

assay inaccuracies, the subsequent reanalysis, and results of the reanalysis were imperative to communicate to the medical community.

#### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jhep.2008.05.009.

#### Reference

[1] Silva M, Poo J, Wagner F, Jackson M, Cutler D, Grace M, et al. A randomised trial to compare the pharmacokinetic, pharmacody-

namic, and antiviral effects of peginterferon alfa-2b and peginterferon alfa-2a in patients with chronic hepatitis C (COMPARE). *J Hepatol* 2006;45:204–213.

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## Spanish reports of hepatotoxicity associated with Herbalife® products

*To the Editor:*

We have read with interest the articles recently published in this journal by Elinav et al. [1] and Schoepfer et al. [2], as well as the editorial by Stickel [3], reporting and discussing two series of cases from Israel and Switzerland of hepatotoxicity associated with the consumption of Herbalife® slimming products. Stickel [3] raises the question of why products which are distributed in at least 60 countries only seem to induce hepatotoxicity in two.

In Spain, as perhaps in other countries, Herbalife® distributes its products through door-to-door salesmen and the internet. Some products are registered as dietetic supplements, but others are not registered at all. In 2005, three cases of hepatotoxicity (two hepatitis and one of increased liver enzymes) were reported to the Pharmacovigilance Centre of Asturias, an area in the north of Spain. Another case of increased liver enzymes was reported in 2006. All the four cases occurred in women between 47 and 57 years old, and all came from the same hospital. Three of these were published last February in a Spanish medical journal [4].

In the two cases of hepatitis the patients were sisters. One of whom developed severe liver damage. After taking Herbalife® products for 1 year and losing 20 kg in weight, she was referred to hospital suffering from widespread pruritus, jaundice, fatigue and abdominal strain. Biochemical tests showed liver transaminases over 1000 U/l and 12 mg/dl of total bilirubin. Test antibodies to hepatitis were negative. Abdominal ultrasound showed a cholelithiasis that was surgically removed. Although she was recommended to cease taking Herbalife® products, she continued to do so for another 2 years and developed chronic liver disease with recurrent exacerbations. Liver biopsy showed acute hepatitis grade 4 on chronic liver disease stage 3. She was diag-

nosed as having idiopathic or toxic autoimmune hepatitis, and is currently being treated with corticosteroids. Her sister took Herbalife® products for six months and developed diarrhea, hyperbilirubinemia, jaundice and pruritus. Biochemical tests showed transaminases over 1000 U/l and 26.7 mg/dl of total bilirubin. Viral antibodies were negative. Subacute cholestatic hepatitis was diagnosed and the withdrawal of Herbalife® products was recommended. Some months later, the patient had totally recovered. The two sisters took the following Herbalife® products: formulas 1, 2, 3 and 4, RoseOx, Herbalifeline, Guaraná, Classic Aromatized Tea and Herbal Aloe.

The patients in the other two cases of reported hepatotoxicity were also taking Herbalife® products over a period of 1 month in one case and 3 years in the other, and developed increased transaminases which were detected on routine analysis. After the withdrawal of Herbalife® products, the enzyme levels returned to normal.

To explain the mechanism involved in the hepatotoxicity induced by Herbalife® products, Elinav et al. [1] have suggested genetic susceptibility to develop an immune-mediated liver toxicity associated with one or more constituents. The family ties between the two cases of hepatitis reported in Spain and the diagnosis of autoimmune hepatitis in one case support this observation. We agree with Stickel [3] when he explains that it is extremely difficult to identify the crucial compounds when consumers of Herbalife® are taking several products. Although toxic or bacteriological contamination of some batches cannot be dismissed, we believe that some components of Herbalife® products could be the hepatotoxicity inducers. Firstly, as Schoepfer et al. [2] have suggested, the green tea contained in the Classic Aromatized Tea and also in other Herbalife® products. In the last 5 years, evidence on the ability of green tea to induce

liver damage has increased [5,6]. In April 2003, the Spanish Agency of Medicine and Health Products withdrew the over the counter medicine Exolise® from the market. This contained an ethanolic extract of green tea, and was the cause of four cases of hepatotoxicity in Spain [7] and nine in France [8]. In none of the Herbalife® products containing green tea is the type of extract or the amount of active substances specified. On the other hand, several authors [9–11] have reported cases of acute hepatitis associated with the consumption of Aloe vera tablets or capsules. Aloe vera is the main component of the drink Herbal Aloe sold by Herbalife®.

We do not believe that the hepatotoxicity of the Herbalife® products is confined to three countries alone. The lower use in some areas, the underreporting of adverse reactions, and the lower ability to detect or report information in the international scientific media could be the reasons for explaining this lack of information from other countries. For some time, Latin American and Spanish health professionals have been discussing the safety of Herbalife® products and similar compounds on internet forums.

Schoepfer et al. [2] and Stickel [3] consider that the hepatotoxicity associated with Herbalife® products does not seem to be a threat to public health and have suggested an incidence lower than that of the non-steroidal anti-inflammatory drugs. In our opinion, the evaluation of this safety problem is impossible because we have no precise consumption data nor isolated active substances of established efficacy. Perhaps the hepatotoxicity we are speaking about is of low incidence and affects patients with genetic susceptibility or other risk factors. However, the growing consumption of products promoted as “natural”, without defined composition, quality control and demonstrated activity and safety is a real health problem that should be kept under control. Today we are speaking only about the products of the Herbalife® brand, but tomorrow we may be speaking about other products or other brands.

## References

- [1] Elinav E, Pinsker G, Safadi R, Pappo O, Bromberg M, Anis E, et al. Association between consumption of Herbalife® nutritional supplements and acute hepatotoxicity. *J Hepatol* 2007;47: 514–520.
- [2] Schoepfer AM, Engel A, Fattinger K, Marbet UA, Criblez D, Reichen J, et al. Herbal does not mean innocuous: ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife® products. *J Hepatol* 2007;47:521–526.
- [3] Stickel F. Slimming at all costs: Herbalife®-induced liver injury. *J Hepatol* 2007;47:444–446.
- [4] Duque JM, Ferreiro J, Salgueiro E, Manso G. Hepatotoxicity associated with the consumption of herbal slimming products. *Med Clin (Barc)* 2007;128:238–239.
- [5] Bonkovsky HL. Hepatotoxicity associated with supplements containing Chinese green tea (*Camellia sinensis*). *Ann Intern Med* 2006;144:68–71.
- [6] Jiménez-Sáenz M, Martínez-Sánchez MC. Acute hepatitis associated with the use of green tea infusions. *J Hepatol* 2006;44:616–617.
- [7] Pedrós C, Cereza G, García N, Laporte JR. Hepatotoxicidad por extracto etanólico seco de *Camellia sinensis*. *Med Clin (Barc)* 2003;121:598–599.
- [8] Vial T, Bernard G, Lewden B, Dumortier J, Descotes J. Hépatite aiguë imputable à l'Exolise® (*Camellia sinensis*). *Gastroenterol Clin Biol* 2003;27:1166–1167.
- [9] Rabe C, Musch A, Schirmacher P, Kruijs W, Hoffmann R. Acute hepatitis induced by an aloe vera preparation: a case report. *World J Gastroenterol* 2005;11:303–304.
- [10] Kanat O, Ozet A, Ataergin S. Aloe vera-induced acute toxic hepatitis in a healthy young man. *Eur J Inter Med* 2006;17:589.
- [11] Bottenberg MM, Wall GC, Harvey RL, Habib S. Oral aloe vera-induced hepatitis. *Ann Pharmacother* 2007;41:1740–1743.

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## More reports of potential hepatotoxicity of Herbalife products: Reply

*To the Editor:*

The Letter to the Editor by Manso and colleagues from Spain [1] reiterates the deep concern recently raised [2–4] regarding the potential hepatotoxicity of one or more Herbalife™ products. This report adds 4 more patients to the already described 22 patients from two countries, who developed a variable degree of liver injury in association with the intake of Herbalife™ products.

Two of the Spanish patients developed quite severe hepatitis with jaundice and 3/4 recovered after stopping intake of the products. Although the information provided is not complete, causality may be established in at least two cases as probable and in the remaining two cases as possible, based on the same criteria as reported in Ref. [2–4]. The development of hepatitis in two sisters, one of whom has or progressed to chronic hepatitis, is an important observation which may shed