Liver injury induced by “natural remedies”: an analysis of cases submitted to the Spanish Liver Toxicity Registry

M. García-Cortés1a, Y. Borraz2a, M. I. Lucena2a, G. Peláez1, J. Salmerón1a, M. Diago1, M. C. Martínez-Sierra1, J. M. Navarro1, R. Planas1a, M. J. Soria1, M. Bruguera9a and R. J. Andrade1a


ABSTRACT

Background: toxic liver damage associated with the use of natural remedies is a growing health problem.

Objectives: to analyze the demographics, and clinical and epidemiological characteristics of patients developing liver injury related to these remedies.

Patients and methods: all DILI cases associated with the use of herbal remedies (HR) or dietary supplements (DS) submitted to the Spanish Registry were analyzed. Type of liver damage, severity, and outcome were specifically evaluated.

Results: thirteen cases out of 521 DILI cases (2%) submitted to the Spanish Liver Toxicity Registry between 1994 and 2006 were related to HR/DS, which ranked as the 10th therapeutic group with a greater number of cases and above pain killers, anxiolytics, and antipsychotic drugs. Nine patients (69%) were female (mean age 45 years). Nine cases (69%) had jaundice at presentation. The predominating type of liver damage was hepatocellular (12; 92%), and 31% of cases exhibited the common features of hypersensitivity. *Camellia sinensis* (3, 23%) was the main causative herb, followed by *Rhamnus purshianus* and isoflavones (Fitosoja®, Biosoja®) (2 cases each, 15%). Three cases (23%) were rechallenged with the offending product.

Conclusions: the incidence of hepatic damage related to HR/DS is not so rare, the most common profile of affected patients being a woman with acute hepatocellular hepatitis. Low suspicion regarding the putative role of herbs in hepatotoxicity makes diagnosis more difficult, and probably increases the incidence of inadvertent rechallenge in these patients.

Key words: Hepatotoxicity. Reacciones adversas hepáticas. Productos herbales. Natural remedies.

RESUMEN

Introducción: la toxicidad hepática asociada al uso creciente de productos de “remedios naturales” es un fenómeno emergente.

Objetivos: valoración de las características epidemiológicas, clínicas y demográficas de los casos de hepatotoxicidad secundaria a productos herbales (PH) y suplementos dietéticos (SD).

Pacientes y métodos: análisis de los casos de hepatotoxicidad debida a PH y SD incluidos en el Registro Español de Hepatotoxicidad.

Resultados: trece casos de un total de 521 casos (2%) de reacciones adversas hepáticas incluidas en el registro entre 1994 y 2006, eran secundarios a PH/SD, representando el décimo grupo terapéutico responsable por orden de frecuencia, por delante de analgésicos, ansiolíticos y antipsicóticos. Nueve pacientes (69%) eran mujeres y la edad media fue de 45 años. Nueve pacientes (69%) presentaron ictericia. El tipo de daño más frecuente fue el hepatocelular (12; 92%) y un 31% de los casos presentaron datos de hipersensibilidad. La sustancia más comúnmente involucrada en los casos de daño hepático fue la *Camellia sinensis* (23%) seguida de *Rhamnus purshianus* e isoflavonas (Fitosoja®, Biosoja®) con dos casos cada uno (15%). Tres casos (23%) presentaron re-exposición positiva.

Conclusiones: la hepatotoxicidad originada por PH/SD no es excepcional, y su perfil es la hepatitis aguda hepatocelular icterica predominantemente en mujeres. La frecuente ocurrencia de reexposición positiva en estos pacientes indica un bajo índice de sospecha y un retraso o ausencia de diagnóstico de este tipo de reacción adversa.


Acknowledgements and support: We are grateful to D. Ramón Hidalgo for his role in the statistical analysis of data. This study was partly supported by a grant from Agencia Española del Medicamento and scholarship FIS 07/0980.
INTRODUCTION

In the last few decades we have witnessed the increasing popularity of natural medicine in developed countries. Within the framework of alternative medicine, the use of plant products has grown most during the last decades, with an estimated prevalence of 18.6 to 37% at present, and wide variations according to different countries and study types (1-3). A study in our country pointed out that one in five patients on drug therapy also used herbal remedies concomitantly (4).

This increase in the use of herbal remedies mainly results from the perception that their “natural” condition makes them beneficial with no health risks. However, while we now know that plant substances do have biological effects, their properties have been poorly studied and discussed (5). Moreover, there is no regulation for botanical compounds in many countries, including the US, where these products are considered dietary supplements, and thus escape effectiveness and safety requirements as demanded for conventional drug products (6). In addition, there are no specific post-marketing surveillance programs, hence the incidence and characteristics of their related adverse effects are unknown. However, evidence on the toxicity risks associated with a wide variety of such remedies has emerged in the last few years, and these remedies are now the most common cause of hepatotoxicity in Asian countries (7).

The Spanish government, together with the Spanish pharmacovigilance agency, has published a list of plants whose sale to the public is forbidden or restricted outside healthcare facilities and outside the legislation on drug products because of their proven toxicity (OM 190/2004, BOE Feb 32, 2004). Unfortunately, the scarce control exerted on preparations sold at herbalists’ and dietetic shops makes it impossible to ensure that some forbidden species are no longer on sale. In said list, products associated with hepatotoxicity events include: ethanolic extract of *Camellia sinensis* (Exolise®), *Actracilys gummi fera*, celandine, eotralaria, ephedra, heliotrope, kava-kava, cascara buckthorn, common groundsel, *Teucrium chamaedrys* (wall germander), comfrey, and *Viscus album*.

This paper discusses the clinical and demographic characteristics of hepatotoxicity cases secondary to HRs/DSs included in the Spanish registry.

PATIENTS AND METHODS

Cases analyzed were taken from the Spanish Hepatotoxicity Registry, a non-restrictive database collecting liver toxicity cases that was founded in 1994 and is coordinated by two of the present authors (R.J.A & M.I.L.). Data collection was based on a structured protocol including the following information: time relation between drug administration or toxic exposure onset and liver disease, and between suspect agent discontinuation and liver function improvement or recovery; exclusion of other liver conditions; presence of established risk factors for hepatotoxicity, including alcohol use (volume converted to grams) or pregnancy; and liver damage outcome. Current and previous drugs were thoroughly reviewed, as well as HRs/DSs and potential toxins. Other causes of liver disease were excluded: ethanol, recent A- (anti-HAV IgM), B- (anti-HBV IgM) or C- (anti-HCV and PCR) virus hepatitis, autoimmune diseases (ANA, antimitochondrial antibodies, anti-LKM1 antibodies, and anti-smooth muscle antibodies), and bile obstruction (abdominal ultrasounds plus magnetic resonance imaging or endoscopic cholangiography when needed). When suggested by the clinical setting, cytomegalovirus, Epstein-Barr virus, herpes virus or hepatitis E infection, and a positive serology for bacteria such as *Salmonella, Campylobacter* and *Listeria* were ruled out. In patients younger than 40 years ceruloplasmin and urinary copper excretion were measured to exclude Wilson’s disease. The presence of other metabolic liver conditions such as hemochromatosis or alpha-1 antitrypsin deficiency was similarly assessed, and ischemic hepatitis was ruled out in patients with a recent history of hypotension. Liver biopsy indication depended on the reporting physician’s judgment, and was restricted to dubious cases -- patients with autoimmunity markers, alcoholics, and subjects with previous liver disease or systemic conditions potentially involving the liver had a liver biopsy indicated in order to obtain further etiologic data.

All cases submitted to the registry were revised by the physician in charge, and then evaluated by three independent experts who assessed causality using their clinical judgment and then the Council for International Organizations of Medical Sciences (CIOMS/RUCAM) scale (8,9). This scale is based on a standardized scoring system according to various criteria (time relations, outcome, risk factors, concomitant medication,
exclusion of alternative non-drug causes, established hepatotoxicity data, reexposure), and results are translated into suspicion categories: definite or highly probable (> 8 points), probable (6-8 points), possible (3-5 points), improbable (< 2 points), and excluded (≤ 0 points). Only cases assessed by the CIOMS scale as possible, probable or definite were included in the database.

The definition and categorization of lesion types was established using criteria from the international consensus group meeting (10). Liver injury was defined as a 2-fold increase in alanine aminotransferase (ALT) or conjugated bilirubin levels above the upper limit of normality (ULN), or a combined increase in aspartate aminotransferase (AST), alkaline phosphatase (AP) and total bilirubin levels, one of them 2 times above ULN. Lesion type was categorized according to pathology findings, or alternatively based on biochemical findings when no biopsy was available. Liver damage was considered hepatocellular for ALT/FA ratios ≥ 5, cholestatic for ratios ≤ 2, and mixed for ratios > 2 but < 5. Baseline laboratory parameters were used for this categorization. The pathogenetic mechanism of liver damage was ultimately established by considering it either intrinsic or idiosyncratic, the latter also immunoallergical when hypersensitivity data were present.

Data obtained were analyzed using SPSS (Statistical package for Social Sciences, version 14.0 for Windows).

RESULTS

From a total of 521 cases of hepatotoxicity included in the Spanish Hepatotoxicity Registry between 1994 and 2006, 13 cases of hepatotoxicity secondary to HRs/DSs were detected, which corresponds to 2% of cases and represents the tenth most common responsible treatment group, ahead of pain killers, sedatives, and neuroleptics. Table I lists the demographic and clinical data for cases included in the present series. Two cases included in this review had already been reported before (11,12). Substances responsible for hepatotoxicity cases in the registry included Camellia sinensis (green tea) in three cases, Rhamnus purshianus (cascara buckthorn) in two cases, and Aesculus hippocastanum (horse chestnut), Coutarea latiflora (copalchi), chitosan, Cassia angustifolia (senna), valerian, Piper methysticum (kava-kava), phytosoy, and biosoy one case each.

The most common therapeutical indication for these substances was obesity in six cases. The remaining patients ingested these substances to relieve menopause symptoms, anxiety, constipation, dyspepsia, peripheral venous insufficiency, and diabetes mellitus, and as a restorative.

Mean age was 45 years (23-78) and nine patients (69%) were females. Mean treatment duration was 94 days (1-540 days), and time delay between treatment onset and disease was 79 days (1-365 days). The most common reason for consultation was jaundice, a symptom that developed in nine (69%) patients. In the remaining subjects the problem was identified upon hypertransaminasemia detection. Four patients (31%) had hypersensitivity data, and the most common liver injury type in the present series was hepatocellular damage in 12 cases (92%). Three patients underwent liver biopsy, and results were consistent with toxic hepatitis in all three (Table I).

Three patients had a positive reexposure, that is, a relapse of liver disease was observed upon the readministration of the substance responsible for liver injury. This reexposure was accidental in all cases, mainly due to lack of suspicion or diagnosis regarding the index episode.

As for severity and outcome, six patients required hospitalization (46%) and no deaths occurred. A female patient required referral to a hospital with a liver transplant program, but her liver failure eventually improved spontaneously. A complete resolution was seen in eleven patients; one patient showed persistently elevated GGT, and one patient exhibited chronicity parameters with evidence of fibrosis in liver biopsy.

The international scale for causality assessment in hepatotoxicity yielded definite or highly probable results for 6 patients (46%), and probable results for 7 patients (54%).

DISCUSSION

The liver is the organ most involved in the metabolism of any foreign substances including botanical products, which makes it particularly susceptible to toxicity by such substances. Contrary to popular belief, herbal remedies are not safe and do entail a risk for liver toxicity that may on occasion prove fatal (13). These “natural” compounds have been associated with a number of liver illnesses, including acute or chronic hepatitis, cholestasis, vascular lesions, and even acute liver failure (14,15). Moreover, a US study revealed that herbal products were responsible for a high percentage of referrals for liver transplant as a result of fulminant liver failure (16).

Factors that may contribute to hepatotoxicity from herbal remedies are their substances’ toxic effects, unidentified product components, selection of a wrong part of the plant, inappropriate storage, plant contamination by chemicals, heavy metals or microorganisms, adulteration during manufacture, and poor or absent labeling (17,18). Therefore, establishing a diagnosis of toxic hepatitis from herbal products, whose use re-
mains often unrecognized, is a complex task (19). Effects are often chronic, nonspecific, and clinically inapparent over some time. Despite current under-reporting with this sort of therapies, more than 5000 adverse reactions secondary to herbs were reported to WHO before 1996, and a total of 2621 cases were submitted to FDA between 1993 and 1998 (20).

In fact, toxicity descriptions with HRs/DSs represent an increasingly common phenomenon during the last few years. The relative contribution of cases attributed to such products in the Spanish registry grew between 2004 and 2007, as compared to the period between 1994 and 2004 (21) (unpublished data).

A recent instance of toxicity related to natural medicine products is Herbalife®, a nutritional supplement with hepatotoxicity case reports in various countries. Twelve cases were reported in Israel, and 10 in Switzerland (22,23). Of these 22 patients, two presented with fulminant liver failure and 5 had positive readministration (24). Finally, 11 cases of liver damage from this product have been reported to Spain’s national pharmacovigilance system, and some were reported in the literature (25,26). Since Herbalife® products have diverse components, and each of these patients used a number of products from this manufacturer, establishing a specific causal agent and toxicity mechanism is

### Table I. Demographic and clinical data for cases with hepatotoxicity secondary to herbal remedies

<table>
<thead>
<tr>
<th>Sex/Age</th>
<th>Substance</th>
<th>Presentation</th>
<th>Duration</th>
<th>Latency</th>
<th>Biochemical data (µULN)</th>
<th>Liver damage pattern</th>
<th>Resolution</th>
<th>Comments</th>
<th>CIOMs RUCAM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute episode/Endpoint</td>
<td>pattern</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F/23</td>
<td>Camellia sinensis</td>
<td>Jaundice</td>
<td>21 19</td>
<td>11.5/0.4</td>
<td>56.9/0.35</td>
<td>0.88/0.20</td>
<td>0.9/0.36</td>
<td>Hepatocellular</td>
<td>3 m</td>
</tr>
<tr>
<td>M/78</td>
<td>Casia angustifolia</td>
<td>Jaundice</td>
<td>161 150</td>
<td>11.7/0.9</td>
<td>35.5/0.55</td>
<td>1.4/1.1</td>
<td>2.3/0.44</td>
<td>Hepatocellular</td>
<td>1 m</td>
</tr>
<tr>
<td>F/34</td>
<td>Kava</td>
<td>Hypertransaminasemia</td>
<td>152 150</td>
<td>0.5/0.15</td>
<td>18/0.8</td>
<td>1.2/0.9</td>
<td>4.3/0.7</td>
<td>Hepatocellular</td>
<td>14 m</td>
</tr>
<tr>
<td>M/55</td>
<td>Valerian</td>
<td>Jaundice</td>
<td>1 1</td>
<td>16.9/0.36</td>
<td>0.6/0.71</td>
<td>0.8/0.71</td>
<td>2.1/0.8</td>
<td>Centrilobular cholestasis and mild fibrosis</td>
<td>6 m</td>
</tr>
<tr>
<td>F/27</td>
<td>Camellia sinensis</td>
<td>Jaundice</td>
<td>17 5</td>
<td>11.4/0.85</td>
<td>83.5/0.88</td>
<td>1.67/0.65</td>
<td>4.5/0.74</td>
<td>Hepatocellular</td>
<td>1.5 m</td>
</tr>
<tr>
<td>F/26</td>
<td>Camellia sinensis*</td>
<td>Jaundice</td>
<td>121 121</td>
<td>16.6/8.1</td>
<td>46.4/32.1</td>
<td>1/1.1</td>
<td>2.8/2.4</td>
<td>Hepatocytonecrosis, centrolobular fibrosis and eosinophils. Bile duct neof ormation</td>
<td>Chronification</td>
</tr>
<tr>
<td>M/44</td>
<td>Rhamnus purshianus</td>
<td>Jaundice</td>
<td>63 63</td>
<td>7.1/1.5</td>
<td>56.1/0.5</td>
<td>0.8/0.4</td>
<td>4.6/0.3</td>
<td>Hepatocellular</td>
<td>3 m</td>
</tr>
<tr>
<td>F/32</td>
<td>Fitosoa</td>
<td>Jaundice</td>
<td>31 23</td>
<td>0.53/0.50</td>
<td>3.2/0.8</td>
<td>0.52/0.8</td>
<td>0.28/0.2</td>
<td>Hepatocellular</td>
<td>7 m</td>
</tr>
<tr>
<td>F/36</td>
<td>Rhamnus purshianus</td>
<td>Jaundice</td>
<td>17 25</td>
<td>14/2.1</td>
<td>54.4/0.7</td>
<td>0.57/0.6</td>
<td>4.3/1.7</td>
<td>Hepatocellular</td>
<td>Persisting GGT</td>
</tr>
<tr>
<td>F/57</td>
<td>Biosoa</td>
<td>Hypertransaminasemia</td>
<td>59 71</td>
<td>9.5/0.82</td>
<td>0.9/0.5</td>
<td>2.1/0.8</td>
<td>Hepatocellular</td>
<td>2 m</td>
<td>Simvastatin, two substances imputed</td>
</tr>
<tr>
<td>F/69</td>
<td>Aesculus Hippocastanum</td>
<td>Jaundice</td>
<td>29 29</td>
<td>3.8/-</td>
<td>11.6/4.2</td>
<td>2.1/9</td>
<td>9.8/8.8</td>
<td>Hepatocellular</td>
<td>Hospitalization</td>
</tr>
<tr>
<td>F/42</td>
<td>Chitosan</td>
<td>Hypertransaminasemia</td>
<td>3 1</td>
<td>0.8/0.6</td>
<td>25.1/16</td>
<td>-/-</td>
<td>-/-</td>
<td>Hepatocellular</td>
<td>Hospitalization</td>
</tr>
<tr>
<td>M/54</td>
<td>Couterea antiflora (Copalch)*</td>
<td>Hypertransaminasemia</td>
<td>540 365</td>
<td>0.7/0.8</td>
<td>3.2/1.1</td>
<td>0.8/0.6</td>
<td>0.8/0.5</td>
<td>Hepatocellular</td>
<td>2 m</td>
</tr>
</tbody>
</table>

no easy task. Potential mechanisms include the presence of substances known for their hepatotoxic effects (Camellia sinensis and Aloe vera concentrates), ingredient interactions, and product contamination or adulteration.

Cases described in the present series had a compatible time sequence both regarding the emergence of the adverse event and its recovery after the alleged substance was discontinued. Furthermore, other causes of liver changes were excluded, and reexposure was positive for three patients, which strengthened the diagnosis with hepatotoxicity.

As reported in prior publications, the present study found some female gender predominance. Such predominance has been traditionally attributed to increased risk or susceptibility regarding the development of liver toxicity episodes in women (13,27). As this statement has been questioned by recent epidemiological studies, whether increased hepatotoxicity rates by natural remedies results from a greater use of said products or increased susceptibility among women remains unclear. At any rate the prototypical profile of a patient in this series was a female with hepatocellular hepatitis and jaundice. This is a risk profile for a fulminating outcome in the context of a hepatotoxic reaction as was demonstrated in a recent study (21). It should be highlighted that in most cases these products were indicated to treat obesity given their weight-reducing properties, or to relieve symptoms such as constipation or anxiety. Losing weight has become a goal for a substantial percentage of the population in developed countries whether for esthetic or health reasons, hence a considerable number of people turn to natural medicine and miracle products rather than dietary and exercise recommendations (28).

The high reexposure rate in this series (23%) when compared to all cases in the registry (6%) may result not only from the perceived harmlessness of these compounds by end-users but also from little clinical suspicion by clinicians regarding herbal remedies as causal agents of liver disease, which leads to infradiagnosis and an inability to prevent further events after substance readministration (29,30).

Regarding substances involved in hepatic adverse reactions in the current series, some have been widely related to this condition. More than 30 cases of hepatotoxicity secondary to green tea (Camellia sinensis) as used for weight loss were recorded through 2007, one of them in the present study (11,31-43). Moreover, a pharmaceutical product containing an ethanolic extract of this substance, Exolise®, was withdrawn by Agencia Española del Medicamento in April 2003 after the report of four such cases to the Spanish pharmacovigilance agency and 9 such cases in France (44). Hepatotoxicity has been commonly attributed to the ethanolic extract, and less commonly to «camiline» or tea leaf powder (Arkocapsulas®). However, cases of liver damage secondary to other forms of Camellia sinensis ingestion, including infusions, have been reported since their withdrawal (33,34).

Hepatic adverse reactions secondary to cascara buckthorn (Rhamnus purshiana) ingestion have also been described in the literature, and some products containing this plant have been pronounced illegal by the Spanish medicines agency. Anthracene glycosides are a part of these remedies, and were previously described as causal agents for chronic liver injury (45). Our case of hepatotoxicity secondary to copalchi had been previously reported together with 4 additional cases, and 6 further reports were found in the literature (12).

Piper methysticum or kava-kava grows mainly in some Polynesian areas and is used for the treatment of depressive-anxiety disorders because of the sedative properties of kavapirones, which are GABA receptor agonists (46). A number of European countries, including Spain, banned the marketing of products containing this plant after more than 20 cases of liver toxicity were reported; such measure was then extended to the other countries in the European Union and Canada (47-59). Kava toxicity seems to result from an idiosyncratic mechanism with three potential pathogenetic mechanisms: CYP450 inhibition, intracellular glutathione reduction, and less likely cyclooxygenase inhibition (60).

Cassia angustifolia (senna) is a product indicated for constipation because of its laxative properties. To this day, 4 cases of liver injury secondary to senna ingestion have been reported, two of them with positive readministration (61-64). Hepatotoxicity may result from its contents of sennosides, alkaloids that confer their laxative actions to this plant and are converted to anthrone by intestinal bacteria, with this substance being similar to danthron, a compound with proven hepatotoxic potential (65).

Valeriana officinalis (valerian) as found in anxiolytic preparations has been pointed out as potentially responsible for 4 acute hepatitis cases, one of which developed acute liver failure, encephalopathy, and liver fibrosis (66). A similar case of hepatotoxicity secondary to Aesculus hippocastanum (67) had been previously reported. Lastly, we have found no prior reports in the literature on hepatotoxicity secondary to other substances such as phytoestrogens or chitosan.

While conclusions or recommendations are difficult to draw from such a small series of cases, the importance of identifying all products ingested by patients with liver changes should be underscored, as well as the need to have natural remedies in mind as a potential cause of liver injury (68). Most likely, our understanding of the risk these products entail would be much more precise if, in addition to their identification and diagnosis, all cases where these products are allegedly involved were reported (28,69).
The increasing use of medicinal plants, the risks and uncertainties of their drug effects, and the potential development of drug interactions should prompt a change of mind in our recording the use of herbal remedies and their potential role as causes of adverse events (70). Moreover, the probability that hepatotoxicity episodes secondary to herbal substances are eventually identified will greatly depend on clinical suspicion and adequate history taking (71). To conclude, knowing that herbal products may bring about adverse effects should encourage clinicians to advise caution to their patients when using these substances (72,73).

### GRUPO ESPAÑOL DE ESTUDIO DE HEPATOPATÍAS ASOCIADAS A MEDICAMENTOS (GEHAM)

**Participating sites:**
- Hospital Universitario Virgen de Valme, Sevilla: M. Romero, A. Madrazo, R. Corpas, E. Suárez.
- Hospital de Mendaro, Guipúzcoa: A. Castiella, E.M. Zapata.
- Hospital Central de Asturias, Oviedo: R. Pérez-Alvarez, L. Rodrigo-Saez.
- Hospital Universitario San Cecilio, Granada: J. Salmerón, A. Gila.
- Hospital Universitario Virgen de las Nieves, Granada: R. Martín-Vivaldi, F. Nogueras.
- Hospital Carlos Haya, Málaga: M. Jiménez.
- Hospital Sant Pau, Barcelona: C. Guarnier, E.M. Román, G. Soriano.
- Hospital Morales Meseguer, Murcia: H. Hallal Hachem.
- Hospital de Puerto Real, Cádiz: J.M. Pérez-Moreno, M. Puertas.
- Hospital La Inmaculada, Huércal-Overa, Almería: H. Sánchez-Martínez.
- Hospital Juan Ramón Jiménez, Huelva: M. Ramos, T. Ferrer.
- Hospital Ciudad de Jaén: E. Baeyens.
- Hospital de Osuna, Sevilla: J. Pérez-Martínez.
- Hospital Marqués de Valdecilla, Santander: F. Pons, R. Taheri.
- Hospital de Ronda, Málaga: V Díaz-Morán.
- Hospital Xeral-Calde, Lugo: S. Ávila-Nasi.
- Hospital de Donosti, San Sebastián: M. García-Bengoetxea.
- Hospital de Basurto, Bilbao: S. Blanco, P. Martínez.
- Hospital Gregorio Marañón, Madrid: R. Banares.
- Hospital General de Valencia: M. Diago.
- Hospital Clínico Universitario Miguel Servet, Zaragoza: M.A. Simón.
- Hospital de Laredo, Cantabria: M. Carrasco.
- Hospital Clinic, Barcelona: M. Bruguera.

### REFERENCES

13. Stickel F, Patsenker E, Schuppan D. Herbal hepatotoxicity. J Hep-


