

across the world, Moe et al. argue that many promising drugs that are ready for late-stage development have not been taken off manufacturers' shelves because of insufficient financial incentives. If true, this is an alarming indictment of the industry. Pharmaceutical development is largely driven by companies that derive their revenues from patent-protected market exclusivity. In addition to inadequately addressing "unprofitable" diseases, this incentive structure has been exploited by manufacturers to garner undeserved revenue at the expense of patients and payers.<sup>3</sup>

It is not a stretch to predict similar behavior after the adoption of a priority-review voucher program. The first voucher is likely to be received by Novartis for the antimalarial treatment artemether–lumefantrine (Coartem), a product that has long been available outside the United States.<sup>4</sup> Yet there is no guarantee that Novartis's windfall of \$100 million (or more) in this case will be invested in delivery of the drug to needy patients or in further research.<sup>5</sup> The optimal way

to address neglected diseases is not to create ever more convoluted incentives that are easily prone to misuse, but instead to enhance public investment in research while ensuring that the results are made available in such a way as to achieve the greatest benefit for the public health.

Aaron S. Kesselheim, M.D., J.D.

Brigham and Women's Hospital  
Boston, MA 02115

1. Carpenter D, Zucker EJ, Avorn J. Drug-review deadlines and safety problems. *N Engl J Med* 2008;358:1354-61.
2. Jackevicius CA, Tu JV, Ross JS, Ko DT, Krumholz HM. Use of ezetimibe in the United States and Canada. *N Engl J Med* 2008; 358:1819-28.
3. Kesselheim AS, Fischer MA, Avorn J. Extensions of intellectual property rights and delayed adoption of generic drugs: effects on Medicaid spending. *Health Aff (Millwood)* 2006;25: 1637-47.
4. McCaughan M. Novartis Coartem malaria NDA may be first for priority review voucher. Pink sheet: prescription pharmaceuticals and biotechnology. November 2008. (Accessed January 30, 2009, at <http://prvinfo.org/files/pink%20sheet%20-%20coartem%20may%20be%20first%20prv.pdf>.)
5. Gagnon M-A, Lexchin J. The cost of pushing pills: a new estimate of pharmaceutical promotion expenditures in the United States. *PLoS Med* 2008;5(1):e1.

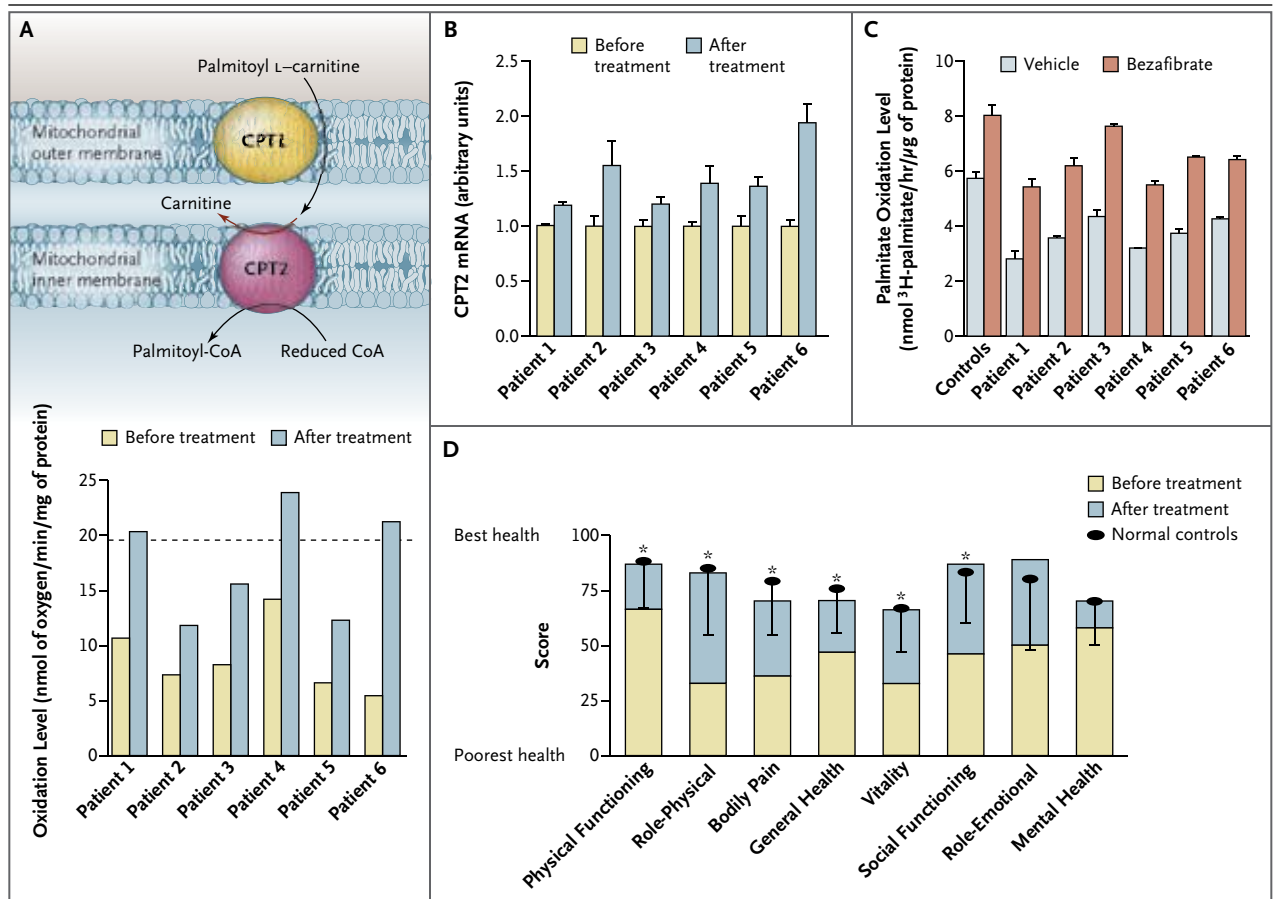
## Bezafibrate for an Inborn Mitochondrial Beta-Oxidation Defect

**TO THE EDITOR:** Carnitine palmitoyltransferase II (CPT2) deficiency is a rare autosomal recessive disorder of mitochondrial fatty acid oxidation. The most common form of this disorder is characterized by muscle stiffness, myalgia, and exercise intolerance,<sup>1,2</sup> and current dietary approaches often do not prevent attacks of rhabdomyolysis. We found that bezafibrate, a commonly used hypolipidemic drug,<sup>3</sup> restored the capacity for normal fatty acid oxidation in muscle cells from patients with a mild form of CPT2 deficiency by stimulating the expression of the mutated gene.<sup>4</sup>

We evaluated the efficacy of bezafibrate as a treatment for the mild form of CPT2 deficiency in six adults; bezafibrate was administered for 6 months (at a dose of three 200-mg tablets per day). The primary end point was the level of fatty acid oxidation in skeletal muscle. Muscle-biopsy specimens were obtained before and after treatment, mitochondria were isolated, and mitochondrial respiration rates were measured in the presence of palmitoyl L-carnitine, the specific substrate of CPT2. Before treatment, the palmitoyl L-carnitine oxidation levels were markedly re-

duced (by 21 to 54% of the normal value), reductions that were consistent with CPT2 deficiency. After bezafibrate treatment, the values increased significantly in the six patients (by 60 to 284%,  $P=0.03$ ) (Fig. 1A). In addition, CPT2 messenger RNA in skeletal muscle increased in all the patients (by 20 to 93%,  $P=0.002$ ) (Fig. 1B), as did the CPT2 protein level (data not shown), findings that were consistent with the increased oxidation levels. In vitro analysis of myoblasts from the patients (Fig. 1C) showed that the initial defect in fatty acid oxidation (49 to 75% of control values) was fully corrected after the cells had been exposed to bezafibrate ( $P=0.002$ ). There were 3 to 24 episodes of rhabdomyolysis per patient over a 6-month period before treatment (mean [±SD] creatine kinase level,  $10,900\pm 3900$  IU per liter) and 0 to 6 episodes per patient during treatment (mean creatine kinase level,  $4700\pm 1900$  IU per liter).

The effects of bezafibrate on health, physical functioning, and quality of life were evaluated with the use of the 36-Item Short-Form General Health Survey, which was completed by each patient before and after treatment. The scores for



**Figure 1. Bezafibrate Treatment in Six Patients with CPT2 Deficiency.**

Panel A shows the level of oxidation of palmitoyl L-carnitine in isolated muscle mitochondria before and after treatment with bezafibrate. Palmitoyl L-carnitine is a specific substrate of carnitine palmitoyltransferase II (CPT2), which is located in the inner mitochondrial membrane. The mitochondrial respiratory levels, measured by means of polarography, are shown as the average of duplicate measurements. The mean control value of palmitoyl L-carnitine oxidation in 16 measurements was  $25.6 \pm 5.9$  nmol of oxygen per minute per milligram of protein. The dashed horizontal line indicates the lower limit of the range of control values in our study (the mean value minus 1 SD). CPT1 denotes carnitine palmitoyltransferase I, and CoA coenzyme A. Panel B shows changes in CPT2 messenger RNA (mRNA) in muscle before and after treatment with bezafibrate. The results of a real-time quantitative polymerase-chain-reaction assay are shown as the mean values for triplicate measurements (+SD) in two different experiments. Panel C shows mean levels of palmitate oxidation in myoblasts (+SD) from four controls and in CPT2-deficient myoblasts from the six patients; the myoblasts were treated for 48 hours with vehicle or  $200 \mu\text{M}$  bezafibrate. Panel D shows the mean scores on the 36-Item Short-Form General Health Survey for the CPT2-deficient patients before and after treatment with bezafibrate, as compared with the scores for population norms. Asterisks denote  $P=0.02$  for the comparison of the baseline scores with the scores after treatment with bezafibrate. The  $\perp$  bars denote standard deviations. The two-sided Wilcoxon signed-rank test was used for paired comparisons.

each domain were calculated for each patient and then averaged (Fig. 1D). Before treatment, scores in five of eight domains were below the population norms,<sup>5</sup> most notably, the scores for “role-physical” and bodily pain — findings that were consistent with symptoms of CPT2 deficiency. After treatment, the scores for all domains reached the control ranges. The largest improvements were seen in the scores for “role-physical” (an increase

by a factor of 2.5) and bodily pain (an increase by a factor of 2.0), indicating less limitation in physical activity and a clear decrease in muscular pain. No adverse effects were reported.

The results of this pilot trial show a therapeutic effect of bezafibrate, suggesting that further study of this agent for pharmacologic treatment of the mild form of CPT2 deficiency may be of interest.

Jean-Paul Bonnefont, M.D., Ph.D.

Jean Bastin, Ph.D.

Université Paris Descartes  
75015 Paris, France

Anthony Behin, M.D.

Assistance Publique–Hôpitaux de Paris Reference Center  
for Rare Neuromuscular Disorders  
75013 Paris, France

Fatima Djouadi, Ph.D.

Université Paris Descartes  
75015 Paris, France  
fatima.djouadi@inserm.fr

Supported by a grant (to Drs. Bonnefont, Bastin, and Djouadi)  
from the Association Française contre les Myopathies.

1. Sigauke E, Rakheja D, Kitson K, Bennett MJ. Carnitine palmitoyltransferase II deficiency: a clinical, biochemical, and molecular review. *Lab Invest* 2003;83:1543-54.

2. Thuillier L, Rostane H, Droin V, et al. Correlation between genotype, metabolic data, and clinical presentation in carnitine palmitoyltransferase 2 deficiency. *Hum Mutat* 2003;21:493-501.

3. Tenenbaum A, Motro M, Fisman EZ. Dual and pan-peroxisome proliferator-activated receptors (PPAR) co-agonism: the bezafibrate lessons. *Cardiovasc Diabetol* 2005;4:14.

4. Djouadi F, Aubey F, Schlemmer D, Bastin J. Peroxisome proliferator activated receptor delta (PPARdelta) agonist but not PPARalpha corrects carnitine palmitoyl transferase 2 deficiency in human muscle cells. *J Clin Endocrinol Metab* 2005;90:1791-7.

5. Perneger TV, Leplège A, Etter JF, Rougemont A. Validation of a French-language version of the MOS 36-Item Short Form Health Survey (SF-36) in young healthy adults. *J Clin Epidemiol* 1995;48:1051-60.

Correspondence Copyright © 2009 Massachusetts Medical Society.

#### INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication, subject to editing and abridgment, provided they do not contain material that has been submitted or published elsewhere. Please note the following: •Letters in reference to a *Journal* article must not exceed 175 words (excluding references) and must be received within 3 weeks after publication of the article. Letters not related to a *Journal* article must not exceed 400 words. All letters must be submitted over the Internet at authors.NEJM.org. •A letter can have no more than five references and one figure or table. •A letter can be signed by no more than three authors. •Financial associations or other possible conflicts of interest must be disclosed. (Such disclosures will be published with the letters. For authors of *Journal* articles who are responding to letters, this information appears in the published articles.) •Include your full mailing address, telephone number, fax number, and e-mail address with your letter.

Our Web site: authors.NEJM.org

We cannot acknowledge receipt of your letter, but we will notify you when we have made a decision about publication. Letters that do not adhere to these instructions will not be considered. Rejected letters and figures will not be returned. We are unable to provide prepublication proofs. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal's* various print and electronic publications and in collections, revisions, and any other form or medium.