Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease; the autoimmune mechanism seems the most likely. As a result, PBC is frequently associated with other autoimmune diseases. The goal of our work is to determine the prevalence and type of autoimmune diseases associated with PBC and to assess their impact on the prognosis of the disease. Materials and methods: This is a retrospective study over a period of 22 years (1998-2019) including all patients followed for CBP. In all these patients, we systematically looked for: autoimmune hepatitis, dysthyroidism, and type 1 diabetes, dry syndrome, and celiac disease, dermatological and joint damage. The statistical analysis of the data was done using the SPSS software. The comparison of the biochemical response to ursodeoxycholic acid between patients with isolated CBP and those with CBP associated with autoimmune pathology was performed using the Chi2 test. A combination of variables was considered statistically significant if p < 0.05. Results: 90 patients (85 women and 5 men) followed for CBP were collected. The average age was 49+/12.3 years. Of these patients, 36 patients (42.9%) had an autoimmune disease associated with PBC. The discovery of these autoimmune diseases preceded the diagnosis of PBC in 9 cases (27.3%) and was concomitant in the remaining cases. Autoimmune hepatitis was found in 10 patients (12%), defining an overlapping syndrome. Other diseases were Hashimoto's thyroiditis (n = 9), basedow (n=1) dry syndrome (n = 10), celiac disease (n = 3), insulin-dependent diabetes (n = 2), systemic scleroderma (n = 1), rheumatoid arthritis (n = 1), Addison disease (n=1) Psoriasis (n = 1) vitiligo (n = 1). The comparison of the biochemical response to ursodeoxycholic acid between patients with isolated CBP and those with CBP associated with autoimmune pathology was statistically non-significant with p=0.67. Conclusion: In our series, the prevalence of autoimmune diseases associated with PBC was 40%. These diseases were dominated by autoimmune hepatitis, Hashimoto's thyroiditis and dry syndrome. Although their association does not appear to alter the prognosis for CBP or the response to AUDC, their screening must be systematic in order to initiate early and appropriate treatment. Although ursodeoxycholic acid is beneficial in the treatment of primary biliary cirrhosis, it has had no measurable effect on the autoimmune disorders associated with the disease.

Keywords: Primary biliary cholangitis; autoimmune diseases; Paris 2 criteria; ursodeoxycholic acid.

INTRODUCTION
Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease; the autoimmune mechanism seems the most likely. As a result, PBC is frequently associated with other autoimmune diseases. The etiology of PBC is unknown; however, it is assumed to be related to autoimmune mechanisms, supported by the discovery of lymphocytes in portal inflammatory infiltrates, the detection of characteristic antimitochondrial antibodies in about 90% of patients and the presence of associated autoimmune pathologies [1, 2]. The most common associated autoimmune disorders include autoimmune hepatitis, Hashimoto's thyroiditis and dry syndrome. Controlled clinical trials have shown that ursodeoxycholic acid (UDCA) improves the biochemical and clinical characteristics of PBC [3, 4]. However, there have been no reports of the effects of ADUC on autoimmune disorders associated with PBC. The goal of our work is to determine the prevalence and type of autoimmune diseases associated with PBC and to assess their impact on disease prognosis and therapeutic response to AUDC; therefore, we reviewed the data from our previously reported trial to determine whether disease improvement was also associated with improvement in these associated autoimmune diseases [4].

MATERIAL AND METHOD
It is a retrospective study over a period of 22 years (1998-2019) including all patients followed for PBC. In all our patients, we systematically searched for: autoimmune hepatitis (according to the Paris criteria the
presence of 2 of the 3 criteria: ALAT 5*LSN; serum IgG level 2*LSN or presence of AML; hepatic biopsy showing moderate to severe interface hepatitis) dysthyroidism (thyroid check-up, antithyroid autoantibodies), type 1 diabetes, dry syndrome (ophthalmological examination, Schirmer test and lip biopsy if clinical signs are present), celiac disease (duodenal biopsies) and dermatological or joint involvement (clinical examination). The statistical analysis of the data was done using the SPSS software. The comparison of the biochemical response to ursodeoxycholic acid between patients with isolated CBP and those with CBP associated with autoimmune pathology was performed using the Chi2 test. A combination of variables was considered statistically significant if $p < 0.05$.

RESULTS
90 patients (85 women and 5 men) followed for CBP were collected. The average age was 49+/-12.3 years. Of these patients, 36 patients (42.9%) had an autoimmune disease associated with PBC. The discovery of these autoimmune diseases preceded the diagnosis of PBC in 9 cases (27.3%) and was concomitant in the remaining cases. Autoimmune hepatitis was found in 9 patients (10%), defining an overlapping syndrome. Other diseases were Hashimoto thyroiditis in 10% (n = 9), basedow (n=1) dry syndrome in 11.1% (n = 10), celiac disease in 3.3% (n = 3), insulin-dependent diabetes (n = 1), systemic sclerosis (n = 1), rheumatoid arthritis (n = 1), Addison disease (n=1) Psoriasis (n = 1) and vitiligo (n = 1) (Figure 1). Patients with and without these associated conditions were clinically similar, age, gender and response to AUDC as shown in Table 1. The comparison of the biochemical response to ursodeoxycholic acid between patients with isolated CBP and those with CBP associated with autoimmune pathology was statistically non-significant with $p=0.67$

Table-1: Comparison of Other Clinical Features in Primary Biliary Cirrhosis Patients with and Without Associated Autoimmune Conditions

| Condition                        | Without Associated Conditions | With Associated Conditions | p Value |
|----------------------------------|-------------------------------|-----------------------------|---------|
| Age (yr)                         | 48.5 +/- 9.2                  | 46.4 +/- 9.3                | 0.12    |
| Gender                           |                               |                             | 0.10    |
| Male                             | 2                             | 2                           |         |
| Female                           | 46                            | 34                          |         |
| Hyper T                        | 36                            | 21                          | 0.82    |
| Asthenia                        | 8                             | 11                          | 0.13    |
| Anemia                          | 27                            | 16                          | 0.34    |
| Bilirubin elevated              | 13                            | 12                          | 0.48    |
| Symptosis                       | 26                            | 17                          | 0.42    |
| Portal II (good response)       | 26                            | 14                          | 0.47    |

Table-2: Comparison of the biochemical response to ursodeoxycholic acid between in Primary Biliary Cirrhosis Patients With and Without Associated Autoimmune Conditions:

| Evaluation Paris2 | P value |
|-------------------|---------|
| Non Replier       | Good Replier |
| Overlap syndrome  | 5 cases  | 4 cases  | 1 (NS) |
| Autoimmune Thyroiditis | 4 cases  | 5 cases  | 1 (NS) |
| Dry syndrome      | 4 cases  | 6 cases  | 0.71 (NS) |
| Celiac disease    | 2 cases  | 1 case   | 1 (NS) |
| Insulin-dependent diabetes | 0 case   | 1 case   | 1 (NS) |
| Systemic sclerosis| 1 case   | 0 case   | 0.45 (NS) |
| Rheumatoid arthritis | 1 case   | 0 cases  | 0.45 (NS) |
| Vitiligo          | 1 case   | 0 case   | 0.45 (NS) |

NS : not significant

DISCUSSION
Primary biliary cirrhosis (PBC) is a chronic cholestatic cholangitis of unknown etiology. It is morphologically characterized by portal inflammation and necrosis of small and medium size bile duct cells. This disease can frequently coexist with other
autoimmune diseases; the treatment is based on ursodeoxycholic acid (AUDC) [5].

Controlled clinical trials have shown that UDCA improves the biochemical and clinical characteristics of PBC [3, 4] and significantly improves survival without liver transplantation [6]. There is no information on the effects of AUDC on associated autoimmune diseases such as dry syndrome, psoriasis, vitiligo, Basedow, Addison's disease, scleroderma, insulin-dependent diabetes, rheumatoid arthritis, celiac disease or Hashimoto's thyroiditis.

In our experience, AUDC has not influenced the resolution or prevented the development of these autoimmune diseases, despite the improvement made during PBC, as previously reported [4]. Previous publications have described the prevalence of associated conditions at the time of diagnosis of PBC, including the four most common conditions assessed in this study (dry syndrome, overlap syndrome, celiac disease and autoimmune thyroiditis), with values comparable to those of our study population.

The prevalence of autoimmune diseases is similar to that of other reports. Culp et al (1) described 113 patients, 84% of whom had at least one associated autoimmune disease, compared to 40% in our study. In other studies comparable to ours by Zukowski et al. [7] out of 180 patients, the prevalence of autoimmune diseases associated with PBC was 43% and in the study by Gharbi et al. the prevalence was 41%. We compared the study of Zukowski et al. [7], Gharbi et al. [5] and our study found that Sec syndrome was the most frequent, occurring in 58/180 patients (32%) in the study of Zukowski et al. against 12.1% in the study of Gharbi et al. [5] versus 11.1% in our study, rheumatoid arthritis in 9% of patients versus 1.1% in our study and in the Gharbi et al. study [5] and hypothyroidism in 12% in both studies [7, 5] versus 10% in our series.

Previous studies in a smaller number of patients have suggested that the presence of associated autoimmune diseases predicts a poorer prognosis than that observed in patients without these conditions [8, 9]. We found no association between the severity of PBC or its evolution and the presence and absence of these specific autoimmune characteristics. We conclude that UDCA does not influence the progression of dry syndrome, celiac disease, polyarthritis or Hashimoto's thyroiditis in patients with PBC as reported in the study by Zukowski et al. [7]. Physicians caring for these patients should be aware that treatment with UDCA does not influence the clinical course of these associated diseases and should therefore provide symptomatic care for these other associated autoimmune disorders.

CONCLUSION

In our series, the prevalence of autoimmune diseases associated with PBC was 40%. These diseases were dominated by autoimmune hepatitis, Hashimoto's thyroiditis and dry syndrome. Although their association does not appear to alter the prognosis for CBP or the response to AUDC, their screening must be systematic in order to initiate early and appropriate treatment. Although ursodeoxycholic acid is beneficial in the treatment of primary biliary cirrhosis, it has had no measurable effect on the autoimmune disorders associated with the disease.

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