Letters

COMMENT & RESPONSE

Retinoids and Amyotrophic Lateral Sclerosis

To the Editor We read with great interest the article by Rosenbohm and colleagues.[1] They conducted a case-control study and reported that retinol-binding protein 4 had an inverse association with both risk for amyotrophic lateral sclerosis (ALS) and disease prognosis. Although we agree with the relevance of the reported results and their interpretation, we would like to comment on 2 issues that might also correlate with these findings.

First, as the authors indicated in the study, growing evidence shows disturbances in energy metabolism levels in patients with ALS who may experience a shift from glucose to lipid metabolism as the main energy source.[2] Interestingly, ALS is a very complex syndrome from a genotypic and phenotypic perspective. In this line, it has been postulated that causes of the disease could vary depending on the clinical form.[2] In their article,[1] Rosenbohm et al reported that 97 (33.6%), 91 (31.5%), and 73 (25.3%) of the patients had lumbar, bulbar, and cervical onset, respectively, but they did not include this grouping category in the analysis of retinol-binding protein 4 levels.[1] In our opinion, because some pathogenic features, as well as several clinical conditions, such as diet, might differ between bulbar and spinal ALS, it would have been interesting to have considered this, for it would might provide further insight into the pathogenesis of the different disease forms.

The second issue refers to the potential therapeutic role of retinoids. Because of the absence of an effective modifying disease therapy, there is a pressing need to search for new therapies for ALS. We previously showed that the retinoid agonist bexarotene has clear neuroprotective associations in ALS murine models.[3] Traditionally, there are important difficulties in translating basic experimental findings into patients with ALS.[4] However, the study by Rosenbohm et al[1] provides further support for the implication of retinoids in ALS. Also, in line with this concept, Nieves et al[5] conducted a study to evaluate the association between nutrients and ALS course in more than 300 patients with ALS at the initial stages of the disease. Interestingly, it was reported that patients who have carotene-enriched diets exhibited a better prognosis.[5] Altogether, these studies suggest that retinoid pathway activation by bexarotene or other retinoids might be considered in a clinical trial for patients with ALS.

Javier Riancho, MD, PhD
Francisco J. Gil-Bea, PhD
Adolfo López de Munaín, MD, PhD

Author Affiliations: Department of Neurology, Hospital Sierrallana-Instituto de Investigación Sanitaria, Centro Investigación Biomédica en Red Enfermedades (CIBERNED), Santander, Spain (Riancho); Neurosciences Area, Biodonostia Health Research Institute, CIBERNED, Torrelavega, Spain (Gil-Bea); Department of Neurology, University Hospital Donostia, Biodonostia Health Research Institute, CIBERNED, San Sebastián, Spain (López de Munaín); Department of Neurosciences, University of the Basque Country Universidad del Pais Vasco/Euskal Herriko Unibertsitatea, CIBERNED, San Sebastián, Spain (López de Munaín).

Corresponding Author: Javier Riancho, MD, PhD, Service of Neurology, Hospital Sierrallana-Instituto de Investigación Sanitaria, Barrio de Ganzo, s/n, 39300, Torrelavega, Spain (javier.riancho86@gmail.com).

Published Online: August 13, 2018. doi:10.1001/jamaneurol.2018.2242

Conflict of Interest Disclosures: None reported.

1. Rosenbohm A, Nagel G, Peter RS, et al; ALS Registry Study Group. Association of serum retinol-binding protein 4 concentration with risk for and prognosis of amyotrophic lateral sclerosis. *JAMA Neurol*. 2018;75(5):600-607. doi:10.1001/jamaneurol.2017.5129

2. Zufiría M, Gil-Bea FJ, Fernández-Torrón R, et al. ALS: A bucket of genes, environment, metabolism and unknown ingredients. *Prog Neurobiol*. 2016;142:104-129. doi:10.1016/j.pneurobio.2016.05.004

3. Riancho J, Ruiz-Soto M, Berciano MT, Berciano J, Lafarga M. Neuroprotective effect of bexarotene in the SOD1(G93A) mouse model of amyotrophic lateral sclerosis. *Front Cell Neurosci*. 2015;9:250. doi:10.3389/fncel.2015.00250

4. Ittner LM, Halliday GM, Kril JJ, Götz J, Hodges JR, Kiernan MC. FTD and ALS—translating mouse studies into clinical trials. *Nat Rev Neurol*. 2015;11(6):360-366. doi:10.1038/nrneurol.2015.65

5. Nieves JW, Gennings C, Factor-Litvak P, et al; Amyotrophic Lateral Sclerosis Multicenter Cohort Study of Oxidative Stress (ALS COSMOS) Study Group. Association between dietary intake and function in amyotrophic lateral sclerosis. *JAMA Neurol*. 2016;73(12):1425-1432. doi:10.1001/jamaneurol.2016.3401