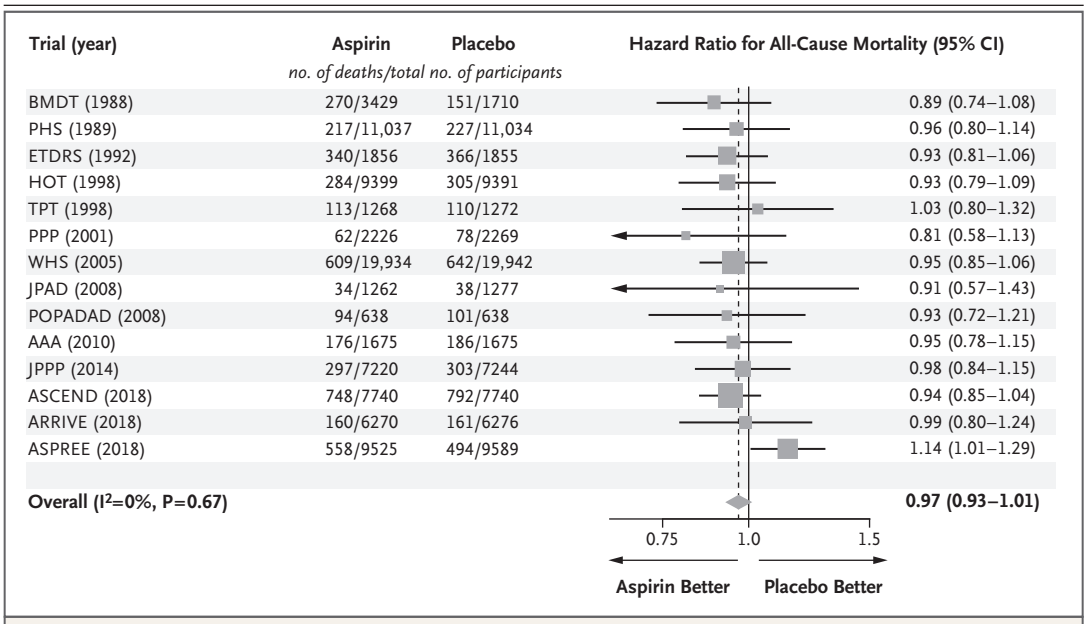

Figure 1. Aspirin and All-Cause Mortality in 14 Primary Prevention Trials.

BMDT denotes British Male Doctors Trial, PHS Physicians' Health Study, ETDRS Early Treatment Diabetic Retinopathy Study, HOT Hypertension Optimal Treatment, TPT Thrombosis Prevention Trial, PPP Primary Prevention Project, WHS Women's Health Study, JPAD Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes, POPADAD Prevention of Progression of Arterial Disease and Diabetes, AAA Aspirin for Asymptomatic Atherosclerosis, JPPP Japanese Primary Prevention Project, ASCEND A Study of Cardiovascular Events in Diabetes, ARRIVE Aspirin to Reduce Risk of Initial Vascular Events, and ASPREE Aspirin in Reducing Events in the Elderly. The meta-analysis was performed with a random effects model (I^2=0% for heterogeneity, P=0.67). The boxes indicate the hazard ratio for all-cause mortality in each trial, with box size proportional to sample size. The diamond indicates the overall hazard ratio and its confidence interval. Arrows on the lines for 95% confidence intervals indicate that the limit is beyond the scale.

the risks of bleeding. In contrast, for primary prevention, in which risk is determined largely by age and the presence or absence of diabetes, the benefit–risk ratio for prophylactic aspirin in current practice is exceptionally small. Thus, beyond diet maintenance, exercise, and smoking cessation, the best strategy for the use of aspirin in the primary prevention of cardiovascular disease may simply be to prescribe a statin instead.

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

From the Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, Boston.

1. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989;321:129-35.
2. Ridker PM, Cook NR, Lee I-M, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293-304.
3. Guirguis-Blake JM, Evans CV, Senger CA, O'Connor EA, Whitlock EP. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 2016;164:804-13.
4. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet 2010;376:1741-50.
5. The ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018;379:1529-39.
6. Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet 2018 August 24 (Epub ahead of print).
7. McNeil JJ, Woods RL, Nelson MR, et al. Effect of aspirin on disability-free survival in the healthy elderly. N Engl J Med 2018;379:1499-508.
8. McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med 2018;379:1509-18.
9. McNeil JJ, Nelson MR, Woods RL, et al. Effect of aspirin on all-cause mortality in the healthy elderly. N Engl J Med 2018;379:1519-28.
10. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016;388:2532-61.

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ORIGINAL ARTICLE

VX-659–Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles

J.C. Davies, S.M. Moskowitz, C. Brown, A. Horsley, M.A. Mall, E.F. McKone, B.J. Plant, D. Prais, B.W. Ramsey, J.L. Taylor-Cousar, E. Tullis, A. Uluer, C.M. McKee, S. Robertson, R.A. Shilling, C. Simard, F. Van Goor, D. Waltz, F. Xuan, T. Young, and S.M. Rowe, for the VX16-659-101 Study Group*

ABSTRACT

BACKGROUND

The next-generation cystic fibrosis transmembrane conductance regulator (CFTR) corrector VX-659, in triple combination with tezacaftor and ivacaftor (VX-659–tezacaftor–ivacaftor), was developed to restore the function of Phe508del CFTR protein in patients with cystic fibrosis.

METHODS

We evaluated the effects of VX-659–tezacaftor–ivacaftor on the processing, trafficking, and function of Phe508del CFTR protein using human bronchial epithelial cells. A range of oral VX-659–tezacaftor–ivacaftor doses in triple combination were then evaluated in randomized, controlled, double-blind, multicenter trials involving patients with cystic fibrosis who were heterozygous for the Phe508del *CFTR* mutation and a minimal-function *CFTR* mutation (Phe508del–MF genotypes) or homozygous for the Phe508del *CFTR* mutation (Phe508del–Phe508del genotype). The primary end points were safety and the absolute change from baseline in the percentage of predicted forced expiratory volume in 1 second (FEV_1).

RESULTS

VX-659–tezacaftor–ivacaftor significantly improved the processing and trafficking of Phe508del CFTR protein as well as chloride transport in vitro. In patients, VX-659–tezacaftor–ivacaftor had an acceptable safety and side-effect profile. Most adverse events were mild or moderate. VX-659–tezacaftor–ivacaftor resulted in significant mean increases in the percentage of predicted FEV_1 through day 29 ($P<0.001$) of up to 13.3 points in patients with Phe508del–MF genotypes; in patients with the Phe508del–Phe508del genotype already receiving tezacaftor–ivacaftor, adding VX-659 resulted in a further 9.7-point increase in the percentage of predicted FEV_1. The sweat chloride concentrations and scores on the respiratory domain of the Cystic Fibrosis Questionnaire–Revised improved in both patient populations.

CONCLUSIONS

Robust in vitro activity of VX-659–tezacaftor–ivacaftor targeting Phe508del CFTR protein translated into improvements for patients with Phe508del–MF or Phe508del–Phe508del genotypes. VX-659 triple-combination regimens have the potential to treat the underlying cause of disease in approximately 90% of patients with cystic fibrosis. (Funded by Vertex Pharmaceuticals; VX16-659-101 and VX16-659-001 ClinicalTrials.gov numbers, NCT03224351 and NCT03029455.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Rowe at the University of Alabama at Birmingham, Gregory Fleming James Cystic Fibrosis Research Center MLCM 706, 1918 University Blvd., Birmingham, AL 35294, or at smrowe@uab.edu.

*A complete list of investigators in the VX16-659-101 and VX16-659-001 trials is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIAL

Triple CFTR Modulator Therapy for Cystic Fibrosis

Fernando Holguin, M.D., M.P.H.

Cystic fibrosis is one of the most common life-threatening autosomal recessive disorders, affecting approximately 80,000 children and adults worldwide.[1] It is caused by mutations that result in deficient or defective function of the cystic fibrosis transmembrane conductance regulator (CFTR), an anion channel that is normally present in epithelial membranes.[2] In addition to the standard symptomatic treatments for cystic fibrosis, two types of CFTR modulator have been approved for treatment. These include a potentiator (ivacaftor), which increases CFTR channel opening at the cell surface, and correctors (lumacaftor and tezacaftor), which increase the amount of CFTR protein at the cell surface.[3] Individually, these therapies have not been proved effective in patients with a Phe508del *CFTR* mutation, which occurs in approximately two thirds of patients with cystic fibrosis and is characterized by a reduction in CFTR trafficking and processing as a result of impaired function.[4]

Combination therapy, with a potentiator and a corrector, on the other hand, improved clinical outcomes in two phase 3 clinical trials. In patients homozygous for the *CFTR* mutation (Phe508del–Phe508del), 24 weeks of treatment with lumacaftor–ivacaftor resulted in an absolute improvement in the percentage of predicted forced expiratory volume in 1 second (FEV_1) of 2.6 to 4.0 points as compared with placebo, whereas 24 weeks of treatment with tezacaftor–ivacaftor increased FEV_1 by 4 points.[5,6] Although exacerbation rates were reduced and respiratory symptoms ameliorated in both trials, the effects on improvement in lung function were modest and within the range of other, established symptomatic therapies for cystic fibrosis, such as hypertonic saline and recombinant human DNase.[7,8] Among patients with the Phe508del–Phe508del mutation, dual-combination therapy with a CFTR corrector (lumacaftor or tezacaftor) and ivacaftor are the current standard of care. However, this combination does not fully restore function to the CFTR protein and is not effective in patients with a Phe508del–minimal function (MF) mutation.

Two accompanying trials, now reported in the *Journal*, each evaluated the efficacy and safety of one of two new-generation, small-molecule CFTR correctors — VX-445 and VX-659 — for the treatment of adults with cystic fibrosis who had either the Phe508del–Phe508del *CFTR* mutation or the Phe508del–MF *CFTR* mutation and were already receiving dual therapy with tezacaftor and ivacaftor. Unlike first-generation correctors, these compounds bind to different sites of the CFTR protein and were shown to have a synergistic effect on dual therapy conducted in vitro with human bronchial epithelial cells from patients with cystic fibrosis. These two separate, multicenter, clinical trials were developed in parallel and shared similar designs and primary efficacy and safety end points.

In the trial conducted by Davies et al.,[9] patients with the Phe508del–MF genotype, for which there is currently no approved CFTR modulator therapy, were randomly assigned to receive 80, 240, or 400 mg of VX-659 in triple combination with tezacaftor and ivacaftor versus triple placebo for 4 weeks. Patients with the Phe508del–Phe508del genotype underwent a 4-week run-in phase with tezacaftor and ivacaftor before being randomly assigned to receive 4 weeks of additional therapy with 400 mg of VX-659 or placebo. In the trial conducted by Keating et al.,[10] participants under-

went the same intervention, according to genotype, with the exception that the VX-445 doses used in patients with the Phe508del–MF genotype were 50, 100 or 200 mg and the VX-445 dose used in patients with the Phe508del–Phe508del genotype was 200 mg.

As compared with placebo, 4 weeks of triple therapy that included VX-659 significantly increased the primary end point of predicted percentage of FEV_1 in the Phe508del–MF and Phe508del–Phe508del groups by an average of 13.3% and 9.7%, respectively. Triple therapy including VX-445 significantly increased FEV_1 in patients with those genotypes by 13.8% and 11.0%, respectively. Both new-generation CFTR modulator therapies improved sweat chloride concentrations and results on Cystic Fibrosis Questionnaire–Revised respiratory domain scores in both genotypes. The majority of patients in both trials had at least one adverse event, with most such events being of mild or moderate severity; 3 of the 122 patients in the VX-445 trial discontinued treatment caused by severe adverse events.

The trials conducted by Davies et al. and by Keating et al. show that triple-combination therapy in patients with a Phe508del–Phe508del *CFTR* mutation improved the percentage of predicted FEV_1 more than double-combination therapy. Both trials also reported efficacy in patients with a Phe508del–MF *CFTR* mutation, and neither reported dose-limiting side effects or toxicity. Only three patients in the VX-445 trial discontinued treatment owing to severe adverse events. These reports represent a major breakthrough in cystic fibrosis therapeutics, with the potential for improving health and possibly survival in all patients who carry the most common *CFTR* mutation.[4] It is unclear whether the effects on lung function can be sustained for longer periods of treatment or whether these compounds will effectively reduce exacerbation rates and address other meaningful outcomes, such as weight gain. These questions should soon be answered in the ongoing phase 3 trials of these regimens.

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

From the Division of Pulmonary Sciences and Critical Care, University of Colorado, Aurora.

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1. Elborn JS. Cystic fibrosis. Lancet 2016;388:2519-31.
2. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the *G551D* mutation. N Engl J Med 2011;365:1663-72.
3. Grasemann H. CFTR modulator therapy for cystic fibrosis. N Engl J Med 2017;377:2085-8.
4. Bobadilla JL, Macek M Jr, Fine JP, Farrell PM. Cystic fibrosis: a worldwide analysis of CFTR mutations — correlation with incidence data and application to screening. Hum Mutat 2002;19:575-606.
5. Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del. N Engl J Med 2017;377:2013-23.
6. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med 2015;373:220-31.
7. Donaldson SH, Bennett WD, Zeman KL, Knowles MR, Tarran R, Boucher RC. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. N Engl J Med 2006;354:241-50.
8. Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. N Engl J Med 1994;331:637-42.
9. Davies JC, Moskowitz SM, Brown C, et al. VX-659–tezacaftor–ivacaftor in patients with cystic fibrosis and one or two Phe508del alleles. N Engl J Med 2018;379:1599-611.
10. Keating D, Marigowda G, Burr L, et al. VX-445–tezacaftor–ivacaftor in patients with cystic fibrosis and one or two Phe508del alleles. N Engl J Med 2018;379:1612-20.

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ORIGINAL ARTICLE

Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer

Pedro T. Ramirez, M.D., Michael Frumovitz, M.D., Rene Pareja, M.D., Aldo Lopez, M.D., Marcelo Vieira, M.D., Reitan Ribeiro, M.D., Alessandro Buda, M.D., Xiaojian Yan, M.D., Yao Shuzhong, M.D., Naven Chetty, M.D., David Isla, M.D., Mariano Tamura, M.D., Tao Zhu, M.D., Kristy P. Robledo, Ph.D., Val Gebski, M.Stat., Rebecca Asher, M.Sc., Vanessa Behan, B.S.N., James L. Nicklin, M.D., Robert L. Coleman, M.D., and Andreas Obermair, M.D.

ABSTRACT

BACKGROUND

There are limited data from retrospective studies regarding whether survival outcomes after laparoscopic or robot-assisted radical hysterectomy (minimally invasive surgery) are equivalent to those after open abdominal radical hysterectomy (open surgery) among women with early-stage cervical cancer.

METHODS

In this trial involving patients with stage IA1 (lymphovascular invasion), IA2, or IB1 cervical cancer and a histologic subtype of squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma, we randomly assigned patients to undergo minimally invasive surgery or open surgery. The primary outcome was the rate of disease-free survival at 4.5 years, with noninferiority claimed if the lower boundary of the two-sided 95% confidence interval of the between-group difference (minimally invasive surgery minus open surgery) was greater than –7.2 percentage points (i.e., closer to zero).

RESULTS

A total of 319 patients were assigned to minimally invasive surgery and 312 to open surgery. Of the patients who were assigned to and underwent minimally invasive surgery, 84.4% underwent laparoscopy and 15.6% robot-assisted surgery. Overall, the mean age of the patients was 46.0 years. Most patients (91.9%) had stage IB1 disease. The two groups were similar with respect to histologic subtypes, the rate of lymphovascular invasion, rates of parametrial and lymph-node involvement, tumor size, tumor grade, and the rate of use of adjuvant therapy. The rate of disease-free survival at 4.5 years was 86.0% with minimally invasive surgery and 96.5% with open surgery, a difference of –10.6 percentage points (95% confidence interval [CI], –16.4 to –4.7). Minimally invasive surgery was associated with a lower rate of disease-free survival than open surgery (3-year rate, 91.2% vs. 97.1%; hazard ratio for disease recurrence or death from cervical cancer, 3.74; 95% CI, 1.63 to 8.58), a difference that remained after adjustment for age, body-mass index, stage of disease, lymphovascular invasion, and lymph-node involvement; minimally invasive surgery was also associated with a lower rate of overall survival (3-year rate, 93.8% vs. 99.0%; hazard ratio for death from any cause, 6.00; 95% CI, 1.77 to 20.30).

CONCLUSIONS

In this trial, minimally invasive radical hysterectomy was associated with lower rates of disease-free survival and overall survival than open abdominal radical hysterectomy among women with early-stage cervical cancer. (Funded by the University of Texas M.D. Anderson Cancer Center and Medtronic; LACC ClinicalTrials.gov number, NCT00614211.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Ramirez at the Department of Gynecologic Oncology and Reproductive Medicine, Unit 1362, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or at peramire@mdanderson.org.

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ORIGINAL ARTICLE

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

G.G. Schwartz, P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, R. Diaz, J.M. Edelberg, S.G. Goodman, C. Hanotin, R.A. Harrington, J.W. Jukema, G. Lecorps, K.W. Mahaffey, A. Moryusef, R. Pordy, K. Quintero, M.T. Roe, W.J. Sasiela, J.-F. Tamby, P. Tricoci, H.D. White, and A.M. Zeiher, for the ODYSSEY OUTCOMES Committees and Investigators*

ABSTRACT

BACKGROUND

Patients who have had an acute coronary syndrome are at high risk for recurrent ischemic cardiovascular events. We sought to determine whether alirocumab, a human monoclonal antibody to proprotein convertase subtilisin–kexin type 9 (PCSK9), would improve cardiovascular outcomes after an acute coronary syndrome in patients receiving high-intensity statin therapy.

METHODS

We conducted a multicenter, randomized, double-blind, placebo-controlled trial involving 18,924 patients who had an acute coronary syndrome 1 to 12 months earlier, had a low-density lipoprotein (LDL) cholesterol level of at least 70 mg per deciliter (1.8 mmol per liter), a non–high-density lipoprotein cholesterol level of at least 100 mg per deciliter (2.6 mmol per liter), or an apolipoprotein B level of at least 80 mg per deciliter, and were receiving statin therapy at a high-intensity dose or at the maximum tolerated dose. Patients were randomly assigned to receive alirocumab subcutaneously at a dose of 75 mg (9462 patients) or matching placebo (9462 patients) every 2 weeks. The dose of alirocumab was adjusted under blinded conditions to target an LDL cholesterol level of 25 to 50 mg per deciliter (0.6 to 1.3 mmol per liter). The primary end point was a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization.

RESULTS

The median duration of follow-up was 2.8 years. A composite primary end-point event occurred in 903 patients (9.5%) in the alirocumab group and in 1052 patients (11.1%) in the placebo group (hazard ratio, 0.85; 95% confidence interval [CI], 0.78 to 0.93; P<0.001). A total of 334 patients (3.5%) in the alirocumab group and 392 patients (4.1%) in the placebo group died (hazard ratio, 0.85; 95% CI, 0.73 to 0.98). The absolute benefit of alirocumab with respect to the composite primary end point was greater among patients who had a baseline LDL cholesterol level of 100 mg or more per deciliter than among patients who had a lower baseline level. The incidence of adverse events was similar in the two groups, with the exception of local injection-site reactions (3.8% in the alirocumab group vs. 2.1% in the placebo group).

CONCLUSIONS

Among patients who had a previous acute coronary syndrome and who were receiving high-intensity statin therapy, the risk of recurrent ischemic cardiovascular events was lower among those who received alirocumab than among those who received placebo. (Funded by Sanofi and Regeneron Pharmaceuticals; ODYSSEY OUTCOMES ClinicalTrials.gov number, NCT01663402.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Schwartz at the Division of Cardiology, University of Colorado School of Medicine, Box B130, Aurora, CO 80045, or at gregory.schwartz@ucdenver.edu.

*A complete list of the ODYSSEY OUTCOMES committee members, investigators, and contributors and their institutional affiliations is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Drs. Schwartz and Steg contributed equally to this article.

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ORIGINAL ARTICLE

Fracture Prevention with Zoledronate in Older Women with Osteopenia

Ian R. Reid, M.D., Anne M. Horne, M.B., Ch.B., Borislav Mihov, B.Phty., Angela Stewart, R.N., Elizabeth Garratt, B.Nurs., Sumwai Wong, B.Sc., Katy R. Wiessing, B.Sc., Mark J. Bolland, Ph.D., Sonja Bastin, M.B., Ch.B., and Gregory D. Gamble, M.Sc.

ABSTRACT

BACKGROUND

Bisphosphonates prevent fractures in patients with osteoporosis, but their efficacy in women with osteopenia is unknown. Most fractures in postmenopausal women occur in those with osteopenia, so therapies that are effective in women with osteopenia are needed.

METHODS

We conducted a 6-year, double-blind trial involving 2000 women with osteopenia (defined by a T score of –1.0 to –2.5 at either the total hip or the femoral neck on either side) who were 65 years of age or older. Participants were randomly assigned to receive four infusions of either zoledronate at a dose of 5 mg (zoledronate group) or normal saline (placebo group) at 18-month intervals. A dietary calcium intake of 1 g per day was advised, but calcium supplements were not provided. Participants who were not already taking vitamin D supplements received cholecalciferol before the trial began (a single dose of 2.5 mg) and during the trial (1.25 mg per month). The primary end point was the time to first occurrence of a nonvertebral or vertebral fragility fracture.

RESULTS

At baseline, the mean (±SD) age was 71±5 years, the T score at the femoral neck was –1.6±0.5, and the median 10-year risk of hip fracture was 2.3%. A fragility fracture occurred in 190 women in the placebo group and in 122 women in the zoledronate group (hazard ratio with zoledronate, 0.63; 95% confidence interval, 0.50 to 0.79; P<0.001). The number of women that would need to be treated to prevent the occurrence of a fracture in 1 woman was 15. As compared with the placebo group, women who received zoledronate had a lower risk of nonvertebral fragility fractures (hazard ratio, 0.66; P=0.001), symptomatic fractures (hazard ratio, 0.73; P=0.003), vertebral fractures (odds ratio, 0.45; P=0.002), and height loss (P<0.001).

CONCLUSIONS

The risk of nonvertebral or vertebral fragility fractures was significantly lower in women with osteopenia who received zoledronate than in women who received placebo. (Funded by the Health Research Council of New Zealand; Australian New Zealand Clinical Trials Registry number, ACTRN12609000593235.)

From the Department of Medicine, Faculty of Medical and Health Sciences, University of Auckland (I.R.R., A.M.H., B.M., A.S., E.G., S.W., K.R.W., M.J.B., G.D.G.), and the Auckland District Health Board (I.R.R., S.B.) — both in Auckland, New Zealand. Address reprint requests to Dr. Reid at the Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand, or at i.reid@auckland.ac.nz.

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EDITORIAL

A Not-So-New Treatment for Old Bones

Clifford J. Rosen, M.D.

Low bone mineral density (i.e., a T score below –2.5) is the current operational definition of osteoporosis. However, low bone mineral density is actually a risk factor for fracture, not a disease marker. Notwithstanding, nearly all osteoporosis treatment algorithms are based on bone mineral density, frequently combined with the clinical risk factors of age and prevalent fractures. Given the high prevalence of low bone mineral density with advanced age, a review of the history underlying determination of risk and the concept of osteopenia is worthwhile.

When measurement of bone density was first introduced 25 years ago, absolute bone mineral density (g per square centimeter) was considered as too onerous for clinicians to understand. At that time, several population studies had shown that bone mineral density was a complex trait with a Gaussian distribution. Hence, a measurement of bone mineral density could easily be represented by the number of standard deviations by which the bone mineral density of an individual patient differed from the mean, termed a T score. Given that approximately 68% of the population should have a bone mineral density within 1 standard deviation from the mean, persons whose measurement fell at or below 2.5 standard deviations from the mean (2.5% of the population) were considered to be at highest risk for fractures.[1] Thus, clinicians tended to recommend treatment to women who had a T score below –2.5. However, it was clear that there was an intermediate, yet substantial, group of patients with a T score between –1 and –2.5 who were subsequently described as having osteopenia and were at risk for fractures, based statistically on the continuous nature of the bone mineral density distribution. The National Osteoporosis Risk Assessment study, a longitudinal examination involving more than 150,000 postmenopausal women, confirmed that the vast majority of fractures occurred in women with osteopenia.[2] Similar findings were also noted in a study involving more than 14,000 women from the Netherlands, known as the Rotterdam study.[3] Still, it was disappointing that in the Fracture Intervention Trial, a study that examined the effect of alendronate treatment on new fractures in 4432 women, treatment with alendronate did not reduce the risk of fractures among women who had bone mineral density in the osteopenic range.[4] Those data, coupled with a growing recognition of atypical femoral fractures as a very rare but devastating side effect of antiresorptive therapy, particularly among women with osteopenia, led to a rapid decrease in new prescriptions for osteoporosis, as well as less adherence to treatment among previously treated women.[5,6] Ultimately, these events led to a treatment gap in patients who had strong clinical risk factors for an osteoporotic fracture (particularly age) but had T scores in the osteopenic range.

Reid et al.[7] now report in the *Journal* the results of a 6-year, randomized, double-blind, placebo-controlled trial of zoledronate at a dose of 5 mg, administered intravenously at 18-month intervals, in 2000 postmenopausal women 65 years of age or older who had osteopenia. Three elements of this trial are unique as compared with earlier studies that showed that annual

administration of zoledronate reduced the risk of fractures in older postmenopausal women.[8,9] First, the current trial showed, with sufficient statistical power, that zoledronate administered less frequently than once a year was associated with not only a greater increase in bone mass than that observed in the placebo group but also a significantly lower risk of vertebral and nonvertebral fractures. The duration of the current trial was twice that of registration trials of newer therapies.[4,8,9] Second, in contrast to the Fracture Intervention Trial of oral alendronate in women who did not have prevalent fractures but had osteopenia, treatment with intravenous zoledronate was effective in preventing fractures among women with an average T score of –1.27 at the total hip and –1.64 at the femoral neck. The reasons for this difference are not clear, although zoledronate is a more potent antiresorptive agent than alendronate, and at least one third of the participants in the current trial had clinical risk factors that placed them at higher risk for fracture (i.e., a baseline 10-year risk of hip fracture of more than 3% or a baseline 10-year risk of any osteoporotic fracture of more than 20%), even though the bone mineral density was considered to indicate osteopenia. Also, the average age of the participants in the current trial was approximately 3.5 years older than that in the Fracture Intervention Trial. Owing to the interaction between age and bone mineral density, the results of the current trial should not be extrapolated to younger postmenopausal women (50 to 64 years of age) with osteopenia. Third, 6 years of intermittent treatment with zoledronate resulted in relatively few adverse events, although the current trial was not powered to assess more rare side effects, such as osteonecrosis of the jaw and atypical femoral fractures.

Taken together, the results of the trial by Reid et al. should have an effect on clinical practice. Given the effectiveness of infrequent administration of zoledronate in reducing the risk of fragility fracture, this treatment can certainly be added to our armamentarium for treating osteoporosis, and it would represent an approach that would not be hindered by adherence issues. But just as importantly, this trial reminds us that risk assessment and treatment decisions go well beyond bone mineral density and should focus particularly on age and a history of previous fractures.

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From the Maine Medical Center Research Institute, Scarborough.

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1. Cummings SR, Black DM, Nevitt MC, et al. Appendicular bone density and age predict hip fracture in women. JAMA 1990;263:665-8.
2. Siris ES, Brenneman SK, Miller PD, et al. Predictive value of low BMD for 1-year fracture outcomes is similar for postmenopausal women ages 50-64 and 65 and older: results from the National Osteoporosis Risk Assessment (NORA). J Bone Miner Res 2004;19:1215-20.
3. Trajanoska K, Schoufour JD, de Jonge EAL, et al. Fracture incidence and secular trends between 1989 and 2013 in a population based cohort: the Rotterdam Study. Bone 2018;114:116-24.
4. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077-82.
5. Black DM, Abrahamsen B, Bouxsein ML, Einhorn T, Napoli N. Atypical femur fractures — review of epidemiology, relationship to bisphosphonates, prevention and clinical management. Endocr Rev 2018 August 29 (Epub ahead of print).
6. Jha S, Wang Z, Laucis N, Bhattacharyya T. Trends in media reports, oral bisphosphonate prescriptions, and hip fractures 1996-2012: an ecological analysis. J Bone Miner Res 2015;30:2179-87.
7. Reid IR, Horne AM, Mihov B, et al. Fracture prevention with zoledronate in older women with osteopenia. N Engl J Med. 2018;379:2407-16.
8. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809-22.
9. Lyles KW, Colón-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007;357:1799-809.

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