

Dichloroacetate causes toxic neuropathy in MELAS: A randomized, controlled clinical trial

To the Editor: We read with interest the report by Kaufmann et al.¹ The investigators studied the efficacy of dichloroacetate (DCA) in the treatment of 30 patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS). At a DCA dose of 25 mg/kg/day, they detected no therapeutic benefit and documented peripheral nerve toxicity resulting in premature study termination. They conclude that peripheral nerve toxicity overshadows any potential benefit from DCA in patients harboring the A3243G mutation.

The high rate of DCA-induced peripheral neuropathy in the Kaufmann et al. study was unexpected because previous studies in a sample of 97 patients with congenital lactic acidosis (including 10 patients with MELAS) did not reveal a high incidence of peripheral nerve toxicity.^{2,3} The new information raises the possibility that patients with MELAS with the A3243G mutation are exceptionally susceptible to DCA toxicity, with diabetes mellitus potentially being a contributing factor.

During the last 12 years, on a compassionate basis we treat patients with chronic lactic acidosis with DCA using an IRB-approved protocol. Of 13 enrolled patients with cerebral lactic acidosis, peripheral lactic acidosis, or both, three had MELAS and harbored the A3243G mutation, but one of these was taken off DCA due to noncompliance. The other two patients with MELAS are still actively enrolled in the protocol and have taken DCA for 7 and 9 years. Both patients developed moderate to severe axonal length-dependent sensorimotor neuropathy manifested primarily as distal weakness in lower extremities.

Ten patients enrolled in our DCA protocol had lactic acidosis due to various metabolic disorders (Leigh syndrome, Kearns-Sayre syndrome [KSS], pyruvate dehydrogenase deficiency, pyruvate carboxylase deficiency, and single or multiple oxidative phosphorylation defects detected enzymatically in biopsied skeletal muscle). Immediately after starting DCA, a single patient with KSS developed subjective symptoms of peripheral neuropathy with severe extremity pain and numbness, and DCA was discontinued. The remaining nine patients, some treated with DCA at a dose of 25 to 50 mg/kg/day for as long as 12 years, show no clinical or electrophysiologic evidence of peripheral neuropathy. Per protocol, all patients are followed closely clinically and with nerve conduction studies every 6 to 12 months.

Despite the small size of our patient sample, our findings seem to confirm the conclusion reached by Kaufmann et al. that DCA

causes toxic neuropathy in patients with MELAS. We are about to resubmit our DCA study protocol to the Children's Hospital Boston IRB for renewal and will include in the application the findings of the Kaufmann et al. study. We are wondering, however, whether the MELAS A3243G patients should be excluded from receiving DCA treatment or be assessed on a case-by-case basis. Since a correlation exists between cerebral lactic acidosis and neurologic impairment in MELAS,⁴ would it be advisable to enroll selected patients with MELAS with severe cerebral lactic acidosis?

Irina A. Anselm, Basil T. Darras, *Boston, MA*

Disclosure: The authors report no conflicts of interest.

Reply from the Authors: We thank Drs. Anselm and Darras for their comments and agree that patients with MELAS 3243 may have an underlying vulnerability of the peripheral nervous system making them particularly susceptible to dichloroacetate toxicity. Due to this toxicity, we could not evaluate for any possible benefit in our study. Discerning drug effects from the natural history of metabolic disease can be challenging without concurrent controls. Therefore, we agree that if dichloroacetate is used, patients should be monitored very closely, both electrophysiologically and clinically, for signs of peripheral neuropathy.

Petra Kaufmann, Darryl De Vivo, *New York, NY*

Disclosure: The authors report no conflicts of interest.

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A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis

To the Editor: I read with great interest the results of the randomized trial by Koch-Henriksen et al.¹ which compared weekly IFN β -1a 22 μ g, SC (Rebif) with every other day IFN β -1b 250 μ g, SC in the treatment of relapsing-remitting multiple sclerosis (RRMS). There are, however, several additional points of clarification and discussion that the authors need to provide so that the readership can place this study into proper context.

First, this 2-year trial finished enrollment in October 1997 and yet the results of this trial were not received by *Neurology* until February 2005.¹ The authors need to explain the reason for the inordinate delay in the publication of this material.

Second, the authors currently (and inappropriately) frame their discussion in the context of the EVIDENCE and INCOMIN trials,^{2,3} each of which compared high-dose and low-dose IFN β products of proven efficacy. By contrast, in the present study, the authors have compared high-dose IFN β -1b against a product that was demonstrated in the OWIMS trial⁴ to be ineffective (a 0% relapse-rate reduction) in the treatment of RRMS. Thus, their study seems to show that IFN β -1b 250 μ g, SC is an ineffective agent—a result that contrasts markedly with the placebo-controlled data in RRMS.⁵ Consequently, the authors need to focus their discussion on why they believe that their trial failed to replicate this earlier placebo-controlled experience.^{4,5}

Third, the group of patients who chose not to be part of the randomized trial (and who received every other day IFN β -1b 250 μ g, SC) seemed similar at baseline in all respects to trial participants (see the authors' table E-1 on the *Neurology* Web site at www.neurology.org). Nevertheless, these patients had a significantly greater relapse rate ($p < 0.009$) and more disease progression ($p = 0.031$) compared to patients treated in the trial. Thus, in this group of patients, treatment with IFN β -1b actually seemed to be harmful. The authors need to discuss why they believe this might be so and, again, why their experience is so different from the placebo-controlled data.⁵

Fourth, the authors suggest that neutralizing antibodies (NAbs) may have played a role in these results. Actually NAbs are considered in only a very cursory manner in the article so the validity of this proposal is unclear. However, if NAbs are the cause, the authors need to explain why the differences (or lack thereof) between the groups were apparent from the very beginning of the trial (see the authors' figure 1). Surely, NAbs did not evolve at the start of the study.

Douglas S. Goodin, *San Francisco, CA*

Disclosure: The author reports no conflicts of interest.

Reply from the Authors: Dr. Goodin has raised some important questions, giving us the opportunity to discuss and clarify our views.

The reason for the delay of our publication was due to unanticipated technical difficulties in transferring MRI scans from different image file formats used at the participating centers to a format that could be processed by the semiautomatic software. We used the time to find and engage qualified software engineers. When started, this task proved to be extremely costly and time consuming. Secondly, the authors spent some time discussing how to interpret the unexpected results of the study.

In the process of revising the article, we had to sacrifice a reference to the OWIMS study⁴ and remove parts of the discussion. We believe that the odd results of the present study can be partially ascribed to lack of blinding, and the study may be regarded as a warning against uncritical interpretation of unblinded comparative studies. Lack of blinding may distort the results in the direction of what is expected by the designers of the studies. In the present study patients and investigators may, consciously or unconsciously, have favored the more convenient and far less expensive treatment with once-a-week subcutaneous administration of IFN-beta 1a (Rebif), which based on the reported results from the pivotal study of IFN-beta-1a 30 µg IM once weekly could be expected to be at least as effective regarding progression of disability as the established treatment with IFN-beta 1b 250 µg every other day. Regarding the OWIMS study, the patients of the IFN-beta 1a QW arm of the OWIMS study had, by chance, a higher baseline mean CU lesion score and a greater BOD than the patients of the placebo arm, indicating more disease activity. In spite of the OWIMS study it is our opinion that IFN-beta 1a 22 mcg QW at least has some effect, and the effect of IFN-beta 1b every other day may be even higher, as we found a trend, however insignificant, in the MRI parameters.

The reason why nonrandomized patients treated with IFN-beta 1b every other day fared worse than the similarly treated patients from the IFN-beta 1b arm of the study may be a matter of self-selection. Even if the nonrandomized patients on average did not differ significantly from the randomized patients at baseline,

decline from randomization may have indicated more pronounced cognitive problems with less capability to make decisions, which may be a sign of a more active disease. It was not a consequence of our study that treatment is harmful for these patients as suggested by Dr. Goodin. In the nonrandomized patients of our study, the annualized relapse rate of 0.85 is in agreement with the 8 MIU IFN-beta 1b treated arm of the original placebo-controlled IFN-beta 1b-study.⁵

Dr. Goodin may have misunderstood our findings and conclusion as to NAb. We have only called attention to a potential confounding role of NAb, but NAb proved not to affect our results (see our table 1).

Nils Koch-Henriksen, Per Soelberg Sorensen, *Aalborg, Denmark*

Disclosure: The authors report no conflicts of interest.

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Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS

To the Editor: We read with interest the article by Kimura et al.¹ describing assessment of progression rate at time of diagnosis using the ALS Functional Rating Scale (ALSFRS-R). It is difficult to measure progression in amyotrophic lateral sclerosis (ALS) trials because there are no biomarkers, and the standard outcomes are clinical.

Six months are needed to detect changes in the ALSFRS-R because of variability, due principally to differing rates of progression among patients. Stratified enrollment lowers variability by reducing heterogeneity in the treatment arms. While site of onset and riluzole treatment may impart modest effects, the person's rate of progression is the most important predictor of outcome.² It is theoretically possible to assign strata using historical information on progression at the baseline visit of a trial using the DeltaFS.¹

We measured the DeltaFS for our clinic patients to find the cutoff value that best dichotomizes the population into two groups for an upcoming phase II trial. We used $\text{DeltaFS} = (48 - \text{baseline ALSFRS-R}) / \text{time from onset to baseline (months)}$. We took first visit to clinic as baseline. Unlike Kimura et al., who considered survival as primary endpoint, our primary outcome is the 6-month change in ALSFRS-R. Of 442 patients with information on DeltaFS (median = 0.55, interquartile range = [0.269, 1.11]), 112 patients had ALSFRS-R scores at baseline and 6 months later. The reduction in variance was maximized when the cutoff 0.50 per month was used to separate fast and slow progression: the mean of the 6-month score in the fast progression group was 4.11 points lower than that in the slow progression group ($p < 0.0001$). Using the cutoff suggested by Kimura et al. (0.67), variance reduction was significant ($p = 0.0005$) with mean for fast progression 3.67 lower than that for slow progression.

The DeltaFS is an excellent measure to determine rate of progression at first encounter, and can be used for stratification in clinical trials. Both 0.50 and 0.67 are acceptable points of dichotomization in terms of reducing heterogeneity in the study population, although 0.50 provides slightly better reduction and is slightly easier arithmetically.

We recommend that individual studies choose a dichotomization cutoff based on their data, as the value could change slightly from region to region. Further analysis may provide a global value of dichotomization for stratification in clinical trials.

Paul H. Gordon, Ying Kuen Cheung, *New York, NY*

Disclosure: The authors report no conflicts of interest.

Reply from the Author: We thank Drs. Gordon and Cheung for their correspondence and confirmation that our progression rate (DFS) at first encounter is a significant clinical marker measuring future progression in ALS trials. A dichotomization of DFS value at baseline in their study of 442 ALS patients was 0.55, compared to our DFS of 0.67 in 82 subjects. A one-point reduction per each 2 months of ALSFRS-R score until diagnosis of ALS was an average.

We also appreciate their investigation of DFS values in the upcoming ALS phase II trial and anticipate that future analyses at various facilities and trials may provide a global standard value. A comparison of detailed clinical characteristics would be necessary to determine whether the difference between our DFS of 0.67 and their indicated DFS value of 0.55 was due to differences in study populations (i.e., racial factors, clinical profiles, or facility characteristics). One possible explanation is that we enrolled patients who had progressed to definite ALS after observing state of progression up to the endpoint, which they used 6 months after diagnosis.

Patients with still probable or possible ALS who did not progress to definite ALS, some of whom tended to display low DFS, were not included. We also took a value of DFS = 0.5 as an important cutoff point and discussed prognosis for the following three arbitrary groupings of DFS in our article: <0.5 , $0.5-1.0$, and >1.0 . In our study, mean duration from initial onset to diagnosis was about 14.2 months, and setting the DFS = 0.55 produces an ALSFRS-R score at diagnosis of 40.19 ($48 - 0.55 \times 14.2$). This score was higher than the actual ALSFRS-R score at diagnosis of 38.7, indicating the inclusion of milder cases at diagnosis. A mean ALSFRS-R score of 38 at diagnosis was previously reported³ and was almost identical to our data.

We concur that progression rate (DFS) at diagnosis represents sequential progression of ALS until respiratory failure and that it is a valid predictor of prognosis. We anticipate the adoption of this simple and meaningful clinical marker in future ALS clinical trials.

Fumiharu Kimura, *Osaka, Japan*

Disclosure: The author reports no conflicts of interest.

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Corrections

Dissociating apathy and depression in Parkinson disease

In the article “Dissociating apathy and depression in Parkinson disease” by L. Kirsch-Darrow et al. (*Neurology* 2006;67:33–38), there is an error in the second author’s name. It should be H.H. Fernandez. The authors regret the error.

Estrogen therapy and cognition: A 6-year single-blind follow-up study in postmenopausal women

In the Brief Communication “Estrogen therapy and cognition: A 6-year single-blind follow-up study in postmenopausal women” by P. Alhola et al. (*Neurology* 2006;67:706–709), there is an error in Table 1 regarding the unit values of serum estradiol. The last row should read S-E₂, pmol/L. The authors regret the error.

Correspondence about Brief Communication “Is protracted low-dose temozolomide feasible in glioma patients?”

In the Letter to the Editor by Eric T. Wong about the Brief Communication “Is protracted low-dose temozolomide feasible in glioma patients?” (Correspondence, *Neurology* 2006;67:543–544), the correspondent’s table was inadvertently omitted. The table should have appeared after this sentence: “However, if the trials were compared based on number of days of temozolomide exposure, dose intensity on a per month basis, and months on temozolomide, then a picture emerges that suggests that lymphopenia from chronic exposure to temozolomide is a function of days exposed to temozolomide, dose intensity, and number of months on temozolomide (table).”

Table Data summary from various temozolomide regimens

Temozolomide regimen*	Dose intensity (per month basis), mg/m ²	Mean months of exposure	Excessive lymphopenia
200 mg/m ² day × 5 days in 28-day cycle (standard)	1,000	5.0	–
75 mg/m ² /day × 21 days in 28-day cycle ¹	1,575	5.0	+
75 mg/m ² /day × 42 days in 70-day cycle ²	1,260	2.5	–
75 mg/m ² /day × 42 days in 56-day cycle ⁵	1,575	4.0	+
150 mg/m ² /day on days 1–7 and 15–21 in 28-day cycle ³	2,100	5.25	–
300 mg/m ² /day on days 1–3 and 14–16 in 28-day cycle ⁴	1,800	4.5	–

* Superscript numbers in column 1 refer to references in the Correspondence on page 544.

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Correspondence about Brief Communication "Is protracted low-dose temozolomide feasible in glioma patients?"

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