Immunosuppressive Agents for the Treatment of Primary Sclerosing Cholangitis: A Systematic Review and Meta-Analysis

Xia Peng a  Xin Luo a  Jing-Ying Hou b  Shu-Yun Wu a  Liang-Zong Li c  Ming-Hua Zheng d  Ling-Yun Wang a

a Department of Gastroenterology, Sun Yat-sen Memorial Hospital, b Department of Emergency, the Sun Yat-sen Memorial Hospital, c Department of Gastroenterology, Nan-cun Hospital, Guangzhou, and d Department of Hepatology, Liver Research Center, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

Abstract

Objectives: Currently, there are no effective therapeutic agents for patients with primary sclerosing cholangitis (PSC). This study aimed to evaluate the safety and efficiency of immunosuppressive agents (IAs) for the treatment of PSC.

Methods: The literatures were searched using the following keywords singly or in combination: PSC, treatments, IAs. The primary outcome was defined as the need for liver transplantation or mortality.

Results: Two hundred sixty six patients from 7 eligible studies were analyzed. IAs had no remarkable effects on the rate of mortality or liver transplantation (relative risk, RR 1.02, 95% CI 0.58–1.62, p = 0.92). Subgroup analyses showed no significant effect of IAs co-administration therapy (IAs co-administered with ursodeoxycholic acid, IA co-administered with IA; RR 1.41, 95% CI 0.40–4.95, p = 0.60). IAs caused adverse events (AEs) such as diarrhea, abdominal pain, and pruritus (RR 1.81, 95% CI 1.07–3.07, p = 0.03). IAs therapy did not significantly improve markers of liver function except for aspartate transaminase (weighted mean difference –9.76, 95% CI –12.92 to –6.6, p < 0.001).

Conclusion: IAs administered as either monotherapy or combination therapy do not reduce the risk of mortality or liver transplantation. IAs monotherapy is associated with AEs.

Keywords
Immunosuppressive agents · Primary sclerosing cholangitis · Meta-analysis

Introduction

Primary sclerosing cholangitis (PSC) is an orphan disease that predominantly affects males and is highly associated with inflammatory bowel disease (IBD), particularly Crohn’s colitis and ulcerative colitis. PSC is characterized by a progressive fibrosis of intra- and/or extra- biliary strictures, resulting in biliary cirrhosis, cholangitis, and end-stage liver disease. The pathogenesis of PSC is unclear and there is still no satisfactory therapy [1–4]. Ursodeoxycholic acid (UDCA) treatment did not favorably affect the progression of PSC or improve patient survival rate [5]. Moreover, increased mortality rate has been reported for patients receiving a high dose of UDCA [6].

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As PSC is characterized at least in part by immune dysfunction, a number of widely studied immunosuppressive agents (IAs) have been evaluated [7–9]. One study suggested a promising effect of colchicine in a patient diagnosed with PSC [10]. A case report showed that 2 PSC patients who received methotrexate (MTX) had improved biochemical test result and remained in clinical remission [11]. An uncontrolled study in 12 patients with co-administration of prednisone and colchicine reported a significant improvement in liver function test at 6 and 12 months [12]. In addition, penicillamine, colchicine, MTX, and mycophenolate mofetil (MMF) have been explored in randomized controlled trials (RCTs) or retrospective comparative studies [3, 4, 12–16]. However, the benefit of IAs to PSC patients is still uncertain. Therefore, we performed this meta-analysis to evaluate the safety and efficiency of IAs therapy for the treatment of patients with PSC.

Materials and Methods

Literature-Search Strategy

We performed a literature-search using PubMed, Web of Science and Cochrane Library, up to February 29, 2016. Data retrieval was performed using the key words or their combination in the Title/Abstract: PSC, treatments, IAs. Seven eligible clinical trials were included in our study with IAs, which included infliximab, MTX, colchicine, penicillamine, colchicine plus prednisone, MMF and MTX. The primary outcome was defined as liver transplantation or mortality and secondary outcomes were adverse events (AEs) and liver biochemical variables (aspartate transaminase [AST], alkaline phosphatases [ALP], albumin [ALB], and bilirubin [BIL]). This study was approved by Institute Ethics Committee.

Inclusion and Exclusion Criteria

RCTs and retrospective comparative studies that concluded IAs as monotherapy or co-administration therapy (which defined as IA co-administered with IA, IA co-administered with UDCA), case reports, editorials, and letters to the editor were excluded. Patients included in the meta-analysis met at least 3 of the following terms: (i) liver biopsy should meet the diagnosis of PSC and show evidence of magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography, (ii) IAs should be administered by oral route, (iii) at least 2 of the liver biochemical indicators: AST, ALP, ALB, and BIL should have been evaluated, and (iv) drug-related AEs should have been reported.

Data Extraction and Outcome of Interest

Two authors (L.-Z.L. and S.-Y.W.) independently reviewed all the eligible articles and extracted the data. Any disagreement regarding data extraction was resolved by the senior author (L.-Y.W.). The primary outcome was defined as liver transplantation or mortality and secondary outcomes were defined as AEs and liver biochemical variables.

Quality Assessment

The methodology of RCTs and retrospective comparative studies was assessed by the Cochrane risk of bias tool [17] and the modified Newcastle–Ottawa scale [18, 19]. The modified Newcastle–Ottawa scale consisted of 3 main factors: patient selection (assignment for treatment, representative treatment group, representative reference group), comparability of the study groups (4 items: 1 = age, 2 = gender, 3 = liver biochemistries, 4 = liver histological stage), and outcome assessment (assessment of outcome, adequate follow-up). Two retrospective comparative studies were evaluated by a score of 0–9 stars; studies that scored at least 6 stars were considered to be of high quality.

Review Manager 5.3 provided by the Cochrane Collaboration was used to perform meta-analysis. Dichotomous and continuous variables were assessed by relative risk (RR) and weighted mean difference (WMD), respectively.

A chi-square test with significance set at $p < 0.10$ was used to assess the statistical heterogeneity and the heterogeneity was quantified by the I$^2$ statistic. If there was heterogeneity between studies, the random-effects model was performed; otherwise, the fixed-effects model was used [17]. Subgroup analysis was performed to compare IAs administered as both monotherapy and co-administration therapy.

Results

Characteristics of Included Trails

Seven studies including 266 cases (144 case for IAs monotherapy or co-administration therapy, 122 cases for placebo or UDCA) met the inclusion criteria and were analyzed (Fig. 1). Five RCTs compared penicillamine [13], colchicine [14], infliximab [16], MTX [4], mycophenolate mofetil plus UDCA [15] with UDCA. Two retrospective comparative studies compared MTX plus UDCA with UDCA [3], colchicine plus prednisone with placebo [12]. The characteristics of the studies are shown in Table 1. The mean age of the treatment group and control group was 43.5 and 43.9 years, respectively. Fifty-eight patients in the treatment group and 51 in the control group had advanced histological stage disease (stage III or IV). The duration of eligible trials varied from 24 to 52 weeks; the mean interval time was 38 weeks.

Methodological Quality of Included Studies

The Centre for Evidence-Based Medicine in Oxford, UK assessed the level of the evidence for the included studies [20]. Six trials reported the dropout numbers in the treatment (29 patients) and the control (6 patients) group [3, 4, 13–16]. One study did not report the exact dropout rate [12]. The matching criteria between the groups in 2 retrospective comparable studies were mainly age, gender, liver biochemistry, and liver histological stage. Intention-to-treat analyses were applied in 3 RCTs [4, 14, 15]. The methodological quality of the eligible studies is summarized in Table 2.
Risk of Bias in Included Studies
The funnel plot analysis and statistical methods did not detect the publication bias and other bias from the included studies.[21, 22].

Primary Outcome
Mortality or Liver Transplantation
Seven eligible studies with 266 patients reported this endpoint. For IAs without significant influence in mortality or liver transplantation (RR 1.02, 95% CI 0.54–1.90,
A subgroup analysis was performed according to IAs monotherapy or co-administration therapy. IAs monotherapy included 4 RCTs with no significant influence of primary outcome (RR 0.94, 95% CI 0.58–1.53, p = 0.80) [4, 13, 14, 16]. Co-administration therapy included 3 trials; 2 were MTX and mycophenolate mofetil combined with UDCA respectively [3, 15] and one was a combination of prednisone and colchicine [12]. There was no significant difference in liver transplantation or mortality for combination or monotherapy therapy.

**Secondary Outcome**

**Adverse Effects**

Twenty-seven patients (IAs monotherapy) and 6 patients (co-administration therapy) reported in 7 trials had AEs, compared with 14 patients in the control group. IAs

\[ p = 0.96 \] there was no significant heterogeneity (I^2 = 0%). A subgroup analysis was performed according to IAs monotherapy or co-administration therapy. IAs monotherapy included 4 RCTs with no significant influence of primary outcome (RR 0.94, 95% CI 0.58–1.53, p = 0.80) [4, 13, 14, 16]. Co-administration therapy included 3 trials; 2 were MTX and mycophenolate mofetil combined with UDCA respectively [3, 15] and one was a combination of prednisone and colchicine [12]. There was no significant difference in liver transplantation or mortality rates for co-administration therapy (RR 1.41, 95% CI 0.40–4.95, p = 0.60; Fig. 2).

**Fig. 2.** Forest plot and meta-analysis of mortality or liver transplantation. IAs without significant influence in mortality or liver transplantation, subgroup analysis was performed according to IAs monotherapy or combination therapy. There was no significant difference in liver transplantation or mortality for combination or monotherapy therapy.

**Table 2.** Risk of bias in the randomized controlled studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Adequate random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Adequate assessment of each outcome</th>
<th>Elective outcome reporting avoided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterling et al. [15]</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Inadequate</td>
<td>Adequate</td>
<td>Inadequate</td>
<td>Adequate</td>
</tr>
<tr>
<td>Hommes et al. [16]</td>
<td>Adequate</td>
<td>Adequate</td>
<td>Adequate</td>
<td>Adequate</td>
<td>Adequate</td>
<td>Inadequate</td>
</tr>
<tr>
<td>Olsson et al. [14]</td>
<td>Adequate</td>
<td>Adequate</td>
<td>Adequate</td>
<td>Adequate</td>
<td>Adequate</td>
<td>Adequate</td>
</tr>
<tr>
<td>Larusso et al. [13]</td>
<td>Unclear</td>
<td>Adequate</td>
<td>Adequate</td>
<td>Adequate</td>
<td>Adequate</td>
<td>Adequate</td>
</tr>
</tbody>
</table>
therapy was associated with a significantly higher AE rate compared with placebo (RR 1.81, 95% CI 1.07–3.07, p = 0.003; Fig. 3). Subgroup analysis showed no significant difference in AE rates for IAs co-administration therapy compared with placebo or UDCA (RR 0.74, 95% CI 0.23–2.32, p = 0.06). However, IAs monotherapy was associated with a significant increase in adverse effects (RR 2.52, 95% CI 1.36–4.69, p = 0.003). Most of the AEs reported were diarrhea, abdominal pain, pruritus, fatigue, dizziness, and hair loss (Table 3).

Liver Biochemical Indexes
AST, ALP, ALB, and BIL were assessed in our study. Table 4 showed that IAs therapy had no significant improvement on liver biochemistry except AST (WMD = 9.76, 95% CI −12.92 to −6.6, p < 0.001).

Discussion
PSC is a chronic cholestatic liver disease with the prevalence of 8.5–13 per 100,000 persons [23–25]. Inflammation and fibrosis of the biliary tree are unique features of PSC. Approximately 70–80% patients with PSC have IBD, while 2–7.5% IBD patients develop PSC [26–29]. Autoimmunity has a strong association for PSC with IBD [1, 30]. Various IAs such as corticosteroid [31, 32], infliximab [16], natalizumab [33], tacrolimus [34], mycophenolate mofetil [15, 35], budesonide, and prednisolone [12, 36, 37] had been investigated. However, the clinical benefit and risk associated with the administration of IAs in PSC patients remain inconclusive. This is the first meta-analysis to assess the potential value of IAs in the treatment of PSC.

This study included 5 RCTs and 2 retrospective studies that compared the safety and efficiency of IAs monotherapy or co-administration therapy in 266 patients. This meta-analysis showed that IAs monotherapy or co-administration therapy did not significantly reduce the mortality or the rate of liver transplantation in PSC patients. On the contrary, IAs monotherapy appear to be associated with a higher chance of AEs.

The pooled data analysis of mortality or liver transplantation indicated that IAs therapy had no significant effect compared with placebo. One possibility is that the estimated median from the time of diagnosis to liver

![Fig. 3. Forest plot and meta-analysis of adverse events. IAs therapy had a significantly higher adverse rate compared with placebo. Subgroup analysis showed no significant difference in adverse events for IAs combination therapy compared with placebo or UDCA, but showed a significant increase in adverse events in IAs monotherapy.](http://example.com/fig3.png)
transplantation or death varied from 9.6 to 18 years [25, 38]. As the duration of the trials generally varied from 2 to 3 years (excluding infliximab [16]), it is challenging to estimate a significant difference on mortality or liver transplantation for trials of shorter duration, and the relationship between the effects of IAs and study follow-up warrants further investigation. Another possibility is that IA is not sufficiently absorbed to be able to exert a beneficial effect. The subgroup analysis showed no significant effect on mortality or liver transplantation for IAs provided as monotherapy or co-administration therapy. A previous meta-analysis showed that treatment with oral glucocorticosteroids did not show significant positive effects on clinical or biochemical outcomes but was associated with increased AEs such as cholangitis with septicaemia, paranoid ideas, and fluid retention [39]. These findings are consistent with our results. However, the outcome may be confounded by other factors, such as the small size, the missing of potentially eligible studies due to the lack of abstract, and the low quality of the studies included in this meta-analysis [38]. Despite these limitations, this meta-analysis provides us a large-scale view on the major clinical outcome profiles of IA treatment in this rare disease. Furthermore, our study shows that IAs therapy did not significantly improve liver function except for AST. In the future, caution should be exercised to monitor the relationship between biochemical improvement and clinical improvement.

The safety of patients is of paramount importance and 6 trials reported AEs, which were generally higher in the IAs group than in the control group. The AEs are related to the different types of IAs described in our study. The major AEs reported in these trials were hair loss and diarrhoea, which only occurred in the IA group and may be directly attributed to IA. IA may also potentially aggravate the bone disease that complicates PSC [40]. Bleeding and ascites were also recorded as most serious AEs in these trials, which may not be directly attributed to IA.

### Table 3. Adverse events in concluded studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>IAs or IAs combined with UDCA</th>
<th>Placebo or UDCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterling et al. [15]</td>
<td>Diarrhea, abdominal pain episode of cholangitis</td>
<td>None</td>
</tr>
<tr>
<td>Knox et al. [4]</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hommes et al. [16]</td>
<td>Abdominal pain, pruritus, fatigue, dizziness, fever, nausea, pyrosis, common cold, headache</td>
<td>None</td>
</tr>
<tr>
<td>Olsson et al. [14]</td>
<td>Diarrhea</td>
<td>None</td>
</tr>
<tr>
<td>Larusso et al. [13]</td>
<td>Allergic, cytopenia, diarrhea, proteinuria, hair loss, hemolysis, arthralgia, lichen planus</td>
<td>Cytopenia, proteinuria, arthralgia</td>
</tr>
<tr>
<td>Lindor et al. [3]</td>
<td>Pulmonary problems (cough and dyspnea) hair loss</td>
<td>None</td>
</tr>
<tr>
<td>Lindor et al. [12]</td>
<td>Ascites and bleeding</td>
<td>Gastrointestinal bleeding ascites</td>
</tr>
</tbody>
</table>

IAs, immunosuppressive agents; UDCA, ursodeoxycholic acid; NR, not reported.

### Table 4. Weighted mean difference of biochemical variables in PSC patients treated with IAs

<table>
<thead>
<tr>
<th>Variables</th>
<th>Numbers of studies</th>
<th>WMD</th>
<th>95% CI</th>
<th>Test of interaction test, p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>6 [3, 4, 12–15]</td>
<td>–9.76, U/L</td>
<td>–12.96 to –6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALP</td>
<td>7 [3, 4, 12–16]</td>
<td>–56.61, IU/L</td>
<td>–186.72 to 73.5</td>
<td>0.39</td>
</tr>
<tr>
<td>ALB</td>
<td>5 [3, 4, 13–15]</td>
<td>0.34, g/L</td>
<td>–0.39 to 1.07</td>
<td>0.37</td>
</tr>
<tr>
<td>BIL</td>
<td>6 [3, 4, 12–15]</td>
<td>0.43, mg/dL</td>
<td>–0.67 to 1.52</td>
<td>0.45</td>
</tr>
</tbody>
</table>

AST, aspartate transaminase; ALP, alkaline phosphatases; ALB, albumin; BIL, bilirubin; IAs, immunosuppressive agents; WMD, weighted mean difference.
because their incidences were high even in the control group.

RR was determined as measurement of effect, and subgroup analyses showed that IAs monotherapy was associated with a significantly higher chance of AEs, while there appeared to be no significant association for patients receiving co-administration therapy. This may contribute to the different dosages of the IAs applied as both monotherapy and co-administration therapy. Generally, IAs were administered in co-administration therapy at lower doses compared to monotherapy [3, 4].

In summary, IAs appear to have no effect on the mortality or morbidity rates of patients with PSC. Monotherapy is associated with significantly more AEs and we would not to recommend administration of IAs as monotherapy to PSC patients. IAs co-administration therapy showed no significant difference on AEs compared with controls. IAs with unique mechanisms of action may have the potential for improved efficacy in an appropriate co-administration regime. Future large-scale, well-designed RCTs with extensive follow-up are needed to confirm the efficacy of IAs in an appropriate co-administration regime for the treatment of PSC patients.

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Disclosure Statements

No conflicts of interest were disclosed by the authors.

References