References

[1] Such J, Frances R, Munoz C, Zapater P, Casellas JA, Cifuentes A, et al. Detection and identification of bacterial DNA in patients with cirrhosis and culture-negative, nonneutrocytic ascites. Hepatology 2002;36:135–141.
[2] Frances R, Benlloch S, Zapater P, González JM, Lozano B, Muñoz C, et al. A sequential study of serum bacterial DNA in patients with advanced cirrhosis and ascites. Hepatology 2004;39:484–491.
[3] Guarner C, Gonzalez-Navajas JM, Sanchez E, Soriando G, Francés R, Chiva M, et al. The detection of bacterial DNA in blood of rats with CCl(4)-induced cirrhosis with ascites represents episodes of bacterial translocation. Hepatology 2006;44:633–639.
[4] Francés R, Zapater P, González-Navajas JM, Muñoz C, Caño R, Moreu R, et al. Bacterial DNA in patients with cirrhosis and noninfected ascites mimics the soluble immune response established in patients with spontaneous bacterial peritonitis. Hepatology 2008;47:978–985.
[5] Heininger A, Binder M, Ellinger A, Pfisterer J, Botzenhart K, Unertl K, et al. Effect of comprehensive validation of the template isolation procedure on the reliability of bacteraemia detection by a 16S rRNA gene PCR. Clin Microbiol Infect 2004;10:452–458.
[6] Frances R, Munoz C, Zapater P, Uceda F, Gascón I, Pascual S, et al. Bacterial DNA activates cell mediated immune response and nitric oxide overproduction in peritoneal macrophages from patients with cirrhosis and ascites. Gut 2004;53:860–864.
[7] Frances R, Gonzalez-Navajas JM, Zapater P, Muñoz C, Caño R, Pascual S, et al. Bacterial DNA induces the complement system activation in serum and ascitic fluid from patients with advanced cirrhosis. J Clin Immunol 2007;27:438–444.
[8] Albillos A, de la Hera A, Gonzalez M, Moya JL, Calleja JL, Monserrat J, et al. Increased lipopolysaccharide binding protein in cirrhotic patients with marked immune and hemodynamic derangement. Hepatology 2003;37:208–217.
[9] Zapater P, Frances R, Gonzalez-Navajas JM, Moreu R, Llanos L, Pascual S, et al. Presence of bacterial DNA is a new survival indicator in patients with cirrhosis and non-infected ascitic fluid. Hepatology 2007;46:251A.

Rubén Francés
José Such
CIBERehd Unidad Hepática, Centro de Diagnóstico, Hospital General Universitario de Alicante, 6ª planta, Avda. Pintor Baeza 12, 03010 Alicante, Spain
E-mail address: frances_rub@gva.es

doi:10.1016/j.jhep.2008.04.002

Antioxidants *plus* corticosteroids in the treatment of severe acute alcoholic hepatitis: The question is still open

To the Editor:

We read with interest the article by Stewart et al. [1]. The authors concluded that the treatment of severe acute alcoholic hepatitis (AAH) with antioxidants (AO) alone or with corticosteroids (C) did not improve survival at 6 months. Combining AO with C is attractive, since excessive TNFα levels in AAH are more damaging on hepatocytes when glutathione reserves are depleted by chronic alcohol intake [2]. The negative results of this work should not oblige us to hastily abandon this strategy. The study had several limits: (i) Sample size calculation was based on the hypothesis of a 40% survival improvement with AO, which seems to be much too optimistic; (ii) AAH was only histologically confirmed in 63% of the cases; (iii) surprisingly, 44% ($n = 34/77$) of the patients with a Maddrey score $\geqslant 32$ were not treated with corticosteroids, for reasons not specified; and (iv) two stratifications (gender and corticosteroids) were applied prior to randomization for AO, resulting in eight small groups, with two without any treatment. Assessment of survival was performed by pooling 34 patients treated by C or not treated, compared with 36 patients treated with AO or placebo, plus C or no treatment. This boils down to testing two hypotheses at the same time (AO vs. C and AO + C vs. C), which is not appropriate – especially since the C vs. AO strategy has been shown to be ineffective [3]. Hence, we believe that it is still worth performing a study which compares a combination therapy (C + AO) with C alone in severe AAH patients.

References

[1] Stewart S, Prince M, Bassendine M, Hudson M, James O, Jones D, et al. A randomized trial of antioxidant therapy alone or with corticosteroids in acute alcoholic hepatitis. J Hepatol 2007;47:277–283.
[2] Colell A, Garcia-Ruiz C, Miranda M, Ardite E, Mari M, Morales A, et al. Selective glutathione depletion of mitochondria by ethanol sensitizes hepatocytes to tumor necrosis factor. Gastroenterology 1998;115:1541–1551.
[3] Phillips M, Curtis H, Portmann B, Donaldson N, Bomford A, O'Grady J. Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis – a randomised clinical trial. J Hepatol 2006;44:784–790.

Eric Nguyen-Khac *
Service d'Hépato-Gastroentérologie, CHU Amiens, Place Victor Pauchet, Amiens 80054, France
E-mail address: nguyen-khac.eric@chu-amiens.fr

Thierry Thevenot
Service d'Hepatologie, CHU Besançon, 3 boulevard A. Fleming, Besançon 25000, France

Marie-Astrid Piquet
Service d'Hépato-Gastroentérologie, CHU Caen Avenue Côte de Nacre, Caen 14033, France

Said Benferhat
Service d'Hépato-Gastroentérologie, CH Saint Quentin, 1 avenue Michel de l'Hospital, Saint Quentin 02100, France

Abdelhamid Hezam
Service d'Hépato-Gastroentérologie, CH Cambrai, 516 avenue de Paris, Cambrai 59400, France

Odile Goria
Service d'Hépato-Gastroentérologie, CHU Rouen, 1 rue Germont, Rouen 76031, France

Blaise Tramier
Service d'Hépato-Gastroentérologie, CHU Amiens Place Victor Pauchet, Amiens 80054, France

Denis Chatelain
Service d'Anatomoathologie, CHU Amiens, Place Victor Pauchet, Amiens 80054, France

Jean Louis Dupas
Service d'Hépato-Gastroentérologie, CHU Amiens Place Victor Pauchet, Amiens 80054, France

doi:10.1016/j.jhep.2008.04.003

Antioxidants *plus* corticosteroids in the treatment of severe acute alcoholic hepatitis: The question is still open: Reply

To the Editor:

We would like to thank Nguyen-Khac et al. for their interest in our article [1] and respond to their points. We would agree that there is *in vitro* evidence that would suggest that antioxidants (AO) should be of benefit *in vivo*. The result of the trial was disappointing. Though the numbers were small, we feel that there is little to suggest that patients benefit from AO at this stage of the disease.

The referenced article by Phillips et al. shows the benefit of corticosteroids over antioxidants in those patients that were eligible for corticosteroids [2]. It does not address the role of antioxidants in patients who cannot receive corticosteroids and it does not enlighten us as to whether antioxidants have a role in addition to corticosteroids.

As suggested we were testing two hypotheses concomitantly in our study, but not the ones suggested in the letter; AO vs placebo in those ineligible for corticosteroids and AO + corticosteroids vs. corticosteroids in those eligible. At no point were we testing the hypothesis of AO vs. corticosteroids. This would have included two different groups of patients with different mortalities; those that were ineligible for corticosteroids but were randomized to AO and those that were eligible for corticosteroids but were randomized to placebo. We feel that our trial reflected the clinical situation where corticosteroids are given if possible.

Bleeding or sepsis precluded this in 44% of our patients. This is not a surprising figure in our unit.

Our trial was designed to pick up a 40% mortality reduction. While a smaller reduction in mortality would require larger numbers to detect, the Kaplan–Meier survival curves are almost superimposed. The authors suggest a further trial focussing only on patients eligible for corticosteroids and randomized to receive antioxidants or placebo. We found the 6-month mortality to be 5/18 (28%) in the steroid only group and 10/20 (50%) in the steroid and antioxidant group. Further, larger trials would of course help to clarify this lack of benefit, or perhaps show some advantage to AO treatment. We feel, however, that given the paucity of new studies in acute severe alcoholic hepatitis, and considering the mortality in a young population, that further efforts should focus on treatments more likely to have clinical benefit.

References

[1] Stewart S, Prince M, Bassendine M, Hudson M, James O, Jones D, et al. A randomized trial of antioxidant therapy alone or with corticosteroids in acute alcoholic hepatitis. J Hepatol 2007;47:277–283.

[2] Phillips M, Curtis H, Portmann B, Donaldson N, Bomford A, O'Grady J. Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis – a randomised clinical trial. J Hepatol 2006;44:784–790.

Stephen Stewart
The Liver Unit, Freeman Hospital, Newcastle Upon Tyne, UK

Christopher P. Day
Centre for Liver Research, School of Clinical Medical Sciences, University of Newcastle, Newcastle Upon Tyne, UK
E-mail address: c.p.day@ncl.ac.uk

doi:10.1016/j.jhep.2008.04.004