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Case–Control Study on Prednisolone Combined With Ursodeoxycholic Acid and Azathioprine in Pure Primary Biliary Cirrhosis With High Levels of Immunoglobulin G and Transaminases

Efficacy and Safety Analysis

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Abstract: To the best of our knowledge, this is the first study to address the use of glucocorticoids in the comparatively special population of pure primary biliary cirrhosis (PBC) patients who have high levels of immunoglobulin G (IgG) and transaminases but do not have PBC-autoimmune hepatitis overlap syndrome. Ursodeoxycholic acid (UDCA) is now assumed to be the standard therapy for PBC patients. However, patients treated with UDCA still have a risk of progression to cirrhosis and end-stage liver disease. The most recent European Association for the Study of the Liver guidelines of 2009 declared that further studies on glucocorticoid therapy in this disease should be a priority. Therefore, we designed this 3-year longitudinal retrospective study, which might provide deep insight into the treatment for PBC.

The aim of this study was to assess whether the combination of prednisolone, UDCA, and azathioprine was superior to UDCA alone in these PBC patients.

Sixty patients were enrolled in this study. Thirty-one patients underwent UDCA monotherapy, and 29 patients were treated with prednisolone, UDCA, and azathioprine. We analyzed their biochemistries, immune parameters, liver synthetic function, and noninvasive assessments of liver fibrosis, as well as treatment efficacy and adverse effects at baseline and at 1, 3, 6, 12, 24, and 36 months.

Alkaline phosphatase (ALP), γ-glutamyl transpeptidase, alanine aminotransferase, and aspartate aminotransferase levels and the aspartate aminotransferase-to-platelet ratio index (APRI) and S-index improved dramatically in both groups, whereas IgG levels only decreased in the combination group (all $P < 0.05$). Albumin (ALB) levels decreased in the UDCA group but increased with the combination treatment at 36 months. Significant differences between the 2 groups were observed at 36 months in ALP ($P = 0.005$), IgG ($P = 0.002$), ALB ($P = 0.002$), APRI ($P = 0.015$), and S-index ($P = 0.020$). Prednisolone combined with UDCA and azathioprine showed a higher efficacy based on our new criteria.

The combination of prednisolone, UDCA, and azathioprine is superior to UDCA alone for the treatment of pure PBC patients with high levels of IgG and transaminases. Side effects were minimal or absent.

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Abbreviations: AIH = autoimmune hepatitis, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, APRI = aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, BMI = body mass index, EASL = European Association for the Study of the Liver, GGT = γ-glutamyl transpeptidase, GLO = globulin, IgG = immunoglobulin G, IgM = immunoglobulin M, PBC = primary biliary cirrhosis, UDCA = ursodeoxycholic acid.

INTRODUCTION

Primary biliary cirrhosis (PBC) is an agnogenic, chronic cholestatic autoimmune liver disease characterized by a high specificity of antimitochondrial antibody and small bile-duct destruction. PBC leads to portal area inflammation, intrahepatic cholestasis, and fibrosis and can progress to cirrhosis and eventually liver failure.[1]

Ursodeoxycholic acid (UDCA) has been considered the standard therapy for improving the biochemical indexes of PBC patients. Although previous meta-analyses[2,3] have suggested that UDCA has a beneficial effect in significantly decreasing liver biochemistry, UDCA has no effect on liver disease related mortality despite the observed reduction in the incidence of liver transplantations. A proportion of patients treated with UDCA in the early stages still have a risk of progression to cirrhosis and end-stage liver disease. Many studies have revealed that the use of glucocorticoids to suppress inflammation is considered an attractive approach among PBC patients.[4–6] Glucocorticoids also appeared to be

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more effective among nonresponders to UDCA.[7,8] In clinical practice, we have found that some patients who do not respond to UDCA still have disease progression, even if additional glucocorticoids are added later. Thus, the prognosis of PBC patients might be improved if we combine UDCA and glucocorticoids earlier and take measures to prevent their side effects; this hypothesis must be further confirmed. Wolfhagen et al[7] showed that the short-term administration of prednisolone (a large dose at the beginning that is tapered rapidly) could improve biochemical parameters and liver histology with no obvious side effects. Patients might be more adaptive to glucocorticoids if we initiate their treatment with a megadose and then taper to a low-maintenance dose rapidly, assuming the necessary prophylaxis is provided.

PBC and autoimmune hepatitis (AIH) are chronic autoimmune liver diseases. Increasingly, studies have agreed that either of these diseases can develop into an overlap syndrome that has features of both PBC and AIH.[9] PBC-AIH overlap syndrome typically has a high level of immunoglobulin G (IgG) and is an indication for the use of glucocorticoids.[10] However, the appropriateness of glucocorticoids remains unclear in the severe PBC patients who have high levels of IgG and transaminase but do not have definite PBC-AIH overlap syndrome. Poupon et al[11] reported that, in patients with PBC, increased levels of IgG and γ-globulin are related to the severity of lymphocytic hepatocellular piecemeal necrosis and lobular inflammation. This relationship between IgG levels and fibrosis reveals that IgG might play an important role in the development of liver fibrosis. An in vitro test showed that prednisolone could reduce the proliferation of IgG-producing cells in combination with Con A.[12] PBC patients with high levels of IgG and transaminases might have more severe necrosis and inflammation of the hepatic lobule than patients with normal levels.[11] The latest European Association for the Study of the Liver (EASL) guidelines of 2009 declared that further studies regarding glucocorticoid therapy in PBC patients should be a priority.[13] This is the first study to address the use of glucocorticoids in a comparatively special pure PBC population who have high IgG and transaminase levels but do not have PBC-AIH overlap syndrome (all patients included did not meet the criteria for PBC-AIH overlap syndrome). We designed this 3-year longitudinal retrospective study to observe the efficacy and safety of a combination therapy with prednisolone, UDCA, and azathioprine for the treatment of these PBC patients.

METHODS

Patient Population

Between June 2009 and December 2012, we reviewed the medical records of the definite PBC patients in our department and chose the cases of initial diagnosis during this period. The diagnosis of PBC was based on the EASL guidelines of 2009.[13] Sixty patients who met the requirements of our inclusion criteria and accepted relevant treatment with comparatively complete follow-up were included after screening. The collection of the follow-up data was terminated in December 2013. The inclusion criteria were as follows: high levels of IgG (1–2 × ULN), high levels of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (1–5 × ULN), and no therapy received before the onset of the study. Patients who met all the 3 criteria above were included. The exclusion criteria were age >75 years; pregnancy; intolerance for prednisolone or azathioprine; osteoporotic spinal fractures; systemic infections; a psychiatric history or cytopenia; and cases of overlap syndrome or cases of PBC combined with other liver diseases such as alcoholic liver disease, viral hepatitis, drug-induced liver disease, and metabolic liver disease. These 60 patients were divided into 2 groups (groups A and B) based on their wills to the use of prednisolone and azathioprine. Thirty-one patients were given UDCA monotherapy (group A), and 29 patients were treated with prednisolone, UDCA, and azathioprine (group B). We analyzed the patients' biochemistries, immune parameters, liver synthetic function, noninvasive assessments for liver fibrosis, as well as the treatment efficacy and adverse effects at baseline and at 1, 3, 6, 12, 24, and 36 months. The 2 noninvasive assessments for liver fibrosis used in this study were the aspartate aminotransferase-to-platelet ratio index (APRI)[14] and S-index.[15] The corresponding formulas are as follows: APRI = {[AST/Upper normal limit for AST] ÷ [Platelet count (10^9/L)]} × 100; S-index = [1000 × γ-Glutamyl transpeptidase (GGT) (U/L)] ÷ [Platelet count (10^9/L) × Albumin (ALB) (g/L)^2].

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the ethics committee of Peking University First Hospital. All of the patients signed the informed consent form.

Duration of Follow-Up

The median follow-up time was 36 months (12–36 months) in group A and 36 months (6–36 months) in group B. Data at baseline and 1, 3, 6, 12, 24, and 36 months were collected. The follow-up time was allowed to fluctuate by 0.5 months for the records of the first 6 months. For the records of 12 to 36 months, the fluctuation limit was 2 months. Only 1 patient dropped out at 12 months in group B. The specific numbers of patients at each follow-up time point are shown in Figure 1. The number of patients at each time point was not consistent, mostly because their courses of treatment were different until the end of our observation period.

Doses of the Drugs

UDCA (13–15 mg/kg/d) therapy was administered in both groups. The mean doses of oral prednisolone at each point in group B are shown in Figure 2. The accurate doses of prednisolone are shown in Supplemental Table 1 (http://links.lww.com/MD/A67). The initial dose of prednisolone ranged from 25 mg/d to 50 mg/d; 83% of patients were treated with an initial dose of 30 mg/d prednisolone. The maintenance dose was 6.9 mg/d (5–10 mg/d). All of the patients in group B received 50 mg/d azathioprine.

Preventive Medications and Monitoring of the Steroid Side Effects

To avoid any steroid side effects, the patients in group B were administered the following preventive medications: calcium tablets 1200 mg/d; alfacalcidol 0.25 μg/wk to 0.25 μg/d based on age, menopause, and the diagnosis of osteoporosis; and H_2 receptor antagonist doses based on gastrointestinal symptoms.

The body mass index (BMI), blood pressure, blood glucose, and serum potassium were tested regularly. We asked the patients whether they had symptoms of stomach ache, heartburn, gastroesophageal reflux, and/or hematochezia at each of the visits, and an upper endoscopy was performed if needed. A bone density test was performed once or twice per year. A fundus examination was performed once per year.

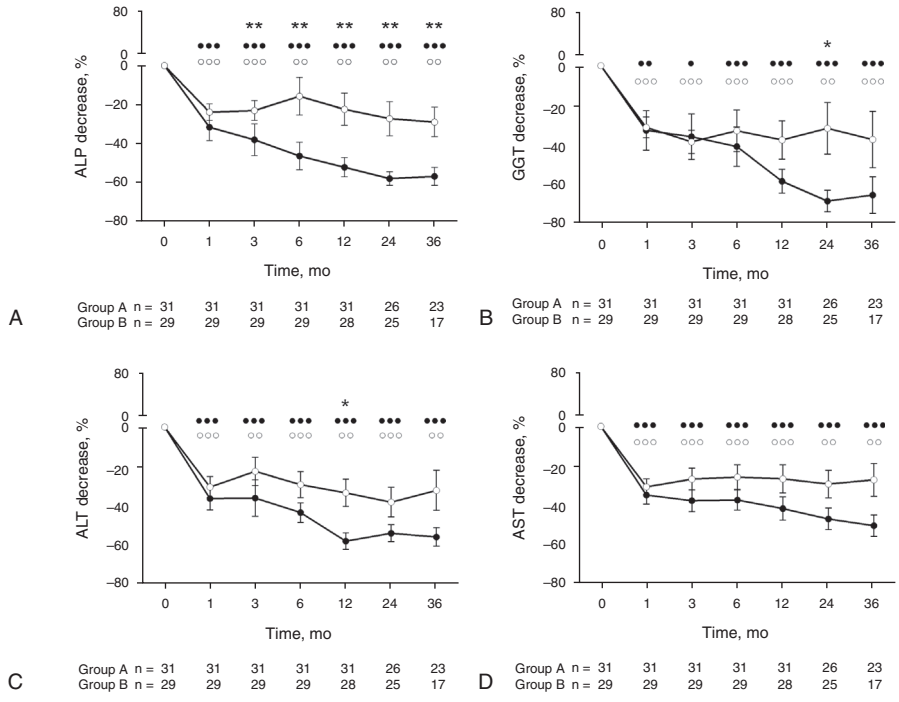

FIGURE 1. Changes in biochemical variables. Changes in (A) ALP, (B) GGT, (C) ALT, and (D) AST (mean ± SEM) values during treatment in group A (○) or group B (●). ○ or ● $P < 0.05$, ○○ or ●● $P < 0.01$, and ○○○ or ●●● $P < 0.001$ for comparisons between pretreatment values and values during therapy. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ for comparisons between group A and group B. ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = γ-glutamyl transpeptidase, SEM = standard error of the mean.

Moreover, we initiated our treatment with a megadose of steroids and tapered rapidly to a low-maintenance dose to prevent adrenal cortical insufficiency. Behavioral interventions (such as controlling diet) were also suggested.

Statistics

For the comparisons, Student *t* test and the Mann–Whitney *U* test were used for normal distribution and nonnormal distribution, respectively, referring to the quantitative data. The χ^2-test and Fisher exact test were used for qualitative data. The level of significance was set at 0.05. All of the values were expressed as the mean ± standard error of the mean, and all percentages were calculated as the formulation [(levels of follow up − levels of baseline) ÷ levels of baseline] × 100%.

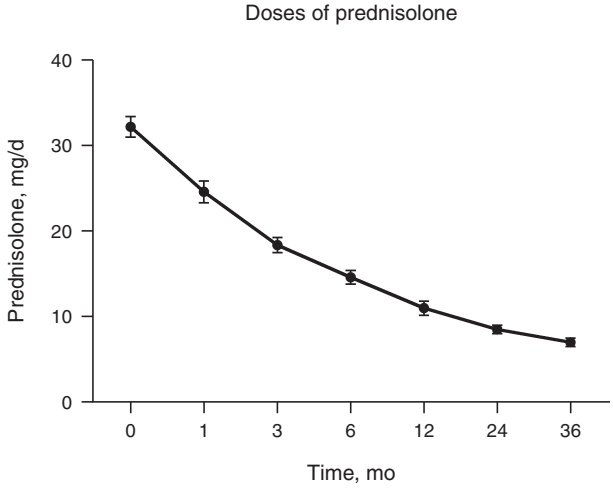

FIGURE 2. Doses of prednisolone.

TABLE 1. Baseline Characteristics of PBC Patients

	Group A	Group B	*P*
Number (men)	31 (1)	29 (4)	NS
Age mean (range)	56.7 (44–71)	52.9 (31–73)	NS
BMI (range), kg/m^2	22.8 (18.1–27.6)	23.1 (19.3–30.3)	NS
ALT, U/L	83.4 ± 7.2	82.3 ± 5.4	NS
AST, U/L	91.3 ± 6.8	80.5 ± 6.1	NS
ALP, U/L	303.5 ± 25.6	307.8 ± 25.2	NS
GGT, U/L	389.0 ± 50.4	332.6 ± 33.9	NS
TBA, μmol/L	24.2 ± 4.9	54.3 ± 12.5	0.021
ALB, g/L	39.5 ± 1.1	38.6 ± 0.9	NS
GLO, g/L	37.3 ± 1.0	38.2 ± 1.2	NS
Bilirubin, μmol/L	22.6 ± 2.2	33.8 ± 4.2	0.022
Platelet count, ×10^9/L	171.6 ± 12.6	138.7 ± 13.2	NS
IgG, g/L	21.6 ± 0.6	20.3 ± 0.7	NS
IgM, g/L	4.3 ± 0.3	4.8 ± 0.5	NS

ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GGT = γ-glutamyl transpeptidase, GLO = globulin, IgG = immunoglobulin G, IgM = immunoglobulin M, NS = nonsignificant, PBC = primary biliary cirrhosis, TBA = total bile acid.

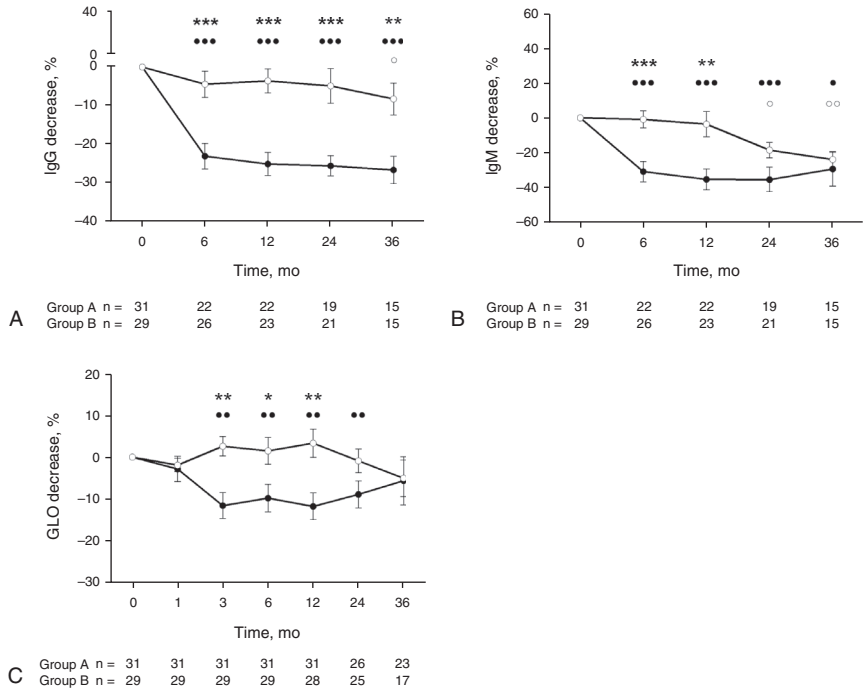

FIGURE 3. Changes in immune variables. Changes in (A) IgG, (B) IgM, and (C) GLO (mean ± SEM) values during treatment in group A (○) or group B (●). ○ or ● $P < 0.05$, ○○ or ●● $P < 0.01$, and ○○○ or ●●● $P < 0.001$ for comparisons between pretreatment values and values during therapy. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ for comparisons between group A and group B. GLO = globulin, IgG = immunoglobulin G, IgM = immunoglobulin M, SEM = standard error of the mean.

RESULTS

Baseline Characteristics

The baseline demographics and clinical features are shown in Table 1. A total of 60 PBC patients were involved, including 55 women and 5 men. The values of sex, age, and BMI were not significantly different between the 2 groups. The biochemical markers were comparable in the groups except for bilirubin and total bile acid, which were higher in group B ($P = 0.022$ and $P = 0.021$, respectively).

Biochemical Variables

All of the biochemical variables began to decrease within the first month of treatment (Figure 1). All of the biochemical markers improved after treatment for 1, 3, 6, 12, 24, and 36 months, with statistically significant differences compared with the original levels (all $P < 0.05$). Although the ALT, AST, alkaline phosphatase (ALP), and GGT levels in group B dropped more than the levels in group A, only ALP showed significant differences between the 2 groups ($P < 0.01$). The decrease in ALP at 36 months in groups A and B was 28.86% and 56.71%, respectively ($P = 0.005$).

Immune Variables

Compared with the baseline, the levels of IgG in group B improved prominently at all points of this study (all $P < 0.001$) (Figure 3). The IgG levels remained unchanged in group A except for a reduction at 36 months ($P = 0.038$). A similar improvement of the immunoglobulin M (IgM) levels was observed. There were statistically significant differences between the 2 groups according to the changes of IgG at 6, 12, 24, and 36 months (all $P < 0.01$). The levels were decreased by 8.25% and 26.65% in group A and group B, respectively, at 36 months ($P = 0.002$). The IgM levels were not different between the groups except at 6 and 12 months ($P < 0.001$ and $P = 0.002$, respectively).

Liver Synthetic Function

The ALB presented a rising trend in group B with significant differences at 12 and 36 months compared with the baseline values ($P = 0.025$ and $P = 0.047$, respectively), whereas a downward trend was detected in group A at 1, 12, and 36 months ($P < 0.001$, $P = 0.014$, and $P = 0.01$, respectively) (Figure 4). Variations of the ALB between the 2 groups were statistically significant for the duration of the therapy. The mean ALB levels were increased by 5.16% in group B and decreased by 6.37% in group A at the end of the study ($P = 0.002$). The bilirubin level in group B improved continuously and remained stable in group A; however, differences between the groups were detected only after 12 and 24 months ($P = 0.009$ and $P = 0.028$, respectively).

Noninvasive Assessment of Liver Fibrosis

APRI[14] and the S-index[15] are noninvasive models for assessing the degree of liver fibrosis (Figure 5). Improvements in S-index at 6, 12, 24, and 36 months compared with baseline levels were significantly different in both groups (all $P < 0.01$). APRI, which is also used for the noninvasive assessment of liver fibrosis, appeared to show a similar trend. For the S-index, significant differences between the 2 groups were observed from month 12 to month 36 (all $P < 0.05$); these changes were 25.05% and 75.1% at the endpoint ($P = 0.020$), respectively. The APRI in group A and group B was lowered by 15.88% and 52.07% at 36 months,

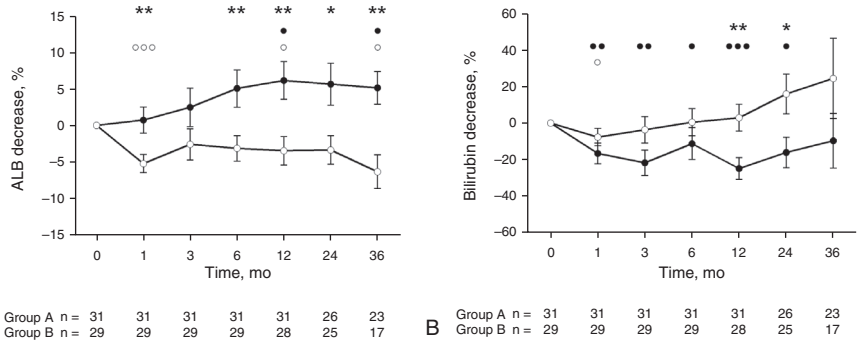

FIGURE 4. Changes in liver synthetic function. Changes in (A) ALB and (B) bilirubin (mean ± SEM) values during treatment in group A (○) or group B (●). ○ or ● $P < 0.05$, ○○ or ●● $P < 0.01$, and ○○○ or ●●● $P < 0.001$ for comparisons between pretreatment values and values during therapy. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ for comparisons between group A and group B. ALB = albumin, SEM = standard error of the mean.

respectively, and the differences were significant between the 2 groups ($P = 0.015$).

The details of all laboratory values before and after treatment are shown in Table 2.

Efficacy Analysis

We evaluated whether the triple therapy was more effective according to the Paris,[16] Barcelona,[17] Toronto,[18] and Ehime[19] criteria, and no significant differences were observed between group A and group B (P = ns, see Supplemental Table 2, http://links.lww.com/MD/A68, Efficacy analysis based on Paris, Barcelona, Toronto, and Ehime Criteria) (Figure 6). We introduced our new criteria, which were stricter than the previously used criteria, and included normal levels of ALP, ALT, and AST. We did find differences between the 2 groups using our criteria (all $P < 0.05$). UDCA combined with prednisolone and azathioprine showed a higher efficacy at all of the time points.

Adverse Effects

Because of the regular supervision and inquiries regarding symptoms, no cases with obvious steroid side effects, such as hypertension, diabetes, hypokalemia, edema, obesity, peptic ulcer, fracture, and adrenal cortical insufficiency, were observed at the 36-month follow-up.

DISCUSSION

UDCA usually has good results among patients at earlier stages of PBC; however, as some patients become nonresponders or partial responders, their diseases will progress. There is currently no consensus on how to treat patients who have a suboptimal biochemical response to UDCA, but 1 suggested approach is the combination of UDCA and budesonide in noncirrhotic patients.[13] In light of this recommendation, we hypothesized that the combination of UDCA and glucocorticoids might be superior to UDCA alone. The patients in our study are not representative of classical PBC cases and were carefully selected. Each subject received glucocorticoid therapy from the time of diagnosis, which is different from the indications for steroids in PBC cases according to the EASL guidelines of 2009.[13] Furthermore, our results showed that earlier interventions with glucocorticoids could improve the biochemical markers, immunological markers, and noninvasive assessment indicators of liver fibrosis. Wolfhagen et al[7] designed a study evaluating treatment with additional prednisolone and azathioprine for 1 year in PBC patients. They announced clear beneficial effects regarding patients' symptoms, biochemistries, and histologies with no obvious side effects. A study by Rabahi et al[8] drew a similar conclusion. Our study enhances these results and further provides new arguments for long-term benefits after a combination therapy of UDCA, prednisolone, and azathioprine in well-selected patients.

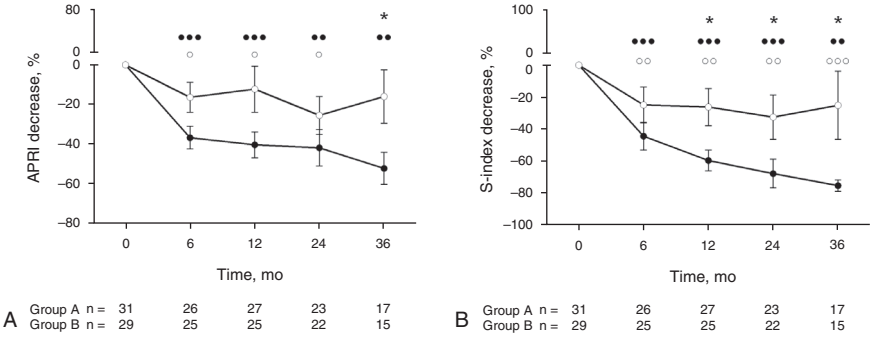

FIGURE 5. Changes in the noninvasive assessment of liver fibrosis. Changes in (A) APRI and (B) S-index (mean ± SEM) values during treatment in group A (○) or group B (●). ○ or ● $P < 0.05$, ○○ or ●● $P < 0.01$, and ○○○ or ●●● $P < 0.001$ for comparisons between pretreatment values and values during therapy. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ for comparisons between group A and group B. APRI = aminotransferase-to-platelet ratio index, SEM = standard error of the mean.

TABLE 2. Laboratory Values at Baseline and at 36 Months

	Group A			Group B			Change Between Groups	
Variables Mean (±SEM)	Baseline	36 Months	*P*	Baseline	36 Months	*P*	*P*	Normal Values
ALT, U/L	83.4 ± 7.2	47.2 ± 5.9	0.001	82.3 ± 5.4	38.2 ± 4.1	<0.001	NS	0–40
AST, U/L	91.3 ± 6.8	61.5 ± 8.8	0.009	80.5 ± 6.1	35.1 ± 3.6	<0.001	NS	0–40
ALP, U/L	303.5 ± 25.6	183.2 ± 17.1	0.001	307.8 ± 25.2	126.2 ± 14.6	<0.001	0.005	50–135
GGT, U/L	389.0 ± 50.4	174.9 ± 41.4	<0.001	332.6 ± 33.9	114.8 ± 23.9	<0.001	NS	0–50
TBA, μmol/L	24.2 ± 4.9	42.4 ± 10.6	0.020	54.3 ± 12.5	19.0 ± 4.8	NS	NS	0–10
ALB, g/L	39.5 ± 1.1	36.7 ± 1.3	0.010	38.6 ± 0.9	43.0 ± 0.8	0.047	0.002	35–50
GLO, g/L	37.3 ± 1.0	35.7 ± 1.7	NS	38.2 ± 1.2	35.5 ± 1.3	NS	NS	20–30
Bilirubin, μmol/L	22.6 ± 2.2	25.2 ± 4.3	NS	33.8 ± 4.2	23.0 ± 6.5	NS	NS	1.7–20
Platelet count, $\times 10^9$/L	171.6 ± 12.6	153.4 ± 15.1	NS	138.7 ± 13.2	168.3 ± 14.9	NS	NS	100–300
IgG, g/L	21.6 ± 0.6	19.6 ± 1.1	0.038	20.3 ± 0.7	15.0 ± 0.7	<0.001	0.002	7.23–16.85
IgM, g/L	4.3 ± 0.3	2.9 ± 0.3	0.001	4.8 ± 0.5	3.3 ± 0.4	0.017	NS	0.63–2.77

The values are presented as mean ± SEM; $P < 0.05$ is considered significant. ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = γ-glutamyl transpeptidase, GLO = globulin, IgG = immunoglobulin G, IgM = immunoglobulin M, ns = nonsignificant, SEM = standard error of the mean, TBA = total bile acid.

In our study, the biochemical parameters improved dramatically in both groups, whereas the immune variable IgG decreased only in the triple therapy group. The ALB levels showed a decreasing trend in the UDCA group; however, there was an increasing trend for ALB with the combination treatment. Significant differences between the 2 groups were observed at 36 months in terms of the percentages of ALP, IgG, and ALB. These results are in accordance with several previously published studies.[4–6] Nevertheless, IgM decreased to a greater extent in the double therapy group (budesonide and UDCA) after treatment for 24 months in a study by Leuschner et al.[5] Our different patient population might have led to these different results, and more consistent results might have been possible if the follow-up had been extended. ALB is an important parameter for assessing the prognosis of PBC patients.[20] Combined therapy has been proposed as a possible therapeutic approach for improving hepatic synthetic function, which remained unchanged or even worsened when UDCA was taken alone.

The severity of fibrosis is related to its long-term prognosis. The APRI and S-index are measures used to evaluate the degree of liver fibrosis, and they are usually applied in cases of hepatitis B and hepatitis C. Trivedi et al[21] showed that the APRI is important for predicating the prognosis of PBC patients. Similar to other studies,[5,6] the APRI and S-index improved significantly in the triple therapy group but showed no significant improvements in the UDCA group compared with the pretreatment parameters. Prior meta-analyses[2,3] have focused on PBC patients and concluded that UDCA had no clear effects on liver histology or liver-related deaths. We believe that the combination of UDCA, prednisolone, and azathioprine is superior to UDCA alone. However, when estimating the efficacy on the basis of 4 published response criteria, the Paris,[16] Barcelona,[17] Toronto,[18] and Ehime[19] criteria, we did not detect significant differences between the 2 groups, despite a higher efficacy rate in the triple therapy group. Still, we did determine that the prednisolone, azathioprine, and UDCA combination therapy was superior in terms of improving the ALP and ALB levels, the noninvasive assessments of liver fibrosis, and the recovery rates of ALT and AST. Therefore, we introduced new criteria for the evaluation of the clinical results. This new criteria included normal levels of ALP, ALT, and AST. Based on this new standard, the rate of response to triple therapy was remarkably higher than the response to UDCA alone.

The use of steroids to suppress inflammation in PBC has been an attractive approach, but serious side effects, including the aggravation of osteopenia in PBC patients,[4] have been observed. However, no serious side effects of prednisolone were noted in our study, most likely because of our positive strategies of reduction, preventive medications, and monitoring. Ruiz-Irastorza et al[22] found that the method

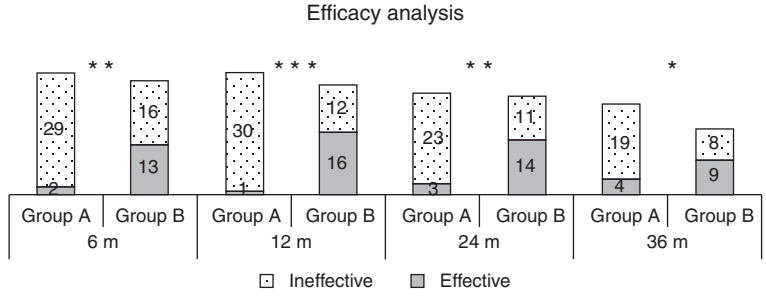

FIGURE 6. Efficacy analysis based on our own criteria. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ for comparisons between group A and group B.

of combining glucocorticoids with immunosuppressives could lower the required dose of steroids, leading to fewer side effects in the patients. In our study, azathioprine was an adjuvant drug. More than 80% patients received an initial prednisolone dose of 30 mg/d, which was rapidly tapered to a maintenance dose of 6.9 mg/d. A large dose of steroids was given in a short time before the rapid taper, and the daily maintenance dose was lower than the doses used in other studies,[4,7,23] which reduced the risk of side effects. Providing prophylaxis, such as H_2 receptor antagonists, calcium tablets, and vitamin D and performing regular monitoring could prevent patients from developing side effects because of glucocorticoid use.[24,25] This suggestion is in accordance with the results of our study. Moreover, relevant studies[4,23] have indicated that the use of prednisolone alone without prophylaxis caused patients to suffer from hypertension, osteoporosis, and other adverse reactions, emphasizing the importance of preventive medications.

Our study still presented some limitations. First, this was not a randomized double-blind controlled study. Second, we could not associate the long-term prognosis with the therapeutic response because of the relatively short follow-up time. However, our experiences with the use of UDCA imply that patients with a good response often live longer than the nonresponders. Finally, statistical errors cannot be fully excluded because of the small sample size, but such studies are difficult to perform because of the low morbidity of PBC.

In conclusion, prednisolone combined with UDCA and azathioprine is superior to UDCA alone for pure PBC patients who have high levels of IgG and transaminases. The biochemical and immune parameters, levels of liver synthetic function, and noninvasive assessment indexes for liver fibrosis, improved more markedly in the triple therapy group. In addition to prophylaxis and behavioral interventions, taking a large initial dose of prednisolone and then rapidly reducing the dose could help to balance the side effects, allowing the duration of glucocorticoid therapy to be increased. Further studies with more patients should be implemented to assess the effects of combined therapy, especially for patients with high levels of IgG and transaminases.

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