Meta-analysis

A meta-analysis of ursodeoxycholic acid therapy versus combination therapy with corticosteroids for PBC-AIH-overlap syndrome: evidence from 97 monotherapy and 117 combinations

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Abstract

In this study, a meta-analysis of randomised controlled trials that compared ursodeoxycholic acid (UDCA) monotherapy with therapies combining UDCA and corticosteroids was performed. We found that combination therapy with UDCA and corticosteroids was more effective than UDCA monotherapy for primary biliary cirrhosis-autoimmune hepatitis-overlap syndrome.

Introduction

Autoimmune liver disease (ALD) is a group of diseases of unknown aetiology and immune-mediated liver diseases, including autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis [1]. Some patients display the characteristics of two diseases based on clinical, biochemical, immunological, or histological analyses, at different stages during the course of their disease. This is called "overlap syndrome", among which primary biliary cirrhosis-autoimmune hepatitis (PBC-AIH) is the most common [2]. However, because of its low incidence and the lack of uniform diagnostic criteria, the exact pathogenesis of PBC-AIH remains unclear. The incidence of PBC-AIH is reported to be between 2% and 20%, based on different diagnostic criteria [3–5]. Because there have been few mechanised large-scale randomised double-blind controlled clinical trials or prospective controlled studies of PBC-AIH, progress in the treatment of this disease is relatively slow. Corticosteroids have had positive effects on AIH [6], and ursodeoxycholic acid (UDCA) can effectively improve PBC-associated cholestasis, prolong survival, and delay histological progression [7, 8]. In some studies of PBC-AIH, the results of a therapy combining UDCA and corticosteroids were encouraging [9, 10], but there have been few local studies [11]. Last year, a meta-analysis of Zhang et al. [12] showed that combination therapy was more effective, but the number of studies included in this analysis was small.

Aim

Therefore, we further conducted this meta-analysis to explore the efficacy and safety of UDCA combined with corticosteroid therapy for PBC-AIH, hoping to provide strong supporting evidence for the use of this treatment in clinical practice.

Material and methods

Determine the research standards

Objectives of the study

The PBC-AIH was strictly defined as the association of PBC and AIH. The presence of at least 2 of the 3 accepted criteria was required for the diagnosis of each disease [13]. The criteria for PBC are: (1) alkaline phospha-
A meta-analysis of ursodeoxycholic acid therapy versus combination therapy with corticosteroids for PBC-AIH-overlap syndrome: evidence from 97 monotherapy and 117 combinations

Data extraction

The data were independently extracted from each study by two researchers (Huawei Zhang and Sainan Li), and any disagreement was resolved by consensus. The following data were extracted from each article included: the name of the first author, year of publication, number of patients, daily dose of oral therapy, duration of treatment, method used to deal with missing data, liver biochemistry (AP, ALT, aspartate aminotransferase (AST), GGT, IgG, IgM), symptoms, liver histology, death, liver transplantation, death and/or transplantation, and adverse events.

Methodological quality

The methodological quality of the studies included in the meta-analysis was scored with the Jadad composite scale (Table I) [15, 16]. This is a 5-point quality scale, with low-quality studies having a score ≤ 2 and high-quality studies a score ≥ 3. Methodological quality was independently assessed by two authors of the study. Each study was given an overall quality score based on the criteria described above, which was then used to rank the studies. Any disagreement was resolved by consensus.

Statistical analysis

All analyses were performed with RevMan5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). The odds ratio (OR) for each clinical event is presented with its 95% confidence interval (CI). We test...
ed heterogeneity using the $\chi^2$ test and the $I^2$ test, and a $p$ value < 0.10 or an $I^2$ value > 50% was considered to indicate substantial heterogeneity. A fixed-effects model was used when the heterogeneity test had a $p$ value > 0.10 or an $I^2$ value < 50%; otherwise, a random-effects model was used. We also constructed funnel plots to evaluate the presence of publication bias.

**Results**

**Descriptive and qualitative assessments**

After we had excluded reviews, case reports, repeated studies, and research whose purpose was unrelated to the evaluation system or inconsistent with the literature, we finally selected eight RCTs from 1578 studies [17–24].

These studies involved 214 patients: 97 were randomised to the UDCA monotherapy groups and 117 to the combination therapy (UDCA and corticosteroids) groups. The mean ages ranged from 44 to 55 years and the mean follow-up periods ranged from 10 to 90 months. The daily dose of UDCA ranged from 10 to 15 mg/kg, and the daily dose of corticosteroids ranged from 0.5 to 1 mg/kg (only Ozaslan [2014] used a dose of 30–60 mg/day). The baseline characteristics of the eight trials are listed in Table II. The descriptive results are shown in Table III.

**Quality assessment of the studies included**

The methodological quality scores ranged from 2 to 5 (Table IV). Six of the eight randomised studies adequately described the way in which they were randomised. All the studies used a double-blind method, and five provided specific descriptions of the blinding used. Six studies described the withdrawals and lost cases. Three studies described allocation concealment, whereas five had no such description. Overall, the Jadad scores of all the RCTs were ≥ 3 points, and so were considered high-quality research.

**Table II. Baseline characteristics of the trials included in the meta-analysis**

| Authors, year | Mean age [years] | Monotherapy (n) | Combination therapy (n) | UDCA dose [mg/kg · day] | Immunosuppression dose [mg/kg · day] | Duration of treatment [months] | Publication type |
|---------------|-----------------|-----------------|-------------------------|-------------------------|--------------------------------------|-------------------------------|-----------------|
| Chazouilleres, 1998 [17] | 50 | 5 | 6 | 13–15 | 0.5 | 23 | Full text |
| Gunsar, 2002 [18] | 44 | 13 | 7 | 13 | 0.5 | 28 | Full text |
| Chazouilleres, 2006 [10] | 41 | 11 | 6 | 13–15 | 0.5 | 90 | Full text |
| Heurgue, 2007 [19] | 44 | 9 | 4 | 11–14.7 | 0.5–1 | 60 | Full text |
| Ozaslan, 2010 [20] | 44 | 3 | 9 | 13–15 | 0.5 | 31 | Full text |
| Tanaka, 2011 [21] | 54 | 15 | 10 | 10 | 0.5 | 73 | Full text |
| Zhu, 2011 [22] | 50 | 11 | 8 | 13–15 | 0.5–1 | 10 | Full text |
| Ozaslan, 2014 [23] | 48 | 30 | 67 | 13–15 | 30–60 [mg/day] | 66 | Full text |

**Table III. Descriptive results of the randomised trials**

| Authors | Symptoms improved | Liver-biochemistry improved | Histology progression | Death | Death or liver transplantation U | Adverse events |
|---------|-------------------|-----------------------------|----------------------|-------|---------------------------------|----------------|
| UDCA | COM | UDCA | COM | UDCA | COM | UDCA | COM | UDCA | COM | UDCA | COM |
| Chazouilleres [17] | 2/5 | 3/6 | 2/5 | 6/6 | 3/5 | 0/2 | 1/5 | 0/6 | 1/5 | 0/6 | 1/5 | 2/6 |
| Gunsar [18] | 1/16 | 0/7 | 8/16 | 7/7 | 5/8 | 1/7 | 0/16 | 1/7 | 0/16 | 1/7 | 1/16 | 0/7 |
| Chazouilleres [10] | 3/11 | 0/6 | 4/11 | 6/6 | 4/8 | 0/4 | NR | NR | 0/11 | 1/6 | NR | NR |
| Heurgue [19] | 1/6 | 1/4 | 3/6 | 3/4 | 3/6 | 1/4 | NR | NR | 0/6 | 0/4 | NR | NR |
| Ozaslan [20] | 3/3 | 3/9 | 3/3 | 3/9 | 0/3 | 6/9 | 0/3 | 2/9 | 0/3 | 3/9 | NR | NR |
| Tanaka [21] | 3/15 | 1/10 | 8/15 | 10/10 | 7/15 | 0/10 | 0/15 | 1/10 | 0/15 | 1/10 | NR | NR |
| Zhu [22] | 0/11 | 0/8 | 6/11 | 8/8 | 3/3 | 0/3 | NR | NR | 0/11 | 0/8 | 2/11 | 1/8 |
| Ozaslan [23] | 0/30 | 0/67 | 19/30 | 56/67 | 18/23 | 12/14 | 0/30 | 5/67 | 0/30 | 9/67 | NR | NR |

UDCA – Monotherapy with ursodeoxycholic acid, COM – combination therapy with UDCA and corticosteroids, NR – not reported.
Meta-analysis

Pruritus and jaundice

Eight trials [10, 17–23], including 214 patients, reported data regarding the endpoints of pruritus and jaundice. The symptoms improved in 13 of 97 patients in the monotherapy groups and in eight of 117 patients in the combination therapy groups. There was no significant heterogeneity ($p = 0.68$, $I^2 = 0\%$), and there were no significant differences between the groups ($OR = 2.12$, 95% CI: 0.72–6.18, $p = 0.17$; Figure 1).

ALT and AP levels

Eight trials, including 214 patients, reported data regarding the endpoints of ALT and AP levels. The symptoms improved in 53 of 97 patients in the monotherapy groups and in 99 of 117 patients in the combination therapy groups. There was no significant heterogeneity ($p = 0.16$, $I^2 = 33\%$), but there were significant differences between the groups ($OR = 0.25$, 95% CI: 0.13–0.48, $p < 0.0001$; Figure 2).

Histological progression

Of the 214 patients (eight trials) who underwent second biopsies, the histology declined in 43 of 71 patients in the monotherapy groups and in 20 of 53 patients in the combination therapy groups. There was no significant heterogeneity ($p = 0.08$, $I^2 = 34\%$), but there were significant differences between the groups ($OR = 2.57$, 95% CI: 1.19–5.52, $p = 0.02$; Figure 3).

Death or liver transplantation

Seven trials, including 214 patients, reported data for the endpoint death or liver transplantation. Death or liver transplantation occurred in one of 97 patients in the monotherapy groups and in 15 of 117 patients in the combination therapy groups. There was no significant heterogeneity ($p = 0.66$, $I^2 = 0\%$), but there were

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Table IV. Jadad quality scores of the trials included in the meta-analysis

| Study                  | Randomisation method | Double blinding | Withdrawals dropouts | Total |
|------------------------|----------------------|-----------------|-----------------------|-------|
| Chazouilleres, 1998    | 2                    | 2               | 1                     | 5     |
| Gunsar, 2002           | 1                    | 2               | 1                     | 4     |
| Chazouilleres, 2006    | 2                    | 2               | 1                     | 5     |
| Heurgue, 2007          | 2                    | 1               | 1                     | 4     |
| Ozaslan, 2010          | 1                    | 2               | 1                     | 4     |
| Tanaka, 2011           | 2                    | 1               | 0                     | 3     |
| Zhu, 2011              | 2                    | 2               | 1                     | 5     |
| Ozaslan, 2014          | 2                    | 1               | 1                     | 4     |

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Figure 1. Effects of monotherapy versus combination therapy on pruritus and jaundice in patients with PBC-AIH
significant differences between the groups (OR = 0.26, 95% CI: 0.08–0.83, p = 0.02; Figure 4).

**Adverse events**
Three trials, including 53 patients, reported data regarding endpoint adverse events. Adverse events were recorded in four of 32 patients in the monotherapy groups and in three of 21 patients in the combination therapy groups. There was no significant heterogeneity (p = 0.82, I² = 0%), and there were no significant differences between the groups (OR = 1.03, 95% CI: 0.21–5.01, p = 0.97; Figure 5).

**Sensitivity analysis**
Jadad scores were used in this study to assess the research quality. All eight studies had scores ≥ 3 points, and were thus considered high-quality research. Therefore, there was no need for a further sensitivity analysis.

**Publication bias**
Figure 6 shows the funnel plots of the meta-analysis. The funnel plots for clinical events show slight asymmetry, suggesting possible publication bias.

**Discussion**
In ALD, AIH is treated with corticosteroids therapy, with commonly used prednisone or prednisolone, and some non-responders or the dose may be adjusted as optional replacement therapy: cyclosporine, cyclophosphamide, budesonide, etc. [24, 25]. Corticosteroids have no significant effect on PBC when used to treat cholestatic disease, while they may increase the degree of osteoporosis in patients. The treatment for PBC is UDCA, which not only improves the indicators of cholestasis, but also significantly reduces transaminase levels [26]. Ursodeoxycholic acid is also commonly used to treat patients with AIH. Because overlap syndrome displays the
A meta-analysis of ursodeoxycholic acid therapy versus combination therapy with corticosteroids for PBC-AIH-overlap syndrome: evidence from 97 monotherapy and 117 combinations

| Study or subgroup | UDCA | COM | Weight [%] | Odds ratio M-H, fixed, 95% CI | Odds ratio M-H, fixed, 95% CI |
|-------------------|------|-----|------------|-----------------------------|-----------------------------|
| Chazouilleres 1998 | 1    | 5   | 0          | 6                           | 2.6                         | 4.33 (0.14, 132.32)          |
| Chazouilleres 2006 | 0    | 11  | 1          | 6                           | 13.5                        | 0.16 (0.01, 4.58)            |
| Gunsar 2002       | 0    | 16  | 1          | 7                           | 14.7                        | 0.13 (0.00, 3.66)            |
| Heurgue 2007      | 0    | 6   | 0          | 4                           | Not estimable               |                             |
| Ozaslan 2010      | 0    | 3   | 3          | 9                           | 13.0                        | 0.27 (0.01, 6.74)            |
| Ozaslan 2014      | 0    | 30  | 9          | 67                          | 43.5                        | 0.10 (0.01, 1.79)            |
| Tanaka 2011       | 0    | 15  | 1          | 10                          | 12.8                        | 0.20 (0.01, 5.54)            |
| Zhu 2011          | 0    | 11  | 0          | 8                           | Not estimable               |                             |
| Total (95% CI)    | 97   | 117 | 100.0      |                             | 0.26 (0.08, 0.83)           |

Total events 4 3 15 1
Heterogeneity: $\chi^2 = 3.28, df = 5 (p = 0.66), I^2 = 0$
Test for overall effect: $Z = 2.26 (p = 0.02)$

![Figure 4](image)

**Figure 4.** Death or liver transplantation in patients treated with monotherapy versus combination therapy for PBC-AIH

| Study or subgroup | UDCA | COM | Weight [%] | Odds ratio M-H, fixed, 95% CI | Odds ratio M-H, fixed, 95% CI |
|-------------------|------|-----|------------|-----------------------------|-----------------------------|
| Chazouilleres 1998 | 1    | 5   | 2          | 6                           | 48.1                        | 0.50 (0.03, 7.99)            |
| Gunsar 2002       | 1    | 16  | 0          | 7                           | 20.5                        | 1.45 (0.05, 40.04)           |
| Zhu 2011          | 2    | 11  | 1          | 8                           | 31.3                        | 1.56 (0.12, 20.85)           |
| Total (95% CI)    | 32   | 21  | 100.0      |                             | 1.03 (0.21, 5.01)           |

Total events 4 3 15 1
Heterogeneity: $\chi^2 = 0.40, df = 2 (p = 0.82), I^2 = 0$
Test for overall effect: $Z = 0.03 (p = 0.97)$

![Figure 5](image)

**Figure 5.** Adverse events in patients treated with monotherapy versus combination therapy for PBC-AIH

characteristics of both AIH and PBC, most patients tend to receive a combination therapy, which seems to induce better biochemical and histological responses in patients with this disease. In 2009, the EASL guidelines also advised that UDCA therapy should be administered for 3 months, and if the biochemical response is poor, corticosteroids combination therapy can be added [27, 28].

This study has shown that the combination therapy did not differ significantly from the monotherapy in improving fatigue, jaundice, mortality, death/liver transplantation, or adverse events, but was significantly superior to the monotherapy in reducing serum AP, ALT, and other biochemical liver markers. The literature evaluated was biased because too few studies were included, so more high-quality studies are required to confirm the conclusions drawn here. Three of the included RCTs reported adverse events, whereas the other five did not. From the perspective of drug safety, the differences in the rates of adverse events between the combination therapy and the monotherapy were insignificant. It has been suggested that the combination therapy is a relatively safe treatment. In clinical trials, the efficacy of treatments and the adverse reactions should be given equal value.

**Conclusions**

We recommend that patients diagnosed with overlap syndrome undertake early treatment that combines UDCA with corticosteroids. This therapy is effective for these patients and can improve their liver biochemical indicators. Although the combination therapy is a relatively safe treatment, adverse effects should be closely monitored when taken at the recommended dose. Because corticosteroids may cause bleeding, fractures, high blood sugar, high blood pressure, high cholesterol, pancytopenia, or severe infections [29–31], PBC-AIH patients require efficient and safe treatment regimens.

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Conflict of interest
The authors declare no conflict of interests.

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Figure 6. Funnel plots of the meta-analysis. A – Symptoms of fatigue and jaundice. B – Liver biochemical parameters (ALT and AP). C – Histopathological assessment. D – Death or liver transplantation. E – Adverse events.
A meta-analysis of ursodeoxycholic acid therapy versus combination therapy with corticosteroids for PBC-AIH-overlap syndrome: evidence from 97 monotherapy and 117 combinations

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