ORIGINAL PAPERS

# Hepatotoxicity associated with statin use: Analysis of the cases included in the Spanish Hepatotoxicity Registry

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## ABSTRACT

**Objectives:** The hepatotoxic potential of statins is controversial. The objectives of this study were to describe the relative frequency of hepatotoxicity caused by statins and the phenotypes found in Spain.

**Patients and methods:** The incidence of hepatotoxicity attributed to statins in the Spanish Hepatotoxicity Registry (REH) were studied and compared with those attributed to other drugs.

**Results:** Between April 1994 and August 2012, the REH included a total of 858 cases of which 47 (5.5 %) were attributed to statins. Of these, 16 were due to atorvastatin (34 %); 13 to simvastatin (27.7 %); 12 to fluvastatin (25.5 %); 4 to lovastatin (8.5 %) and 2 to pravastatin (4.3 %). Statins represented approximately half of the cardiovascular group which occupied 3er place (10 %), after anti-infectious agents (37 %) and central nervous system drugs (14 %). The hepatocellular pattern was predominant, especially in the simvastatin group (85%), the cholestatic/mixed pattern was more frequent with fluvastatin (66 %) and had a similar distribution to atorvastatin. Patients with statin-induced toxicity were older (62 years versus 53 years, $p < 0.001$) and more often demonstrated an autoimmune hepatitis phenotype (8.5 % versus 1.4 %, $p < 0.003$).

**Conclusions:** Statins are not a common cause of hepatotoxicity in Spain. Atorvastatin is the statin involved in the greatest number of incidents. The liver injury pattern varies among the different statins. The hepatitis phenotype with autoimmune features appears to be a characteristic signature of statin-induced hepatotoxicity.

*Key words:* Hepatotoxicity. Statins. Atorvastatin. Causality. Autoimmunity.

## INTRODUCTION

Liver damage caused by drugs, herbal products or dietary supplements, also known as DILI (Drug Induced Liver Injury) is an adverse reaction that is generally unpredictable and is associated with many commonly used drugs that constitutes a significant cause of potentially severe acute and chronic liver damage (1). DILI is responsible for approximately 11 % of cases of acute liver failure cases in the US (2) and 13 % in Spain (3). Adverse liver reactions are also the primary cause of developmental interruptions, usage warnings and removal of drugs from the market (4). Statins are a group of drugs used widely for first line treatment to lower LDL cholesterol levels and for the primary and secondary prevention of cardiovascular events.

The hepatotoxic potential of statins continues to be controversial. Only a small proportion of patients who participated in clinical trials with statins experienced transaminase elevations. Elevations achieved at least 3 times the upper limit of normal in 0.1-2.7 % of cases (5). The risk of liver profile changes associated with statins seen in clinical trials is no greater in the placebo group when low or moderate dosages are used (< 40 mg/day), less than 1 %, and the rate reaches 3 % with high dosages (80 mg/day) (6). These elevations are rarely

associated with clinically-expressed DILI (7). Despite the pharmacokinetic, lipophilic and metabolic differences among statins, they all appear to be capable of producing hepatotoxicity (8).

It is well known that the most common cause of mild alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations in patients who use statins is non-alcoholic fatty liver (5). A widely-held belief was to consider patients with non-alcoholic fatty liver or other varieties of chronic liver disease to be at an increased risk of statin-induced DILI. However, statins are not only safe and effective in patients with fatty liver (9), they also improve underlying biochemical and histological alterations (5). In addition, other beneficial effects include decreased portal vein pressure and decreased risk of hepatocellular carcinoma in patients with diabetes (10,11).

Since coming on the market, the published cases on statin-induced hepatotoxicity have been scarce when considering the large number of consumers, making them still considered as safe and well tolerated (7).

We have performed this study using the Spanish Hepatotoxicity Registry in order to evaluate the relative importance of statin-induced hepatotoxicity in Spain as compared to other drugs, as well as the potential hepatotoxicity among them, and to describe the injury patterns and prognosis.

## MATERIALS AND METHODS

The data used were extracted from the Spanish Hepatotoxicity Registry founded in 1994 and coordinated by 2 of the authors (RJA and MIL). The REH includes more than 40 clinical units from around Spain (12) that use a uniform methodology for identifying cases and collecting information and their subsequent inclusion in the Registry. This methodology has previously been described in detail (12,13).

Patients in the registry were identified using a search according to type of statin. A structured protocol containing the following elements was used to collect the data (13): Relevant clinical data on the patient; risk factors for liver disease; regular treatment and start and duration of use of each of the drugs; temporal relationship between the start of medication use and the onset of symptoms and/or laboratory changes; temporal relationship between discontinuance of the suspected agent and recovery from liver dysfunction. In addition, other causes of liver disease were ruled out: Recent viral hepatitis A (HAVab IgM), B (HBV-ab IgM) or C (HCVab and RNA by PCR); autoimmune diseases [antinuclear antibodies (ANA), antimitochondrial antibodies and anti-smooth muscle antibodies (ASMA)] and biliary obstruction by imaging study (abdominal ultrasound or MR cholangiography). In the same manner, if the clinical context warranted, CMV, EBV, herpes virus infection and HEV infection were ruled out.

Causality was evaluated using clinical judgment and later evaluated by applying the scale proposed by the Council for International Organizations of Medical Sciences (CIOMS), also called the Roussel-Uclaff Causality Assessment Method (RUCAM) (14). Only those cases scored by the CIOMS scale as possible, probable or highly probable were included in the database.

Two successive liver injury definitions were used. The standard definition of liver damage formulated by the international consensus group in 1989: Increase of two times the upper limit of normal (ULN) in ALT or conjugated bilirubin; or the combination of the increase in aspartate aminotransferase (AST), AP and total bilirubin with one of these greater than twice the ULN (15). The liver damage criteria were redefined in 2011 by an expert group, raising the cut-off threshold for ALT or AST when these are elevated in an isolated manner ≥ 5 ULN. Also considered as criteria for liver damage in this consensus group were an AP ≥ 2 x ULN or the combination of an increase in ALT > 3 x ULN and total bilirubin > 2 x ULN (16). This last criteria complies with the Hy's Law, which predicts at least 10 % fulminant disease (4). The liver damage pattern was established based on the (ALT/ULN)/AP (ULN) ratio. In this way, if it was greater than 5 it was hepatocellular, lower than 2 cholestatic and between 2 and 5 mixed damage. The term chronic DILI is reserved for cases in which the damage persisted for more than one year (15).

DILI was defined as an autoimmune phenotype when it combined the presence of autoantibodies with histological findings suggestive or compatible with autoimmune hepatitis and/or an at-risk HLA serotype.

The data obtained were analysed using IBM SPSS Statistics Version 20. A descriptive analysis was done for the cases of statin-induced hepatotoxicity found in the registry and a comparative analysis was made with the remaining cases of hepatotoxicity. The Chi-squared parametric test was used for comparison of qualitative variables. The ANOVA or Kruskall-Wallis test was used for comparing qualitative variables with quantitative variables. Student's t test was used for comparison of quantitative variables. Differences were considered statistically significant if the $p$-value was less than 0.05.

## RESULTS

Between 1994 and August 2012, 858 cases were included in the Spanish Hepatotoxicity Registry. Anti-infectious agents (36 %), CNS drugs (14 %) and cardiovascular drugs (10 %), including statins, are responsible for the majority of cases in the hepatotoxicity registry.

Of the 858 cases, 47 were attributed to statins and 811 to an agent other than a statin. The comparative demographic characteristics of the patient cohort are shown in table I. The mean age of presentation in the statin group was greater than

**Table I. Characteristics of the statins group vs. other treatments group**

| Variable | Statins (n = 47) | Other treatments (n = 811) | p value |
|---|---|---|---|
| Age (range) | 62 (39-83) | 53 (11-90) | 0.001 |
| Sex (men) | 23 (49 %) | 418 (52 %) | 0.72 |
| Time of onset ± SD | 131.80 ± 304 | 84.30 ± 376 | 0.40 |
| Median, days | 57 | 21 | |
| Treatment duration days ± SD | 153.77 ± 305 | 101.35 ± 375 | 0.35 |
| Median, days | 62 | 27 | |
| Jaundice | 25 (53.2 %) | 515 (64 %) | 0.18 |
| Hospitalization | 19 (40 %) | 398 (49 %) | 0.34 |
| DILI with autoimmune findings, n (%) | 4 (8,5 %) | 11 (1.4 %) n = 790 | 0.003 |
| Positive antibodies, n (%) | 10 (25 %) n = 40 | 127 (21 %) n = 594 | 0.17 |
| Type of liver injury: | | | |
|   Hepatocellular | 24 (51.1 %) | 449 (55.36 %) | 0.25 |
|   Cholestasic/mixed | 23 (48.94 %) | 309 (38.10 %) | |
| Initial laboratory parameters, average (range): | | | |
|   TB (mg/dL) | 5.3 (0.2-20.4) | 7.5 (0.2-45.6) | 0.06 |
|   ALT (xULN) | 17 (1.95-90.17) | 20 (0.34-203.37) | 0.53 |
|   AP (xULN) | 2.96 (0.51-15.92) | 2.04 (0.07-22.18) | 0.007 |
|   Hy´s Law | 9 (19.1 %) | 266 (32.8 %) | 0.4 |
| Chronicity (n/ %) | 9 (19.1 %) | 174 (21.4 %) | 0.26 |

ALT: Alanine aminotransferase; AP: Alkaline phosphatase; TB: Total bilirubin; ULN: Upper limit of normal.

the overall group (62 *versus* 53, $p < 0.001$). The latency, hospitalization rate, severity defined by the percentage of cases that meet Hy's Law and the mean resolution time was similar in both patient groups. About 25 % of the overall group had hypersensitivity phenomena, meaning fever, rash, eosinophilia, lymphopenia, autoantibodies and/or arthralgias, with these manifestations seen in 17 cases (36 %) from the statin group. Although the distribution of hepatocellular, cholestatic and mixed liver injury patterns was similar in both groups, AP values > ULN were more elevated in the statin group (2.96 *versus* 2.04, $p < 0.007$) and the average bilirubin levels was lower without achieving statistical significance (5.3 mg/dL *versus* 7.5 mg/dL, $p < 0.06$). The proportion of DILI cases with an autoimmune phenotype was significantly greater in the statin group (8.5 % *versus* 1.4 %, $p < 0.003$).

Of the 47 cases of statin-induced hepatotoxicity, 22 were men (47 %). The majority (72 %) took another medication concomitantly. However, 32 patients (68 %) had only been taking lipid-lowering treatment for 3 months. Jaundice was present in 25 patients (53 %) and presented in similar proportion in both genders. Nineteen per cent of cases complied with Hy's Law. Hospitalization resulted in 19 patients (40 %). The predominant liver damage pattern was hepatocellular, which occurred in 24 cas-

es (51 %). Sixty-four per cent of patients had a CIOMS/RUCAM scale score between 6 and 8. The recovery time was within the first three months in 34 % of cases with a mean recovery time of 153 days. 19 % of patients (9 cases) had chronic damage. There were 2 deaths in the 47 cases reported but they were due to causes other than the liver damage caused by the suspected agent (Table II).

The distribution by type of statin was: 16 were due to atorvastatin (34 %); 13 to simvastatin (27.7 %); 12 to fluvastatin (25.5 %); 4 to lovastatin (8.5 %) and 2 to pravastatin (4.3 %). Six of these 47 cases met the liver damage criteria established by the International Consensus Group in 1989 (14). However, they did not achieve transaminase levels to meet the recent definition by Aithal et al. (15). Of these 6 cases, 3 were due to simvastatin, 2 to pravastatin and 1 to atorvastatin; 5 were women; the average ALT and AP levels compared to the ULN were 2.25 and 1.25 IU/L, respectively, and all had a CIOMS score equal to or greater than 6 (5 cases were probable and 1 highly probable). It should be noted that 2 of these episodes occurred in the same patient. Neither of the two episodes presented with jaundice or hypersensitivity phenomena and the liver profile normalized shortly after discontinuing the drug. The remaining cases met the most stringent criteria for lever injury currently used in the majority of studies (15).

**Table II. Characteristics of statins-induced liver damage by specific agents**

| Variable | Atorvastatin (n = 16) | Simvastatin (n = 13) | Fluvastatin (n = 12) | Lovastatin (n = 4) | Pravastatin (n = 2) | Total (n = 47) |
|---|---|---|---|---|---|---|
| *Male* | 10 | 4 | 7 | 0 | 1 | 22 |
| < 55 | 3 | 1 | 5 | 0 | 1 | 10 |
| > 55 | 7 | 3 | 2 | 0 | 0 | 12 |
| *Female* | 6 | 9 | 5 | 4 | 1 | 25 |
| < 55 | 0 | 0 | 2 | 0 | 0 | 2 |
| > 55 | 6 | 9 | 3 | 4 | 1 | 23 |
| *Treatment duration* | | | | | | |
| < 1 month | 4 | 2 | 6 | 4 | 1 | 17 |
| > 1-3 months | 5 | 7 | 3 | 0 | 0 | 15 |
| 3-6 months | 3 | 2 | 3 | 0 | 0 | 8 |
| 6-12 months | 1 | 1 | 0 | 0 | 0 | 2 |
| > 1 year | 1 | 0 | 0 | 0 | 1 | 2 |
| > 5 years | 2 | 0 | 0 | 0 | 0 | 2 |
| Jaundice | 9 | 6 | 7 | 3 | 0 | 25 |
| Hy's Law | 5 | 3 | 0 | 1 | 0 | 9 |
| Hypersensibility | 8 | 4 | 5 | 0 | 0 | 17 |
| Hepatocellular pattern | 8 | 11 | 4 | 1 | 0 | 24 |
| Cholestasic/mix pattern | 8 | 2 | 8 | 3 | 2 | 23 |
| Hospitalization | 8 | 5 | 4 | 2 | 0 | 19 |
| *CIOMS/RUCAM score* | | | | | | |
| 3-5 | 2 | 2 | 2 | 0 | 0 | 6 |
| 6-8 | 11 | 7 | 9 | 1 | 2 | 30 |
| > 8 | 3 | 4 | 1 | 3 | 1 | 11 |
| *Recovery time* | | | | | | |
| 3 months | 4 | 3 | 7 | 1 | 1 | 16 |
| 3-6 months | 3 | 4 | 0 | 0 | | 7 |
| 6-12 months | 1 | | 1 | 1 | | 3 |
| > 12 months | 3 | 2 | 2 | 2 | | 9 |

## Atorvastatin-induced hepatotoxicity

Sixteen cases of DILI attributed to this drug were identified. Of these, 10 were in men (63 %). Hypersensitivity phenomena occurred in 50 % of cases. Nine patients (56 %) had jaundice. The hepatocellular pattern was present in half of cases. The CIOMS/RUCAM score had a probable value in 69 % of cases. Of these 16 patients, 6 underwent liver biopsy and 4 of these showed eosinophils. Two of the cases were classified as drug-induced autoimmune hepatitis. One of these cases had levels of ANA + 1/640 and IgG levels of 25/7 g/L. The liver biopsy revealed differentiated areas of micronodular cirrhosis and signs of subfulminant hepatitis (suggestive of drug-induced toxicity *versus* auto-immune hepatitis). The liver profile continued to be altered one year after onset. In another case, liver biopsy was not done but the ANA was positive at a titer of 1/160, as well as HLA DR-3 with an HAI index of 13. The recovery time was 6 months in this patient. Ten month prior, pravastatin had been discontinued due to elevated transaminase levels.

## Simvastatin-induced hepatotoxicity

Thirteen cases were found in the registry, 4 of which (31 %) were men. Jaundice was present in 6 patients (46 %).

The hepatocellular pattern was clearly predominant in this group. Two patients in this group died of causes other than liver damage. One case was classified as drug-induced autoimmune hepatitis. This case had ANA titers of 1/1,280 and the biopsy revealed panlobular and portal-periportal hepatitis with intense lymphoplasmacyte infiltrate and pyknocytic necrosis, hepatocellular ballooning with rosette formation and hemosiderin deposits in the Kupffer cells. This patient was put on steroid treatment. The recovery time was 2 months.

## Fluvastatin-induced hepatotoxicity

There were 12 cases of DILI associated with fluvastatin use in the registry at the time of analysis. Of these, 7 were men (58 %). The hepatocellular pattern was present in 33.3 % of cases. Liver biopsy was carried out in 4 cases. Only one of these revealed eosinophils. One case was classified as drug-induced autoimmune hepatitis with ANA titers of 1/640 and homozygous for HLA DR 3. The biopsy revealed periportal hepatitis with slight inflammatory activity and mild hemosiderosis. Treatment was started with corticosteroids 4 months after onset of the index episode which were tapered until complete discontinuation 16 months later. Azathioprine treatment was added 6 months after the index episode. The liver profile normalized 8 months after the index episode.

## Lovastatin-induced hepatotoxicity

There were only 4 cases recorded in the registry. The 4 patients were women. Three of these had jaundice. None had hypersensitivity phenomena. The hepatocellular pattern was only present in one case. Liver biopsy was carried out in two patients and neither had eosinophils.

## Pravastatin-induced hepatotoxicity

There were only 2 were registered, one from each gender. There was no jaundice. The 2 cases had a cholestatic/mixed pattern. Both recovered from the liver injury.

## DISCUSSION

Statins are drugs used worldwide to control cholesterol levels in order to prevent cardiovascular events.

The use of lipid-lowering medications in Spain went from 18.9 DDD (defined daily doses, per inhabitant per day) in 2000 to 102.6 DDD in 2012, an increase of 442 %. Statins are the most widely used drugs, representing 89.3 % of lipid-lowering agents in 2012. The most widely-used drug during the study period was atorvastatin, which went from 3.8 DDD in 2000 to 42.8 DDD in 2012 (increase of 1,012 %). It should also be noted that simvastatin was the second most commonly used statin over the course of this period. The sum of atorvastatin and simvastatin represented 78.2 % of total statin consumption in 2012 (17).

Toxic liver injury is an adverse effect of many commonly used medications. A characteristic element of toxic hepatitis is that it may present with several phenotypes capable of resembling other liver diseases and because specific markers for hepatotoxicity are not still available, the diagnosis is based on a compatible chronology between drug intake and the appearance of the liver dysfunction as well as the exclusion of alternate causes (16). Hepatotoxicity registries constitute a useful tool for reinforcing detection of cases with quality information which increases guarantees on certainty and allow for analysis of large series of well-phenotyped cases (12), as well as collecting biological samples to carry out genotype and mechanistic studies (18). This study had the objective of establishing the frequency with which statins are involved in episodes of hepatotoxicity compared with other drugs and describing their clinical presentation phenotypes and severity. In order to do this, we analysed cases of hepatotoxicity attributed to statins in the REH, a registry that is not restricted to drugs or drug groups. As a result, this registry includes any suspected case of hepatotoxicity that participating investigators detect. This circumstance, while not allowing for incidence figures to be established since there was no data on the exposed population (denominator) nor was it likely that the total number of cases that occurred was actually collected (numerator) (just probably some of the more severe ones), enables to diagram the relative frequency of induction of liver damage from drugs and drug groups.

In this analysis, statins constituted 5.5 % of cases of hepatotoxicity in the REH. This represents approximately half of all drugs from the cardiovascular group, which at 10 % constituted 3rd place. These data show that although statins are not a common cause of hepatotoxicity in our area, their appearance is not exceedingly rare either. In fact, there is a large debate on whether or not statins are drugs with significant hepatotoxic potential. There are authors who suggest that the liver toxicity of statins is a myth and they argue that statin-induced acute liver failure is no greater than idiopathic causes (19,20). Nevertheless, of a series of 133 incidents of drug-induced liver failure (excluding paracetamol) from different hospitals in the US, 10 were attributed to statins either on an isolated basis or in combination with other drugs (3). It is interesting to note that in the recently published populational study on the incidence of DILI in Iceland, of the 96 cases identified prospectively over the course of 2 years, one statin (atorvastatin) was responsible for 2 incidents (2 %), placing it on the low end of drugs with the highest incidence. Resources from the national health system of Iceland were used in this study. This has a powerful database with information on the total number of subjects exposed to each

drug in order to calculate the risk of hepatotoxicity with each medication entered, which in the case of atorvastatin was 1/3,696 patients treated, greater than that seen with diclofenac, a drug that is widely known for its hepatotoxic potential (21).

The higher frequency of cases caused by atorvastatin is also consistent with the findings from two recently published case series (7,22). Russo et al. (2009) (7) reviewed all of the cases of statin-induced hepatotoxicity published up to that time. They identified 40 cases from 26 different publications. For their part, Björnsson et al. performed a review of suspected cases of statin-induced adverse events report to the Swedish Adverse Drug Reaction Advisory Committee (SADRAC) between 1998 and 2010. The most common adverse reaction was DILI in 57 % of cases. They only included cases with aminotransferase levels greater than 5 above the ULN and/or twice the upper limit of normal for alkaline phosphatase, resulting in a total of 73 cases (22). The general characteristics of both series compared with the series analysed in the present study are shown in table III. A differential finding for statin-induced hepatotoxicity in our series is that it affected to subjects of more advanced age. This peculiarity was seen in the other series (7,22). However, it risky to conclude that advanced age increases the risk of hepatotoxicity caused by these compounds and a prescribing bias cannot be excluded due to the clinical context in which these drugs are normally used. The latency period was also highly variable and occasionally long, both in our series (with latency periods greater than 1 year in several cases up to 5 years on one occasion) and in the analysis by Russo et al. (from 5 days to 4 years). These prolonged latency periods occurred with atorvastatin in our series. In another recently published series, atorvastatin was also responsible for a case of hepatotoxicity after 2.5 years of treatment (23). A very prolonged latency period constitutes and argument against the responsibility of a given drug, making it difficult to attribute a liver injury to hepatotoxicity, in addition to involving a challenge from an etiopathogenic point of view.

Idiosyncratic hepatotoxicity may be partially dose dependent according to the results of a study that evaluated the incidents of acute liver failure, death and liver transplant registered in 2 pharmaceutical databases corresponding to the 200 most commonly prescribed drugs in the US which found a linear association between the daily dose and the risk of severe liver toxicity. The greatest risk was in those who used a dosage greater than 50 mg/day when compared to those prescribed a lower dosage (24). The different statins were prescribed at highly variable dosages. Twelve (23 %) cases in our series took dosages greater than 50 mg/day (11 fluvastatin and 1 atorvastatin). This proportion is lower than that seen with other therapeutic groups such as antibiotics and NSAIDs and may, at least in part, explain the lower hepatotoxic potential of statins as a therapeutic group. However, it is worth establishing an association between the total daily dosage consumed and the greater relative toxic potential of fluvastatin and atorvastatin since in order to do this, we would have to know the relative rate of exposure for both statins compared to the total. However, it appears to be improbable that at least in the case of atorvastatin, the dosage has a relevant influence given that only 1 in 16 cases took a dosage greater than 50 mg/day.

On the other hand, although 2 patients died in our analysis, none of these were due to complications of the liver injury, unlike that reported in the series by Russo et al. (7) and Björnsson et al. (22), which included 2 cases of death due to the liver injury, translating to a mortality of 5 % and 2.7 %, respectively (7,22). This underscores the potential severity of statin-induced hepatotoxicity.

**Table III. Comparison of our series with those previously published**

| Hepatotoxicity associated with statin use | Our series | Russo et al. (7) | Björnsson et al. (22) |
|---|---|---|---|
| Number of cases | 47 | 40 | 73 |
| Atorvastatin (%) | 34 | 45 | 41 |
| Simvastatin (%) | 28 | 20 | 38 |
| Fluvastatin (%) | 25 | NR | 15 |
| Pravastatin (%) | 8 | 5 | NR |
| Lovastatin (%) | 4 | 25 | NR |
| Male (%) | 47 | 42 | 55 |
| Average age (years) | 62 | 6th-7th decade | 64 |
| Predominant pattern | Hepatocellular | Hepatocellular | Hepatocellular |
| Autoimmune DILI | 4 | 6 | NR |
| Jaundice (%) | 53 | NR | 34 |
| Mortality (n.º cases) | 0 | 2 | 2 |

NR: Not reported.

One differential finding in this series with respect to the collection of other cases of hepatotoxicity included in the registry was the greater number among statins of an autoimmune phenotype with the presence autoantibodies typically found in type-I autoimmune hepatitis (ANA and ASMA). The occasional presentation of statin-induced toxicity with an autoimmune phenotype has previously been described in the literature (7). Of the 4 cases identified as statin-induced autoimmune hepatitis, 3 were in women. Autoimmune hepatitis is an unknown etiopathogenic entity. However, it has sometimes been suggested that a viral agent (virus A and especially virus C), as well as drugs (25), could act to unmask the disorder, which raises questions on the spontaneous origin of classic autoimmune hepatitis for one author (26).

Nevertheless, a retrospective study that analysed a large database from the Mayo Clinic indicated that toxic hepatitis with an autoimmune phenotype characteristically improved with discontinuance of the responsible drug and if steroid treatment was required, it was possible to discontinue treatment permanently once remission was achieved without relapse of the disease (27), while recurrence after discontinuing the drug is the rule in "idiopathic" autoimmune AIH (28-30). Two of the 4 cases with an autoimmune phenotype in our series required steroid treatment and had an excellent response, making discontinuance possible without reactivation of the liver injury. An emerging topic of interest that can only be approached prospectively in large patient cohorts is the role of toxic (isolated or recurrent) liver injury (31) as a predisposing factor to the later development of autoimmune hepatitis.

In conclusion, this analysis confirms previous studies that indicate that statin-induced hepatotoxicity, though not especially common, is not exceptional. The study describes the most common phenotypes for DILI associated with the use of these drugs. Autoimmune hepatitis is a characteristic signature of statin-induced hepatotoxicity. Therefore, a rigorous inquiry of the use of these drugs is needed in patients with liver alterations and manifestations of autoimmunity.

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