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Retrieval and treatment of patients with primary biliary cholangitis who are lost in the health system

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AO: Conceptualization, Funding acquisition, Methodology, Supervision, Writing – original draft; JY: Methodology, Data curation, Investigation; CA: Data curation, Investigation; MT: Data curation, Writing – review & editing; PE: Data curation, Investigation; MHP: Data curation, Investigation; CSC: Data curation, Investigation; IS: Data curation, Investigation; CSF: Formal Analysis; DMA: Data curation, Investigation; IC: Data curation, Investigation; FDF: Data curation, Investigation; RR: Data curation, Investigation; SL: Project administration, Resources, Software; EM: Conceptualization, Supervision, Writing – review & editing.

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KEY WORDS
Primary biliary cholangitis. Lost in the system. Lost to follow-up. Linkage to care.

ABBREVIATIONS
PBC: Primary biliary cholangitis; UDCA: Ursodeoxycholic acid; AMA: Antimitochondrial antibody; ALP: Alkaline phosphatase.

CONFLICT OF INTEREST
Antonio Olveira: Grant, personal fees, and nonfinancial support from Intercept Pharmaceuticals.
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ABSTRACT
The existence of hepatitis C patients who are lost to follow-up in the health system is shown to have negative consequences. We aimed to investigate this issue in primary biliary cholangitis. We analysed the databases (Immunology, Biochemistry, clinical reports, drug dispensation, appointments) of 4 reference hospitals in Spain (serving a population of 1.450.000 persons). The diagnosis of primary biliary cholangitis was based on an antimitochondrial antibody titer ≥1:80, chronically elevated alkaline phosphatase, and absence of other liver disease. Patients were classified as lost in the absence of reports indicating a diagnosis, specific medical follow-up, and/or treatment with bile salts. A total of 1372 patients with antimitochondrial antibody titers ≥1:80 were included between January/2010-June/2019. We classified 697 (50.8%) as having
primary biliary cholangitis and identified 100 patients (14.3%; 95%CI: 11.8-17.2) as lost. Of these, 30 were contacted and retrieved: Median age 70 years, 93% female, median alkaline phosphatase 185 IU/L, 10% had pruritus, and 27% had a transient elastography value >9.5 kPa. The disease was confirmed and ursodeoxycholic acid was started in all 30 patients. Death was liver-related in 6 of the 100 patients classed as lost. Up to 14.3% of patients (1 out of 7) with a definitive diagnosis of primary biliary cholangitis remain undiagnosed, thus preventing monitoring and treatment. More than a quarter are at risk of advanced liver disease and its complications. It is necessary to identify and retrieve patients lost in the system. Searching hospital databases is a suitable approach for this goal.

**INTRODUCTION**

Renewed interest in primary biliary cholangitis (PBC) (1,2) is evidenced by the intense research carried out in recent years to improve our knowledge of the natural history of the disease, its complications, and the outcome of the only treatment available for decades, namely, ursodeoxycholic acid (UDCA). UDCA leads to biochemical and histologic improvement in most patients, with the resulting benefits in terms of need for liver transplant and mortality (1-4). Therefore, it has been and continues to be almost universally administered for the treatment of PBC. Recent developments in treatment provide a better prognosis for patients with an inadequate response to their first line of therapy with UDCA. Obeticholic acid leads to significant decreases in alkaline phosphatase, bilirubin, and transaminases (5), as well as to stabilization or regression of liver fibrosis in 71% of cases (6). This agent has been approved as second-line treatment (1,2). Bezafibrate also leads to a marked decrease in liver biochemistry values and an appreciable improvement in pruritus (7,8), and it has been proposed as off-label second-line treatment (1,2). The combination of both drugs was recently shown to be cumulative and safe (3). Furthermore, the longer the time lag between diagnosis of PBC and initiation of treatment, the lower the probability of response (9).

Therefore, it is very important to ensure that patients with PBC are identified so that they can have access to follow-up and appropriate treatment, thus modifying progress to cirrhosis and its associated complications. However, this objective clashes with the
scarce prevalence and incidence of PBC, with usual values of 1.9-40.2/100,000 and 0.3-5.8/100,000/year, respectively (1). In Spain, prevalence is estimated at 19.5/100,000 and incidence at 1.7/100,000/year (10). These figures indicate that PBC is a rare disease and, as such, not usually suspected by physicians, with the risk that patients can be lost at any point during linkage to care. A similar loss has been reported in several countries in other liver diseases, such as hepatitis B (11-13) and, more particularly, hepatitis C (12-18). Therefore, based on data from 4 Spanish hospitals (Hospital Universitario La Paz, Madrid; Hospital Universitario de Canarias, Santa Cruz de Tenerife; Hospital Universitario de Santiago de Compostela, Santiago de Compostela; Hospital Universitario de Valdemoro, Valdemoro), we aimed to identify patients with PBC who were lost in the system and to provide access to appropriate care. To our knowledge, this is the first such initiative in PBC.

METHODS

The 4 study hospitals serve a population of 1,450,000 persons within the public health network and are the reference institutions for primary and specialized care in their covered areas. They are also the reference centers for liver disease in their covered areas and perform all biochemical, microbiological, and immunological analyses. The results are computerized and can be accessed via the intranet at each center. The system also provides access to all episodes of care received by the individual patient, medical reports (all specialties), and current and previous drug prescriptions.

Design of the study

First, the immunology laboratories generated all of the results for antimitochondrial antibody (AMA) titers ≥1:80 between January 2010 and June 2019. These results were cross-referenced with alkaline phosphatase values (ALP). Registries were analysed for the laboratory results from other possible liver diseases, medical reports, treatment with UDCA, and episodes of care by any specialty. Patients with AMA ≥1:80, ALP above the upper limit of normal on at least 2 separate occasions, and absence of other liver disease were considered to have PBC (1,2). The results were reviewed individually, and patients were classified as baseline PBC (diagnosed and treated from diagnosis), baseline PBC lost in the system (no diagnosis, follow-up, or treatment of the disease),
PBC developed and detected (baseline normal ALP increased over time, with detection and treatment), and PBC developed and lost in the system (normal baseline ALP increased over time, with no detection or treatment). The department requesting the AMA test was analysed (Gastroenterology, Internal Medicine, Rheumatology, other). All of the patients considered lost and rescuable were contacted by telephone or by mail in order to inform them that they might have the disease and to invite them to attend the Hepatology Outpatient Clinic. At this visit, we took a history, performed a full physical examination and laboratory analysis to confirm PBC and to rule out other causes of liver disease, and performed abdominal ultrasound. We also performed transient elastography, with a value of >9.5 kPa considered to indicate a poorer prognosis (1). A reasonable effort was made (at least 3 calls) in the case of patients who could not be contacted initially. Patients were asked about the reason for foregoing follow-up of their disease, with 2 options: patient’s decision or not being aware of the disease. Lost patients with a confirmed diagnosis of PBC after this evaluation were treated in line with daily clinical practice.

**Ethical issues**

Our project was assessed and approved by the Ethics Committee of Hospital Universitario La Paz (Madrid, Spain). Specific approval was requested to contact patients, taking into account the restrictive data protection laws in force in Spain (Law 3/2018 of 5 December 2018) and the European Union (Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016). This legislation enables access to patient data in order to prevent a risk of serious danger for a patient’s health, provided that there is sufficient reason and professional secrecy is maintained. The Ethics Committee considered that the protocol fulfilled the bioethical principles of autonomy, beneficence, nonmaleficence, and justice and that contact was ethically desirable, thus exempting us from the need for previous informed consent.

**RESULTS**

During the study period, we identified 1372 patients (86% women) with AMA ≥1:80. Of these, 697 (50.8%) were classified as having PBC: 579 (83.1%) were diagnosed and
treated from the outset, 18 (2.6%) had increased ALP during follow-up after being detected and treated, 91 (13.1%) were identified as lost in the system at baseline, and 9 (1.3%) had increased ALP during follow-up without being detected. Therefore, we detected a total of 100 patients (14.3%; 95%CI: 11.8-17.2) as having PBC and being lost in the system. ALP remained permanently normal in 675 patients (49.2%) over a mean follow-up of 2.96±2.41 years, and 3.8% (27/702; 95%CI: 2.5-5.5) developed PBC during this period. No statistically significant differences were detected between patients who developed PBC over time and those who did not with respect to age, sex, AMA titer, or baseline ALP (data not shown).

The departments requesting AMA testing in the 697 patients with PBC were Gastroenterology (368 [52.8%]), Internal Medicine (143 [20.5%]), Rheumatology (51 [7.3%]), and other (135 [19.4%]). The percentage of PBC patients lost (both at baseline and with increased ALP during follow-up) for each was 6%, 14%, 31.4%, and 31.1%, respectively (p<0.001 for a lower proportion of patients lost in Gastroenterology compared with the other departments [chi-square]).

Of the 100 patients lost in the system, 31 had died, 2 refused care, and 37 were unable to be contacted owing to a lack of data or lack of response. Of the 31 patients who died, 6 died of liver disease, that is, without an etiological diagnosis of PBC. Thirty patients agreed to be treated at the hepatology clinic. The reason for the lack of follow-up in all of these patients was unawareness of the disease. PBC was confirmed in all 30 patients, who are now receiving treatment with UDCA. Table 1 and Figure 1 show their main clinical, laboratory, and elastography data.

DISCUSSION

Despite increased interest in PBC in recent years, our data show that 1 in every 7 affected patients is unaware of the disease and does not receive appropriate medical attention, including treatment. To our knowledge, this is the first study aimed at detecting and rescuing patients with PBC lost to follow-up.

The percentage of patients rescued (30%) seems satisfactory and comparable to that reported in other projects of the same nature in hepatitis C (14). First, diagnosis is straightforward and was confirmed in all patients, thanks to the high sensitivity and
specificity of AMA, which make this antibody a very reliable marker (2). Second, all patients started treatment with an effective treatment, UDCA, for which experience is broad (19) and which has been shown to improve both liver biochemistry and the natural history of the disease (1-4). In addition, it does not have severe adverse effects (20), and failures can be managed with alternative therapies (1,2). Therefore, patients clearly benefited from our initiative. In fact, 27% of rescued patients had transient elastography values higher than 9.5 kPa, which is associated with a greater risk of liver decompensation, transplantation, or death (1). Furthermore, 6% of lost patients had died of a liver-related cause without being diagnosed with PBC. While these patients had a primary liver disease (mainly alcoholism and fatty liver), we do not know how the patient’s very probably undiagnosed PBC affected the course of the disease or how this could have been modified if the patient had been diagnosed and treated. Therefore, in order to prevent disease progression, lost patients must be detected and rescued. To do so, they must be identified using a combined laboratory analysis (AMA and ALP), which is an effective and easily applied strategy.

The problem of patients being lost in the health system is not to our institutions or to our health system and has been investigated elsewhere. Thus, within our specialty, similar situations have been reported in Canada, Holland, the United Kingdom, and Saudi Arabia, both for hepatitis C virus and hepatitis B virus (11-17). The largest study published to date was performed in Utrecht (The Netherlands) (14), where 14.1% of 1913 HCV serology results were identified as being lost to the system. Our finding was almost identical, thus demonstrating how widespread the problem is. Health care professionals have always considered data protection legislation to constitute an insurmountable barrier for access to lost patients; therefore, we have been reticent when searching for them, or the only initiatives undertaken have been somewhat timid. In the section on special categories, European regulations authorize the use of medical data in situations of interest for public health and to guarantee quality levels in health care. Similarly, the evaluation by our ethics committee supported the search for and contact with these patients. Therefore, we believe that our study and others could be used as the basis for future initiatives in PBC and other liver diseases.
Given that results are inadequately evaluated, the problem can be mitigated by setting up prospective warning mechanisms. The process to do so should not be complicated if based on an updated electronic clinical history (21). Furthermore, every attempt should be made to advance our knowledge of PBC. While these losses were significantly greater in specialties such as Internal Medicine and Rheumatology, which are more directly involved in PBC, patients are also lost in Gastroenterology. Successful rescue of these patients depends on direct access to a clinic specialized in liver diseases, where simplifying the cascade of care may increase the chances of successful rescue. Reaching patients will probably be facilitated by the fact that PBC is a rare disease and by telephone contact, which is much more dynamic.

Our study is subject to some limitations. First, we examine a problem and a course of action in Spain that may differ in other countries. Nevertheless, data from other countries lead us to believe that although the situation occurs in different settings, the incidence and solutions applied are similar to ours. Second, the retrospective design of the study prevents us from obtaining the reason for requesting AMA (e.g., increase in ALP, incidental finding in the study of rheumatic diseases), and this may have affected the probability of loss. Third, initiatives such as ours are time-consuming and expensive and require the participation of appropriately qualified staff. In our case, the whole process was carried out by medical staff. Given that our results were favourable, the process might be managed by specialized nursing staff in the future (14). Finally, PBC-AMA negative patients would be missed applying our searching strategy. Adding antiSP100 and antiGP210 antibodies to the Immunology database request would be of help (1,2).

In conclusion, a significant number of patients with PBC and confirmatory diagnostic data have not been evaluated and are therefore lost in the health system. Since lost patients are not treated or followed, they are at risk of advanced liver disease, including cirrhosis and its complications. Affected patients can be searched for and rescued effectively by analysing previous laboratory results in health system databases.

REFERENCES


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To Intercept Pharmaceuticals for its financial support of translation into English.

**TABLES**

Table 1.- Main characteristics of patients retrieved.

<table>
<thead>
<tr>
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<th>N=30</th>
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<tbody>
<tr>
<td>Age [years], median (IQR)*</td>
<td>70 (60-80)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>28 (93)</td>
</tr>
<tr>
<td>Other autoimmune disease, n (%)</td>
<td>14 (47)</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2)), median (IQR)</td>
<td>26.9 (26-29-1)</td>
</tr>
<tr>
<td>Pruritus, n (%)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Asthenia, n (%)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>ALP† (IU/L), median (IQR)</td>
<td>185 (135-321)</td>
</tr>
<tr>
<td>GGT‡ (IU/L), median (IQR)</td>
<td>101 (70-204)</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL), median (IQR)</td>
<td>0.6 (0.4-0.9)</td>
</tr>
<tr>
<td>Elastography (kPa), median (IQR)</td>
<td>7.1 (5.2-10)</td>
</tr>
<tr>
<td>Elastography &gt;9.5 kPa, n (%)</td>
<td>8 (27)</td>
</tr>
</tbody>
</table>

*IQR: interquartile range. †ALP: alkaline phosphatase. ‡GGT: gamma-glutamyl transpeptidase.