Second-line Agents in Pediatric Patients With Autoimmune Hepatitis: A Systematic Review and Meta-analysis

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ABSTRACT

Background and Aims: Ten percent to 20% of children with autoimmune hepatitis (AIH) require second-line therapy to achieve remission. Although current guidelines exist on first-line management, evidence for second-line therapy in treatment-refractory patients is lacking. Our aim was to perform a systematic review and meta-analysis of the efficacy and safety of second-line treatments used in this population.

Methods: Electronic and manual searches were used to identify potential studies for inclusion. Studies were selected based on reported response rates to second-line therapies in children who failed response to prednisone and azathioprine. Data extraction and risk of bias assessment were performed independently by 2 reviewers. Meta-analysis using weighted estimate of response rates at 6 months was performed for each treatment option. Heterogeneity was assessed.

Results: Fifteen studies of 76 pediatric patients with AIH were included in the review. Overall response rates at 6 months were estimated as 36% for mycophenolate mofetil (MMF) (N = 34, 95% confidence interval [CI] [16–57]), and 50% for tacrolimus (N = 4, 95% CI [0–100%]) and 83% for cyclosporine (N = 15, 95% CI [66%–100%]). Adverse effects were most frequent with cyclosporine (64% experiencing at least 1 adverse effect) followed by tacrolimus (54%) and MMF (48%). Pooled estimates of adverse events were 78% for cyclosporine (95% CI [54–100%]), 42% for tacrolimus (95% CI [0%–83%]) and 45% for MMF (95% CI [25%–68%]). Sensitivity analyses were not performed due to small sample size.

Conclusions: Cyclosporine had the highest response rate at 6 months in children with standard-treatment-refractory AIH; however, it also had the highest rate of adverse events. MMF was the second most efficacious option with a low adverse effect rate.

Key Words: autoimmune hepatitis, children, cyclosporine, mycophenolate mofetil, tacrolimus

WHAT IS KNOWN

• Standard first-line therapy in management of pediatric autoimmune hepatitis is well accepted.

• Twenty percent of children fail first-line therapy.

• Current guidelines do not provide insight into which second-line therapy to consider first.

WHAT IS NEW

• First systematic review and meta-analysis of second-line therapies in children with autoimmune hepatitis.

• Reported adverse effects of each commonly used agent may influence choice of therapy, along with the respective agent’s rate of response.

• Highlights need for multicenter prospective registries addressing efficacy of second-line agents in autoimmune hepatitis.

Autoimmune hepatitis (AIH) is an important pediatric disease that has the potential to progress to end-stage liver disease resulting in need for liver transplantation or death (1). Standard first-line therapy involves induction with high-dose prednisone, followed by a gradual taper and maintenance on combination of prednisone and azathioprine (2). Most children with AIH respond well to standard therapy, but 10% to 20% require second-line agents to achieve remission (3). Although current guidelines and expert opinion provide insight into the choice of potential treatments in the face of failed response to standard therapy (2,4), no data currently exist comparing the efficacy of second-line agents in pediatric AIH.

Several reviews propose mycophenolate mofetil (MMF) use in children with steroid-resistant AIH (3,5,6); however, other immunosuppressants such as cyclosporine, tacrolimus, rituximab, and budesonide are also being used (4,7). The mechanisms of action of these suggested second-line agents vary. For instance, cyclosporine and tacrolimus are calcineurin-inhibitors, whereas MMF is a prodrug that decreases T-cell and B-cell proliferation (4). Because each agent possesses a different adverse effect profile, exploring which therapy may be most effective at achieving overall disease control with the fewest adverse effects is clinically relevant.

Differences in AIH between adults and children support solely selecting pediatric patients for this analysis. First, children tend to have more significant liver disease at presentation with a more rapid progression to cirrhosis (8). Second, pediatric dosing is calculated in milligrams per kilogram (mg/kg), which leads to higher relative doses per kilogram than in adults. These features may imply that children have more aggressive disease requiring higher doses to maintain adequate therapeutic levels, which may influence overall treatment options and responses. Third, children with AIH may also have biliary changes on initial biopsy suggesting...
an overlap syndrome with primary sclerosing cholangitis, also referred to as autoimmune sclerosing cholangitis (ASC). The diagnosis of ASC presents other challenges in the management of autoimmune liver diseases and is more frequently noted in children compared with adults (9,10). Our objective was to conduct a systematic review and meta-analysis of second-line agents used in the management of pediatric AIH.

OBJECTIVES

The objectives of the study were:

1. To evaluate the response rates of different second-line agents after 6 months of treatment in children with AIH when first-line therapy has failed to induce remission.
2. To assess the rate of adverse events experienced by children with AIH on these agents.

PATIENTS AND METHODS

Literature Search

An experienced librarian performed the electronic-based search using key relevant terms determined by the authors (A.N.Z. and B.M.K.). The database search was performed including results in any language from MEDLINE (from 1946 to April 2015), MEDLINE(R) In-Process & Other Non-Indexed Citations (April 15, 2015), Embase Classic and Embase (from 1947 to April 2015), the Cochrane Central Register of Controlled trials (April 2015), ProQuest Dissertations & Theses Full Text (from 1861 to 2014), and SCOPUS. The 3 main domains used as key search terms were “autoimmune hepatitis,” “pediatrics,” and the chosen intervention types. A sample search conducted using the Medline database is shown in Supplemental Digital Content, Appendix, http://links.lww.com/MPG/A908. Abstracts from the last 5 years and dissertations addressing any of the identified second-line agents in relation to pediatric AIH management were included. A manual search of the first 200 hits in “Google scholar” and a review of reference articles were performed for additional studies. Consultation with field experts was also performed to identify any additional published or unpublished studies.

Study Selection

While being widely inclusive, a single author (A.N.Z.) selected any relevant randomized controlled trials (RCTs) (including quasi-randomized studies) and observational studies (case series or cohorts) published in any language by reviewing titles and abstracts from the search results. Results were not restricted to type of study to capture the entire spectrum of available evidence. It was anticipated that many pediatric studies addressing the clinical question would be retrospective and observational in nature. Single case reports, letters to the editor, and commentaries were excluded. To confirm their relevance, 2 reviewers (A.N.Z and P.L.V.) assessed in full any study that could meet criteria for inclusion. Disagreements between reviewers on included studies were brought forth to content expert (B.M.K.) for consensus. Studies were excluded if they only included adult patients, included only 1 pediatric case, or if the interventions of interest were being used as first-line therapy.

Study Inclusion/Exclusion Criteria

Included studies needed to contain the following pertinent information: children less than 18 years with a diagnosis of AIH, a description of initial treatment with standard therapy of prednisone and/or azathioprine, a description of treatment failure defined as either intolerance to treatment adverse effects or failure to reach normalization of liver transaminases based on age cutoffs (11), and second-line intervention with any dose of either MMF, cyclosporine, tacrolimus, rituximab, budesonide, or sirolimus because no specific guidelines currently delineate therapeutic ranges in AIH treatment (12). These agents were included in the search because they are most commonly described alternative options in review articles for the management of children with AIH (3,13–17). A minimum duration of 6 months on second-line therapy was needed to measure the primary outcome. Exclusion criteria were limited to the following: duplicate publications to avoid reporting bias, in which case the most updated manuscript was included if relevant information was retrievable; and studies where second-line agents were used in treatment-naive patients. Authors of included studies that did not provide a defined time-to-response on second-line therapy were contacted for clarification.

Qualitative Assessment of Risk of Bias

Qualitative analysis of the different studies was performed by the authors (A.N.Z, P.L.V.) and disagreements were resolved by consensus with a third-party expert (B.M.K.). Based on a predominance of case series, a modification to the Newcastle-Ottawa scale (NOS) that did not include comparability was used to systematically assess for bias (18). The Cochrane Collaboration tool for RCTs (19) was used for any randomized controlled trials selected from the search results. An analysis of RCTs alone would have been done separately if both observational and non-observational studies were included. The NOS tool includes judgments measured by multiple-choice answers that differentiate studies based on varying risk of bias. The option with the lowest risk of bias for each statement in the tool is identified by a star. In our modified scale, a maximum of 6 stars was achievable per study. This tool evaluated the studies for selection bias and quality of outcome assessment. In the case of any unclear description, study authors were contacted for clarification.

Data Extraction and Management

Relevant information was independently extracted by 2 reviewers (A.N.Z and P.L.V.) from all included studies using a custom data collection sheet. Information collected included type of AIH (type 1 vs type 2), presence of overlap (ASC), age, sex, dose in milligrams per kilogram of the chosen agent, time from diagnosis to switch to second-line agent, reason for the switch from first-line to second-line therapy, time to normalization of liver enzymes on second-line agent, drug trough levels where applicable, and type as well as rate of described adverse effects attributable to the second-line agent. Information relating to missing participants, number of patients in each study and on each treatment was extracted. Documentation of each study’s definition of treatment failure was also collected. Authors were contacted via e-mail for any relevant missing data. Patients who were labeled as having a diagnosis of ASC, based on overlapping features of AIH with primary sclerosing cholangitis on liver biopsy and/or imaging, were subsequently excluded from the data analysis because this disease is known to potentially be more difficult to treat than AIH (3,9).

Data Analysis/Synthesis

The primary outcome was the response rate after 6 months on a second-line agent. Response was determined as complete normalization of liver aspartate aminotransaminase (AST) and/or alanine transaminase (ALT). This was defined as normalization of both transaminases to less than normal ranges based on age cutoffs (11). All studies were reviewed using software Stata 10.1 (StataCorp, College Station, Texas). Only studies with a NOS score of 4 or above were included.
The treatment effect estimate and 95% confidence intervals (CI) were determined for each study. If information on rate of response at 12 months was also measurable then an additional effect estimate and 95% CI for that length of follow-up was calculated. In order to confirm study response rates, corresponding ALT and AST values at 6 and 12 months of follow-up were needed. When a patient was studied for less than 6 months but had already shown evidence of remission based on ALT and AST normalization, they were included in the group of responders at 6 months. When a patient was studied for less than 6 months without having yet responded, they were removed from the total study count of potential responders at 6 months. Thus, in the latter case, the sample size for that particular study would decrease.

The secondary outcomes of interest were the rate and type of adverse reactions attributed to the individual interventions. These included leukopenia and diarrhea for MMF; renal insufficiency, arterial hypertension, neurotoxicity, gum hyperplasia and hypertrichosis for tacrolimus and cyclosporine; obesity, growth failure, hypertension and osteopenia for budesonide; neutropenia, infection, chronic hypogammaglobulinemia and infusion reactions for rituximab (12).

No issues related to unit of analysis were anticipated because the clinical question was determining time to normalization of liver enzymes and adverse effect profile of various second-line agents. In looking at final AST and ALT values, the international system of units (SI units) were used. Both of these findings were present and reported similarly among the studies.

Clinical heterogeneity among the different studies was assessed by comparing patients’ demographic profile based on age, sex, AIH type, and first-line treatment dosage. Statistical heterogeneity was assessed using the Q test. This test is known to have low power and as such, a threshold of 0.10 was used. When heterogeneity was present using the Q test, the results were quantified with the I² statistic.

As a conservative measure to address the observational study design, DerSimonian and Laird random-effects model was used. The response rates to second-line treatment were reported graphically in a forest plot with a weighted estimate and 95% CI. To facilitate analysis, if a response rate of zero was obtained, then it was statistically replaced with a correction factor of 0.5. Comparisons between types of second-line therapeutic agents were made based on both the pooled estimate per treatment and a description of the key adverse events reported per study. No statistical comparisons were made. All calculations were performed using the Open Meta-Analyst statistical software (available at http://www.cebm.brown.edu/static/oma/doc/OpenMA_help.html).

Subgroup and Sensitivity Analyses

Based on the small study number, no additional subgroup or sensitivity analyses could be performed. Desired sensitivity analyses determined a priori would have included comparing the results from only pediatric designed studies to the overall response rates in studies that included children from combined adult and pediatric patients. A second sensitivity analysis looking at the effect of change in outcome definition from 6 to 12 months would have been performed to test the robustness of the results. This reporting meets the Meta-analysis Of Observational Studies in Epidemiology guidelines (20) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (21) for the reporting of meta-analysis.

RESULTS

Study Selection

The details on search results and study selection are provided in Figure 1 (47–74). A total of 21 studies were included in qualitative synthesis and 15 were included in quantitative synthesis.

Study Characteristics

For each of the 15 studies included in the meta-analysis, overall patient and study characteristics are shown in Table 1. All studies included had the initial combination treatment of prednisone and azathioprine. Indications to change to second-line therapy were similar across studies and were mainly reflective of failure to achieve remission or maintain remission. Patients with failure due to intolerance to first-line therapy were included in the analysis. Follow-up periods ranged from 6 months to 15 years. One study solely included patients with type 2 AIH (22) and another only non-European-Caucasian pediatric patients (23). From the total 15 studies included, 6 studies reported the rate of response to MMF (23–28), 3 to tacrolimus (25,29,30), 4 to cyclosporine (22,28,31,32), 1 to budesonide (33), 1 to sirolimus (34), and 1 to rituximab (35). One study was solely used for its description of adverse effects to second-line agents (31). Some studies presented rates of response to 2 different second-line agents.

One included retrospective pediatric case series of 4 patients (mean age 13 years) assessed the response of sirolimus as an alternative treatment in patients with AIH unresponsive to standard first-line treatment (34). Three of the 4 patients were first treated with MMF and then switched to sirolimus 3 months later due to transaminase elevation and worsening disease activity on repeat liver biopsy. Follow-up measures of treatment response to sirolimus were determined for a 6-month period.

Another case series of 2 pediatric patients assessed the response rate of treatment-refractory AIH to rituximab (35). Both patients had previously been treated with prednisone at a dose of 2 mg/kg. The first patient was on prednisone monotherapy for 12 months with minimal response. The addition of MMF and cyclosporine for an additional 6 months did not improve the biochemical profile. The second patient had initially responded to prednisone but relapsed during steroid wean. The addition of azathioprine and subsequent trial on MMF did not improve the patient’s biochemical profile. Follow-up measures of treatment response to rituximab were determined for a 12-month period.

Quality Assessment

The maximal obtainable score was 6 stars based on a modified version of the NOS (18) bias assessment tool. This score was obtained by 12 of 15 studies included for assessment of primary outcome based on criteria shown in Table 2. The remaining studies obtained a score of 5 of 6. Two studies lost 1 point each since they included only a demographic subset of patients with AIH such as solely non-European patients (23) or patients with type 2 AIH only (22). The study by Kurowski et al (34) lost 1 point since a minimum follow-up time of 6 months after change to second-line agent was
Effect of Interventions

Rate of Response

Six studies (N = 34) contributed to the overall response rate to MMF. Each study provided information on the rate of response after 12 months on second-line therapy, but only 5 provided information at 6 months. Aw et al provided detailed information at 6 months through correspondence and was also included in the analysis. The overall proportion of standard-treatment-refractory patients who responded to MMF after 6 months was estimated at 36% (95% CI 16–57%; I² = 51%).

Two studies (N = 4) contributed to the overall rate of response of tacrolimus and 1 additional study for its adverse effect profile. The overall proportion of standard-treatment-refractory patients who responded to tacrolimus therapy after 6 months was estimated at 50% (95% CI 16–57%; I² = 51%).

Four studies (N = 15) measured the effect of cyclosporine in this patient population. The overall proportion of standard-treatment-refractory patients who responded to cyclosporine as a second-line agent after 6 months of therapy was estimated at 83% (95% CI 66–100%; I² = 12%). Reported cyclosporine trough levels ranged from 150–250 in these children. A summary forest plot is shown in Figure 2.

One study by Zandieh et al (33) measured the effect of budesonide on children with AIH that were not responding to standard first-line therapy with prednisone and azathioprine. They reported 100% response in their 2 patients, based on normalization of ALT and AST levels following 6 months of budesonide therapy.

The study by Kurowski et al described 4 children with AIH who were treated with sirolimus as second-line. Of the 2, that were studied to at least 6 months, both were reported as responders. Data on time to response on 1 of the 2 patients were missing. The 2 other patients only had data up to 3 months during which time they had not shown evidence of response. The study by D’Agostino et al (35) described 2 children with AIH who were treated with rituximab and both responded by 3 months.

Adverse Events

Studies on MMF reported no occurrences of nausea or vomiting. The study by Hennes et al (27) reported abdominal pain in 1 of 4 children. The study by Aw et al (26) reported leukopenia in 28% (7/25) of children and abdominal pain in 2 of 25 children. The
<table>
<thead>
<tr>
<th>Study</th>
<th>Second-line therapy</th>
<th>Mean length of time on Pred/Aza before change, mo</th>
<th>Study design</th>
<th>N Common type</th>
<th>Mean age, y</th>
<th>AIH type</th>
<th>Follow-up length</th>
<th>Definition of response</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richardson (2000)</td>
<td>MMF</td>
<td>14</td>
<td>Combined single-center prospective case series</td>
<td>2</td>
<td>1</td>
<td>16.5</td>
<td>121–59 mo</td>
<td>ALT normalization</td>
<td>2/2 by 3 mo</td>
</tr>
<tr>
<td>Zolfino (2002)</td>
<td>MMF</td>
<td>N/A</td>
<td>Combined single-center prospective case series</td>
<td>1</td>
<td>0</td>
<td>14</td>
<td>124 mo</td>
<td>ALT normalization</td>
<td>0/1 by 24 mo</td>
</tr>
<tr>
<td>Hennes (2008)</td>
<td>MMF</td>
<td>28</td>
<td>Combined multi-center retrospective case series</td>
<td>4</td>
<td>3</td>
<td>15.5</td>
<td>10–38 mo</td>
<td>ALT normalization</td>
<td>0/4 within follow-up period</td>
</tr>
<tr>
<td>Aw (2009)</td>
<td>MMF</td>
<td>19.6</td>
<td>Pediatric single-center retrospective cohort</td>
<td>18</td>
<td>5</td>
<td>9.9</td>
<td>1238 mo</td>
<td>AST normalization</td>
<td>8/18 by 6 mo, 10/18 complete by 12 mo</td>
</tr>
<tr>
<td>Jimenez (2012)</td>
<td>MMF; tacrolimus</td>
<td>4.63</td>
<td>Pediatric multi-center retrospective cohort</td>
<td>9</td>
<td>N/A</td>
<td>11.9</td>
<td>124 mo</td>
<td>AST and ALT normalization</td>
<td>5/9 on MMF by 24 mo, 3/3 on tacrolimus by 12 mo</td>
</tr>
<tr>
<td>Lee (2015)</td>
<td>MMF; CsA</td>
<td>N/A</td>
<td>Pediatric multi-center retrospective case series</td>
<td>2</td>
<td>N/A</td>
<td>7.7</td>
<td>126 mo; 18 mo</td>
<td>ALT and AST normalization</td>
<td>0/2 on MMF by 6 mo, 1/2 on CsA</td>
</tr>
<tr>
<td>Larsen (2007)</td>
<td>Tacrolimus</td>
<td>Min of 3 (Further details N/A)</td>
<td>Combined single center case series</td>
<td>2</td>
<td>0</td>
<td>16.5</td>
<td>12 mo</td>
<td>AST, IgG, and histological normalization</td>
<td>2/2 with significant decrease in ALT and fibrosis score by 18 mo</td>
</tr>
<tr>
<td>Marlaka (2012)</td>
<td>Tacrolimus</td>
<td>N/A</td>
<td>Pediatric single-center prospective case series</td>
<td>3</td>
<td>0</td>
<td>15</td>
<td>12 mo</td>
<td>Clinical, biochemical, and histological remission</td>
<td>1/3 have biochemical remission at 12 mo</td>
</tr>
<tr>
<td>Debray (1999)</td>
<td>CsA</td>
<td>60–180</td>
<td>Pediatric retrospective chart review</td>
<td>5</td>
<td>5</td>
<td>14.6</td>
<td>24 y</td>
<td>ALT normalization</td>
<td>5/5 within 3 mo</td>
</tr>
<tr>
<td>Malekzadeh (2001)</td>
<td>CsA</td>
<td>N/A</td>
<td>Combined prospective longitudinal study</td>
<td>4</td>
<td>N/A</td>
<td>16</td>
<td>126 wk</td>
<td>AST and ALT normalization</td>
<td>2/4 within 6 mo</td>
</tr>
<tr>
<td>Scriveres (2004)</td>
<td>CsA</td>
<td>N/A</td>
<td>Pediatric case series</td>
<td>4</td>
<td>2</td>
<td>8</td>
<td>1218 mo–15 y</td>
<td>AST, ALT normalization</td>
<td>4/4 within 3 mo</td>
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<tr>
<td>Nastasio (2011)</td>
<td>CsA</td>
<td>N/A</td>
<td>Pediatric multi-center case series</td>
<td>10</td>
<td>N/A</td>
<td>10</td>
<td>126.5 y</td>
<td>Clinical remission undefined in abstract</td>
<td>Used data for adverse effect profile only</td>
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<td>Zandieh (2008)</td>
<td>Budesonide</td>
<td>N/A</td>
<td>Combined multi-center retrospective review</td>
<td>2</td>
<td>0</td>
<td>14.5</td>
<td>126 mo</td>
<td>AST, IgG normalization, and histological improvement</td>
<td>2/2 by 6 mo</td>
</tr>
<tr>
<td>Kurowski (2014)</td>
<td>Sirolimus</td>
<td>4</td>
<td>Pediatric case series</td>
<td>3</td>
<td>0</td>
<td>12.5</td>
<td>126 mo</td>
<td>ALT normalization</td>
<td>1/3 within 6 mo</td>
</tr>
<tr>
<td>D’Agostino (2013)</td>
<td>Rituximab</td>
<td>10</td>
<td>Pediatric case series</td>
<td>2</td>
<td>0</td>
<td>12.5</td>
<td>126 mo</td>
<td>ALT, ALT normalization</td>
<td>2/2 respond by 3 mo</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransaminase; ASC = autoimmune sclerosing cholangitis; AST = aspartate aminotransaminase; AZA = azathioprine; CsA = cyclosporine; MMF = mycophenolate mofetil; mo = month; Pred = prednisone; y = years; N = number; Min = minimum; N/A = not available.

*Number of patients who went to second-line therapy after being on standard first-line.

†Studies that also had ASC patients in their cohort (excluded for purpose of study).

‡Studies where first-line therapy included patients on prednisone monotherapy before change to second-line therapy.

§Treatment-naïve patients in their cohort (excluded for purpose of study).
TABLE 2. Assessment of bias based using a modified Newcastle-Ottawa scale

<table>
<thead>
<tr>
<th>Study</th>
<th>Representativeness of exposed cohort</th>
<th>Ascertainment of exposure</th>
<th>Demonstration that outcome of interest was not present at the start of study</th>
<th>Assessment of outcome</th>
<th>Was follow-up long enough for outcome to occur</th>
<th>Adequacy of follow-up of cohorts</th>
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Studies on mycophenolate mofetil

<table>
<thead>
<tr>
<th>Study</th>
<th>Estimate (95% C.I.)</th>
<th>(Ev/Trt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richardson et al. 2000</td>
<td>0.833 (0.412, 1.000)</td>
<td>2/2</td>
</tr>
<tr>
<td>Zolfino et al. 2002</td>
<td>0.250 (0.000, 0.850)</td>
<td>0/1</td>
</tr>
<tr>
<td>Hennes et al. 2008</td>
<td>0.100 (0.000, 0.363)</td>
<td>0/4</td>
</tr>
<tr>
<td>Aw et al. 2009</td>
<td>0.444 (0.215, 0.674)</td>
<td>8/18</td>
</tr>
<tr>
<td>Jimenez et al. 2012</td>
<td>0.429 (0.062, 0.795)</td>
<td>3/7</td>
</tr>
<tr>
<td>Lee et al. 2015</td>
<td>0.167 (0.000, 0.588)</td>
<td>3/2</td>
</tr>
<tr>
<td>Overall (I² = 50.86%, P = 0.070)</td>
<td>0.364 (0.158, 0.570)</td>
<td>13/34</td>
</tr>
</tbody>
</table>

Studies on tacrolimus

<table>
<thead>
<tr>
<th>Study</th>
<th>Estimate (95% C.I.)</th>
<th>(Ev/Trt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larsen et al. 2007</td>
<td>0.167 (0.000, 0.588)</td>
<td>0/2</td>
</tr>
<tr>
<td>Jimenez et al. 2012</td>
<td>0.833 (0.412, 1.000)</td>
<td>2/2</td>
</tr>
<tr>
<td>Overall (I² = 79.17%, P = 0.028)</td>
<td>0.500 (0.000, 1.000)</td>
<td>2/4</td>
</tr>
</tbody>
</table>

Studies on cyclosporine

<table>
<thead>
<tr>
<th>Study</th>
<th>Estimate (95% C.I.)</th>
<th>(Ev/Trt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debray et al. 1999</td>
<td>0.917 (0.696, 1.000)</td>
<td>5/5</td>
</tr>
<tr>
<td>Malekzadeh et al. 2001</td>
<td>0.500 (0.010, 0.990)</td>
<td>2/4</td>
</tr>
<tr>
<td>Sciveres et al. 2004</td>
<td>0.900 (0.937, 1.000)</td>
<td>4/4</td>
</tr>
<tr>
<td>Lee et al. 2015</td>
<td>0.500 (0.000, 1.000)</td>
<td>1/2</td>
</tr>
<tr>
<td>Overall (I² = 12.46%, P = 0.330)</td>
<td>0.836 (0.661, 1.000)</td>
<td>12/15</td>
</tr>
</tbody>
</table>

FIGURE 2. Summary forest plot and meta-analyses of the proportions of response rates at 6 months per second-line agent in included studies of children with standard-treatment-refractory AIH. AIH = autoimmune hepatitis; CsA = cyclosporine; FK = tacrolimus; GFR = glomerular filtration rate; MMF = mycophenolate mofetil.

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Most studies on tacrolimus reported no occurrences of renal insufficiency, arterial hypertension, generalized edema, or opportunistic infections. One study reported headache in 30% (6/20) of children and 25% (4/20) had abdominal pain (29). The pooled overall adverse event rate was estimated at 42% (95% CI (0–85%).

Studies on cyclosporine reported no occurrences of paresthesias. The study by Debray et al (22) reported 1 child developing tremor and another, hypertension. They also reported a decrease in glomerular filtration rate that quickly improved with a dose decrease in 3 of their patients. Gum hyperplasia and hypertrichosis were reported in 2 studies (32,36) with the majority of data originating from the abstract publication by Nastasio et al. These adverse effects were described as mild and resolved with dose tapering in all but 1 patient who required the drug to be discontinued. The pooled adverse event rate was estimated at 78% (95% CI (54%–100%)). The study by Zandieh et al (33) stated that no adverse events had been reported on budesonide but does not specify how this was determined. All adverse effect descriptions are depicted in Table 3.

In summary, the estimate of the rate of response at 6 months for a second line agent in pediatric AHI was highest for cyclosporine at 86%, followed by MMF at 38%. The results for tacrolimus were not reliable based on a high degree of heterogeneity with the CI range approaching 0. In addition, the 95% CIs overlap between the 3 main agents considered for second-line in the literature. This makes it challenging to determine the statistical significance of the differences noted in overall response rates among them. Although the rate of response at 6 months would appear strongest for cyclosporine, at least 1 adverse effect occurred in 64% of all patients in included studies, followed by tacrolimus with 54% and MMF with 48%.

**Sensitivity Analysis**

Based on small sample size and small number of studies, planned sensitivity analyses were not conducted.

**DISCUSSION**

This is the first systematic review and meta-analysis of the use of second-line agents in children with AIH. The overall estimate of rate of response within 6 months would suggest that cyclosporine may be most effective at inducing remission following failure with first-line options. This finding needs to be evaluated in conjunction with other factors that may affect treatment decisions.

The therapeutic success of cyclosporine is challenged by the high frequency of undesirable cosmetic effects. Gingival hyperplasia and hypertrichosis have been reported at an incidence of 88% to 100% of patients on cyclosporine (37,38). Drawing on the experience of a different patient population, studies of renal transplant patients have demonstrated that long-term cyclosporine use and the development of cosmetic effects, have an underappreciated psychological impact (39), and have contributed to poor adherence in adolescents (40). Furthermore, cyclosporine use in children with AIH is more often described in the literature for use in induction of remission in the initial 6 months of therapy post-AIH diagnosis. Following this, most studies report a change to standard first-line therapy; prednisone and azathioprine, or another immunosuppressive combination (36,41,42). When considered as a second-line agent in children with AIH, the treatment course is of unknown extended duration. As such, although reversible, the cosmetic adverse effects associated with cyclosporine would need to be accounted for within this framework.

The use of cyclosporine is also more difficult based on the need for frequent drug level monitoring to avoid nephrotoxicity and neurotoxicity. In a recent review, the lack of consensus or evidence for a target trough level in the management of AIH posed as an additional challenge to using this treatment modality long term in this patient population (43). Taking these considerations into account becomes relevant when considering the potential options for children with refractory AIH to standard first-line therapy.

Based on the good efficacy and a more desirable adverse effect profile, MMF may be considered as the more likely treatment of choice as second-line agent in children with AIH. Several recent reviews promote MMF as the preferred choice for second-line therapy in pediatric AIH (8,14,44). Our data indicated a 38% estimated response rate at 6 months to MMF as an alternative agent in standard-treatment-refractory AIH. At first glance, this response rate would appear modest. One explanation for the low observed efficacy rate may be the fewer number of patients in the included case series and cohorts that provided a rate of response at 6 months than for tacrolimus and cyclosporine. If more studies had consistently provided information at 3 and 12 months, then sensitivity analyses assessing the robustness of the 6-month result for all 3 immunosuppressive agents could have been performed.

Complete normalization of liver enzymes at 6 months following onset of second-line therapy may be too short a time to ascertain full response to treatment. As such, this review is not intended to define failed response to therapy as persistent elevation of liver enzymes at 6 months but is rather using this time frame to compare rate of response to different treatments currently in use. The decision to keep the cutoff at 6 months for the analysis was

| TABLE 3. Summary of adverse effects documented per treatment in included studies |
|---------------------------------|---------------------------------|----------------|----------------|----------------|----------------|
| **Side effect** | **MMF (Studies 2 of 6)** | **Tacrolimus (studies 2 of 3)** | **Cyclosporine (studies 3 of 4)** | **Budesonide (studies 1 of 1)** |
| **Events, N (%)** | **Events, N (%)** | **Events, N (%)** | **Events, N (%)** | **Events, N (%)** |
| Leukopenia | 7 (22) | 0 (0) | Decreased GFR | 3 (7) | Moon facies | 0 (0) |
| Nausea/vomiting | 0 (0) | 0 (0) | Paresthesia | 0 (0) | Acne | 0 (0) |
| Abdominal pain/diarrhea | 3 (9) | 6 (27) | Headache | 1 (3) | Skin Striae | 0 (0) |
| Headache/dizziness | 2 (6) | 0 (0) | Generalized edema | 1 (3) | Hypertension | 0 (0) |
| | | | Opportunistic infections | 2 (9) | | 0 (0) |
| | | | Recurrent abdominal pain | 4 (18) | | 0 (0) |
| **GFR** | **glomerular filtration rate** | **MMF** | **mycophenolate mofetil** | **N** | **number** | **%** | **percentage of patients with reported adverse effect.**
based on greatest availability of results, as most studies provided information at this time point. In addition, 6 months is a clinically relevant and generalizable time interval, as any given treatment regimen is typically assessed for response over this period of time before changing therapy. Therefore, even if the estimated response rate with MMF at 6 months is less than with cyclosporine, it may still represent the clinically preferred choice based on its ease of monitoring and better adverse effect profile (5,6,26,45). It is still necessary to maintain close monitoring of patients who are started on MMF to avoid missing the patients who may not respond to this second-line agent.

To our knowledge, this is the most extensive review on the efficacy and safety of second-line agents in the management of children with AIH. It also represents the first meta-analysis addressing efficacy of second-line treatments in this population. By searching for literature in any language and incorporating information from various pediatric populations, this review minimized publication bias by increasing the possibility for detection of negative studies. It also makes the results generalizable to children with AIH from different ethnic backgrounds. Although the summarized results were derived from children who were either a part of combined case series or pure pediatric cohorts, these studies were all deemed as having low to moderate risk of bias based on potential for selection bias (discussed below). Despite this potential, the comparative response rates between treatment options can begin to provide clinicians with a more global summary of the currently available data specific to children with AIH refractory to first-line treatment.

Limitations

Certain limitations are identified within this meta-analysis. The small number of patients included from each study challenges any definitive conclusions from being made. In fact, the number of patients reported in each study ranged from 2 to 18 with the total number of patients included for the tacrolimus response rate at 6 months reaching only 4 (2 studies), and in the case of cyclosporine only 15 (4 studies). It was not possible to perform any subgroup analyses of patient-features based on the sample size of each included study. Assessment of the impact of cirrhosis on different treatment response rates would have been valuable information to ascertain since it is already known that budesonide should not be considered in this context (46). Assessment of the impact of having either AIH type 1 or type 2 on different treatment response rates would have also been valuable to determine in the context of second-line agents available.

Furthermore, the studies were largely observational in nature. Observational studies allow for a more heterogeneous and generalizable sample population within which to analyze results. Comparing responses to different treatments is, however, difficult because it requires the assumption that patients are similar enough between studies to be comparable. Comparison is also challenging since each study shared a different definition of what successful response meant. As such, we chose to include any patient who achieved complete normalization of their liver enzymes rather than solely those who achieved normalization of autoantibody levels and histological remission when this distinction was possible based on information provided in the studies included in this review. In doing so, we were able to increase our sample size from which to determine the response rate for each therapy. Among the different studies, patients were mainly AIH type 1, shared similar demographics (as shown in Table 1), were restricted on having similar initial treatments and definitions of treatment refractoriness, and shared similar outcome measures. Therefore, these studies were similar enough to allow for crude comparisons as is depicted by the response rates. More statistical analyses comparing responses to different treatments, such as network analysis and meta-regression, would require prospectively designed controlled trials.

Some of the included studies provided information on the number of patients who were changed to second-line therapy based on intolerance from adverse effects or refusal to treatment at first-line therapy after relapse. This may very well influence results since patients who were switched due to intolerance to first-line therapy may have disease that is easier to treat regardless of therapeutic option rather than those who were switched based on failure of liver enzyme normalization alone while on first-line therapy. All 3 major second-line agents, however, discussed in this review included patients who were treated due to adverse effects. This may minimize the potential bias in the results. In addition, since not all studies distinguished between those who were changed due to adverse effects and those who were not, the decision was made to keep all patients who were switched from first-line to second-line therapy as both scenarios would be encountered in clinical practice.

Another limitation corresponds to the risk of selection bias with having a large proportion of case series as the main study design available in the literature addressing our clinical question. In order to increase the chance of capturing data on pediatric patients with non-response to second-line therapy, we included studies that presented the results from children with AIH who were either a part of a combined adult-pediatric case series or a pure pediatric cohort. Some of these case series did include patients who did not respond to second-line agents. We therefore present these results of this meta-analysis acknowledging the moderate risk of bias associated with results of case series.

Implications for Future Research and Practice

Despite these limitations, the results from this meta-analysis provide clinicians with valuable available information regarding response rates and adverse effects of second-line therapies in pediatric AIH. It is an important challenge to determine which second-line therapy to use when a child with AIH does not respond to first-line therapy. This study emphasizes the value for future collaborations that will address this clinical question. This population represents a small yet relevant cohort of pediatric patients and as such, future multicenter projects and prospective registries documenting all cases requiring second-line therapy and all chosen treatments are needed.

CONCLUSION

Based on this analysis, the current approach for considering MMF the primary choice for second-line therapy in standard-treatment-refractory AIH in children seems reasonable. The alternative option of cyclosporine could, also however, be supported pending results of prospective studies and larger cohort studies. Further discussions around adverse effect profiles of both medications may help guide family decision as well as clinician decisions. We cannot provide any further recommendation regarding either second-line agent as the best option based on the small sample size obtained by currently available data.

REFERENCES


