Review Article

Immunosuppressive treatments for immunoglobulin A nephropathy: A meta-analysis of randomized controlled trials

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SUMMARY: Immunoglobulin A (IgA) nephropathy is a worldwide disease that causes end-stage kidney disease (ESRD) in up to 15–20% of affected patients within 10 years from the apparent onset of disease and in up to 30–40% of individuals within 20 years from diagnosis. No specific treatment has been established and there is wide variation in current practice. This systematic review evaluates the use of immunosuppressive agents to treat patients with IgA nephropathy. The Cochrane Renal Group Specialized Register, Cochrane Controlled Trial Registry, MEDLINE, EMBASE and article reference lists were searched for randomized or quasi randomized trials. Two independent reviewers assessed studies for inclusion criteria (biopsy proven IgA nephropathy, randomized trial, use of immunosuppressive agents) and extracted data regarding the effects of immunosuppressive agents on ESRD, doubling of serum creatinine, glomerular filtration rate, urinary protein excretion and side-effects. Data were analysed with a random effects model. The published trials were few (13 trials, 623 patients) and were generally of poor quality. Compared with placebo, steroids were associated with a lower risk of progression to ESRD (six trials, 341 patients, RR 0.44, 95% CI 0.25–0.80) and lower end-of-trial proteinuria (six trials, 263 patients, weighted mean difference (WMD) –0.49 g/day, 95% CI –0.25 to –0.72). Treatment with alkylating agents significantly reduced end of treatment proteinuria (two trials, 122 patients, WMD –0.94, 95% CI –0.46 to –1.43). Although the optimal management of patients with IgA nephropathy remains uncertain because of limitations with the existing published data, immunosuppressive agents are a promising strategy and should be investigated further.

KEY WORDS: immunoglobulin A glomerulonephritis, immunoglobulinA nephropathy, immunosuppressive treatment.

INTRODUCTION

Immunoglobulin A (IgA) nephropathy was initially thought to be a rare and benign cause of recurrent haematuria.1 It has since become apparent that IgA nephropathy is neither rare nor benign. Although biopsy practices differ from region to region affecting the frequency and stage of diagnosis of IgA nephropathy, it has been demonstrated that IgA nephropathy is the most common glomerular disease worldwide.2 Furthermore, the natural history of IgA nephropathy is now known to be variable and far from benign. While up to 23% of patients experience lasting remission,3 30% can develop end-stage kidney failure (ESRD) by 20 years, while another 30% experience decreased kidney function.4 Overall, IgA nephropathy causes ESRD in 15–50% of affected individuals.3,6 Studies have demonstrated that continued proteinuria7 and certain advanced renal biopsy findings8 are risk factors associated with disease progression. These studies may help stratify those patients at greatest need for effective therapy.

In the 30 years since the characterization of this disease, the causes of IgA nephropathy have eluded discovery. Animal models suggest the disease is an immune mediated process.9,10 Most patients have some immune system abnormalities at some time in their disease course,
Inclusion criteria

METHODS

usual consisting of increased circulating IgA or some other humoral or cellular abnormality. Recent studies have demonstrated a defect in galactosylation of IgA1, but the role of this defect remains unclear. In the absence of a thorough understanding of its pathogenesis, a consensus on optimal treatment has yet to be established.

Immunoglobulin A nephropathy often progresses very slowly, taking decades to reach the clinical endpoints usually studied in clinical trials. It has thus been difficult to establish the most effective treatment regimen for IgA nephropathy. Recent reviews have examined the evidence for treatment of both adults and children with IgA nephropathy to find optimal regimens. These analyses included studies of varying methodological quality; mostly case series and other forms of non-randomized evaluation. These data have resulted in conflicting information regarding the optimal therapy. The most commonly used regimens include immunosuppressive agents such as glucocorticoids, cyclosporin A or cyclophosphamide. Additionally, non-immunosuppressive medications including fish oils, anticoagulants, antihypertensive agents and surgical tonsillectomy have been tested in a variety of studies including randomized controlled trials.

Given the burden of disease and the known risks of progression, as well as the lack of an accepted effective therapy, we performed a systematic review of these treatments to aid health-care providers in managing this condition. This study summarizes currently available randomized and quasi randomized controlled trial evidence on the effect of immunosuppression (corticosteroids, cytotoxic agents, and others) for the treatment of patients with IgA nephropathy.

Inclusion criteria

We included head-to-head or placebo/no treatment randomized and quasi-randomized controlled trials assessing the effects of different immunosuppressive agents in adult or paediatric patients with biopsy proven IgA nephropathy.

Search strategy

Electronic searches were performed in MEDLINE (1966–2002) and EMBASE (1988–2002) by using optimally sensitive search strategies for identification of randomized controlled trials developed by the Cochrane Collaboration. The Cochrane Renal Group Specialized Register was also searched. The following medical subject heading terms and text words were used: immunoglobulin A nephropathy, IgA nephropathy, Berger’s disease, glomerulonephritis. Trials were considered without language restriction. The results of these searches were analysed in title and abstract form by two independent investigators according to the inclusion criteria. Reference lists from all identified articles were also searched. Additionally, the conference proceedings of the American Society of Nephrology (1998–2002) were searched for abstracts of trials in this area. Information about unpublished trials was sought from experts in the field and pharmaceutical companies involved in the production of steroids and other immunosuppressive agents.

Data extraction and quality assessment

Each trial was assessed by two independent reviewers (JAS, GFMS). Data were extracted from all included trials in terms of patient characteristics of the study sample, doses and modalities of treatment, methodological characteristics of the trials and the following reported outcomes: ESRD requiring renal replacement therapy, doubling of serum creatinine, and remission of proteinuria (as defined by a reduction in urinary protein excretion to less than 1 g/24 h in three consecutive daily samples), urinary protein excretion (g/24 h), serum creatinine (μmol/L), glomerular filtration rate (GFR; either creatinine clearance (mL/min) or Cockcroft clearance (mL/min per 1.73 m²)). All reported data on adverse events of treatment were also collected.

The quality of the trials was assessed by using standard criteria (allocation concealment, blinding, analysis by intention to treat and completeness of follow up). Any differences in data extraction were resolved by discussion among authors and discussion with a third investigator (JC). Where data were missing or incomplete, the authors of the trial were contacted for clarification.

Statistical analysis

Dichotomous outcome data from individual trials were analysed by using the relative risk (RR) measure and its 95% confidence intervals (CI). For continuous outcomes, the difference in means and their 95% CI at the end of treatment or difference in mean change between baseline and end of treatment value were calculated for individual trials, and the weighted mean difference (WMD) was used as a summary estimator.

Heterogeneity of treatment effects between studies was investigated visually by examination of plots and statistically by using the heterogeneity χ² and the I² statistics.

RESULTS

The combined search identified 1196 articles, of which 1133 were excluded during initial review. The major reasons for exclusion were because selected studies were not randomized, were randomized controlled trials (RCT) evaluating other interventions (e.g. non-immunosuppressive agents for treatment of IgA nephropathy), or did not study any of the renal outcomes of interest. Additionally, animal and basic research studies were excluded, along with a number of review articles on the topic. The full-text version of the remaining 63 articles were analysed and 50 were excluded for similar reasons. Overall, 13 trials (16 publications), enrolling a total of 623 patients, were included in this analysis (Fig. 1). Four of eight authors of the included trials were contacted so that additional unpublished information could be obtained and, in some cases, were asked to clarify data relating to their publications. At least three other trials
Systematic review of immunosuppression for IgAN

are still in progress and not yet published in full-text form. The characteristics of the populations and interventions in the included trials are presented in Table 1. The 13 trials could be grouped into three subsets. The first group of studies tested the efficacy of steroids against a control group receiving some other treatment (placebo or no treatment or other non-immunosuppressive regimens). A second group compared the efficacy of cytotoxic agents plus steroids versus a control group receiving placebo, no treatment or anticoagulants. Finally, a third group of trials compared the efficacy of cytotoxic agents without steroids against a control group receiving placebo, no treatment or anticoagulants. No studies performing head-to-head comparisons between different immunosuppressive agents or different doses of the same immunosuppressive agents were identified.

Quality of trials

Table 2 presents data on the quality of the individual trials. By current standards, trial quality of the 13 trials was suboptimal. In all 13 trials, allocation concealment was unclear, participants were blinded in only two of 13 trials, investigators in only one of 13 trials and outcome assessors in only one of 13 trials.

Trials of corticosteroids

There was a lower risk of reaching ESRD in the steroid treated group compared with the control group (six trials, 341 patients, RR 0.44, 95% CI 0.25–0.80). This analysis was dominated by a single trial, and there was no significant heterogeneity between the trials (heterogeneity $\chi^2 = 2.00, I^2 = 0\%, P = 0.57$; Fig. 2). Steroids also conferred a lower risk of doubling of serum creatinine compared with the control group (six trials, 341 patients, RR 0.45, 95% CI 0.29–0.69, heterogeneity $\chi^2 = 1.43, I^2 = 0\%, P = 0.70$; Fig. 3). The GFR at the end of treatment was significantly higher in patients receiving steroids compared to patients in the control groups receiving placebo/no treatment or dipyridamole (four trials, 138 patients, WMD $17.87, 95\% CI 4.93–30.82$). There was no significant heterogeneity between these trials (heterogeneity $\chi^2 = 6.41, I^2 = 53.2\%, P = 0.09$; Fig. 4).

Urinary protein excretion at the end of treatment was significantly lower in patients receiving steroids than in the control groups (two trials, 122 patients, WMD $-0.49$ g/day, 95% CI $-0.25$ to $-0.72$, heterogeneity $\chi^2 = 7.44, P = 0.19$); this analysis was dominated by the trial of Kobayashi et al. (Fig. 5).

Trials of cytotoxic regimens without steroids

The use of cytotoxic agents or cyclosporin without steroids resulted in no statistically significant difference in the risk of ESRD compared to the control group (two trials, 106 patients, relative risk 0.35, 95% CI 0.04–3.22). There was no significant heterogeneity between these trials (heterogeneity $\chi^2 = 0.00, P = 0.97$).

Patients receiving cytotoxic agents or cyclosporin alone had a significantly lower urinary protein excretion at the end of treatment compared to patients receiving placebo or no treatment (two trials, 122 patients, WMD...
Table 1 Characteristics of the participants, interventions, comparisons and outcomes in the included randomized controlled trials

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Intervention (treatment)</th>
<th>Intervention (control)</th>
<th>Baseline renal function and/or proteinuria</th>
<th>No. patients</th>
<th>Follow up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Julian and Barker</td>
<td>Alternate day prednisone 60 mg × 3 months</td>
<td>No treatment</td>
<td>Creatinine clearance &gt;25 mL/min per 1.73 m²</td>
<td>35</td>
<td>6–24</td>
</tr>
<tr>
<td>Katafuchi et al.</td>
<td>Prednisolone 20 mg/day × 1 month and tapering in 18 months, plus dipyridamole 150–300 mg/day</td>
<td>Dipyridamole 150–300 mg/day (same duration as overall treatment)</td>
<td>Serum creatinine 136.2 μmol/L</td>
<td>189</td>
<td>60</td>
</tr>
<tr>
<td>Kobayashi et al.</td>
<td>Prednisolone 40 mg/day and tapering in 7 months</td>
<td>No treatment</td>
<td>Creatinine clearance &gt;70 mL/min</td>
<td>46</td>
<td>120</td>
</tr>
<tr>
<td>Lai et al.</td>
<td>Prednisolone 40–60 mg/day × 2 months, then 1/2 dose in subsequent 2 months</td>
<td>No treatment</td>
<td>Serum creatinine &lt;132 μmol/L</td>
<td>34</td>
<td>38</td>
</tr>
<tr>
<td>Pozzi et al.</td>
<td>Methylprednisolone 1 g i.v. × 3, then prednisone 0.5 mg/kg per day × 6 months</td>
<td>No treatment</td>
<td>Serum creatinine &gt;130 μmol/L</td>
<td>86</td>
<td>60</td>
</tr>
<tr>
<td>Shoji et al.</td>
<td>Prednisolone 0.8 mg/kg per day and tapering to 10 mg qod × 1 year</td>
<td>Dipyridamole 300 mg/day × 1 year</td>
<td>Urinary protein excretion &lt;1.5 g/day</td>
<td>21</td>
<td>13.4</td>
</tr>
<tr>
<td>Welch et al.</td>
<td>Prednisolone 2 mg/kg per day × 2 weeks, then prednisolone 2 mg/kg qod × 10 weeks</td>
<td>Placebo</td>
<td>Serum creatinine &gt;140.8 μmol/L</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Combined cytotoxic agents plus steroids versus placebo/no treatment/dipyridamole/heparin/coumadins</td>
<td>Prednisolone 40 mg/day and tapering to 10 mg/day in 2 years, continued for 6 years, plus cyclophosphamide 1.5 mg/kg per day × 3 months, then azathioprine 1.5 mg/kg per day × 2–6 years</td>
<td>No treatment</td>
<td>Serum creatinine &gt;130 μmol/L</td>
<td>38</td>
<td>24–72</td>
</tr>
<tr>
<td>Ballardie and Roberts</td>
<td>Prednisolone 40 mg/day and azathioprine 100 mg/day × 4 months</td>
<td>No treatment</td>
<td>Well preserved renal function</td>
<td>43</td>
<td>60</td>
</tr>
<tr>
<td>Hamankaya</td>
<td>Prednisolone 2 mg/kg per day with tapering in 2 mg/kg per day × 2 years, heparin/coumadin/dipyridamole 5 mg/kg per day × 2 years</td>
<td>Heparin/coumadin/dipyridamole</td>
<td>No clinical inclusion criteria provided</td>
<td>78</td>
<td>24</td>
</tr>
<tr>
<td>Yoshikawa</td>
<td>Prednisolone 2 mg/kg per day and azathioprine 100 mg/day</td>
<td>No treatment</td>
<td>No clinical inclusion criteria provided</td>
<td>52</td>
<td>23</td>
</tr>
<tr>
<td>Walker et al.</td>
<td>Prednisolone 2 mg/kg per day and azathioprine 100 mg/day</td>
<td>No treatment</td>
<td>No clinical inclusion criteria provided</td>
<td>48</td>
<td>36</td>
</tr>
<tr>
<td>Woo et al.</td>
<td>Prednisolone 2 mg/kg per day with tapering in 2 mg/kg per day × 2 years, heparin/coumadin/dipyridamole 5 mg/kg per day × 2 years</td>
<td>Heparin/coumadin/dipyridamole</td>
<td>No clinical inclusion criteria provided</td>
<td>48</td>
<td>36</td>
</tr>
<tr>
<td>Lai et al.</td>
<td>Cyclosporin A 3-mg/kg per day × 12 weeks</td>
<td>Placebo</td>
<td>Proteinuria &gt;1.5 g/day</td>
<td>19</td>
<td>3</td>
</tr>
</tbody>
</table>

No clinical inclusion criteria provided

Creatinine clearance >5 mL/min per 1.73 m²
Table 2 Quality of randomized controlled trials of immunosuppressive treatment for immunoglobulin A (IgA) nephropathy

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>Intention-to-treat analysis</th>
<th>Lost to follow up (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Julian and Barker</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>2/35 (5.7)</td>
</tr>
<tr>
<td>Katafuchi et al.</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>13/90 (14.4)</td>
</tr>
<tr>
<td>Kobayashi et al.</td>
<td>Inadequate</td>
<td>No</td>
<td>No</td>
<td>44/90 (49.0)</td>
</tr>
<tr>
<td>Lai et al.</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>0/34 (0.0)</td>
</tr>
<tr>
<td>Pozzi et al.</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>3/86 (3.5)</td>
</tr>
<tr>
<td>Shoji et al.</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>2/21 (9.0)</td>
</tr>
<tr>
<td>Welch et al.</td>
<td>Unclear</td>
<td>Participants, Investigators</td>
<td>Unclear</td>
<td>3/20 (15)</td>
</tr>
<tr>
<td>Ballardie and Roberts</td>
<td>Unclear</td>
<td>Outcome assessors</td>
<td>Yes</td>
<td>0/30 (0.0)</td>
</tr>
<tr>
<td>Harmankaya</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>0/43 (0.0)</td>
</tr>
<tr>
<td>Yoshikawa</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
<td>4/78 (5.1)</td>
</tr>
<tr>
<td>Walker et al.</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>1/52 (1.9)</td>
</tr>
<tr>
<td>Woo et al.</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>0/48 (0.0)</td>
</tr>
<tr>
<td>Lai et al.</td>
<td>Unclear</td>
<td>Participants</td>
<td>Yes</td>
<td>0/22 (0.0)</td>
</tr>
</tbody>
</table>

Fig. 2 Effect of steroids on end-stage renal failure in patients with immunoglobulin A (IgA) nephropathy. CI, confidence intervals; RR, relative risk.

Fig. 3 Effect of steroids on doubling of serum creatinine in patients with immunoglobulin A (IgA) nephropathy. CI, confidence intervals; RR, relative risk.
Trials of combined cytotoxic and steroid treatment

With the combined treatment approach, there was no statistically significant difference in the risk of reaching ESRD compared to controls (two trials, 152 patients, relative risk 0.59, 95% CI 0.06–6.03). There was no statistically significant difference in the end of treatment urinary protein excretion between patients receiving combination therapy with steroids plus cytotoxic agents and the control patients (three trials, 154 patients, WMD $-1.25$, 95% CI $-2.71$ to $-0.21$). However, the results of the trials in this meta-analysis were significantly heterogeneous (heterogeneity $\chi^2 = 74.30$, $P < 0.00001$; Fig. 7). The Ballardie and Roberts trial was an outlier in this analysis and was responsible for the heterogeneity. In this trial, higher renal risk patients were enrolled compared to the ones in the trial by Harmankaya and Yoshikawa.17,28

Adverse effects of treatment

The analysis of adverse effects of treatment was problematic because reports of adverse events were few or absent in most trials, and it is unclear whether this is because there were no events or because they were not properly recorded.

We were not able to evaluate publication bias with a funnel plot or other methods because of the small number of trials. Similarly, there were insufficient data to explore whether the duration of treatment or disease severity influenced the effect of treatment.
DISCUSSION

Key findings

The use of glucocorticoids in patients with IgA nephropathy is associated with a statistically significant reduction of the risk of ESRD (RR 0.44, 95% CI 0.25–0.80), the doubling of serum creatinine (RR 0.45, 95% CI 0.29–0.69) and a significant reduction in urinary protein excretion (WMD −0.94, 95% CI −1.43 to −0.46 g/day). Glomerular filtration rate is better preserved with steroids as compared to placebo/other non-immunosuppressive treatment (WMD 17.87, 95% CI 4.93–30.82). There is no statistically significant evidence that cytotoxic agents (without steroids) significantly reduce the risk of ESRD or doubling of serum creatinine, however, they are associated with a significant reduction of urinary protein excretion compared with placebo/no treatment (WMD −0.94, 95% CI −1.43 to −0.46 g/day). Combined treatment with alkylating agents and steroids is not associated with a statistically significant reduction in proteinuria. The apparent conflict in these findings may be explained by the existence of significant heterogeneity across the available published trials, which enrolled patients with different renal risk profiles and, on average, had low power to detect major end-points because of low sample size. The adverse effects of the different immunosuppressive treatments individually and in combination are inadequately reported in the available randomized trials to allow for valid and precise estimates to be determined.

Comparison with existing knowledge

Evidence-based recommendations for the management of IgA nephropathy were published in 1999 and have been partly criticized by subsequent studies, including our own. The main criticism of these recommendations was that they were based on a variety of sources, including non-randomized controlled trial data. The recommendations by Nolin and Courteau indicate that patients with proteinuria over 3 g/day, mild glomerular changes, and preserved renal function (creatinine clearance over 70 mL/min) should be treated with prednisone because steroids reduce proteinuria and stabilize kidney function. These recommendations appear stronger than the evidence base supporting them. Uncertainty exists with available data given the small number of trials, the very small sample size of the trials and the suboptimal methodological quality. At present, steroids are the most promising intervention in terms of both renal function and proteinuria, but there is not enough information to provide strong recommendations. The previous guide-
lines from Nolin and Courteau also indicated that a combination of cyclophosphamide, dipyridamole and warfarin should not be used, nor should cyclosporin A. We found a significant reduction of daily proteinuria with cytotoxic treatment, but no significant benefit for the preservation of renal function. These findings support the view that the potential benefits from efforts directed at proteinuria reduction in patients with IgA nephropathy are yet to be determined.

Strengths and limitations

In the present analysis, we only included randomized trials in an attempt to minimize bias. While the results of this analysis are promising, the applicability of these data remains limited. The available trials tend only to report favourable or surrogate outcomes and lack a thorough reporting of adverse effects of treatment. The quality of trial reporting is generally suboptimal, and trials of suboptimal quality generally tend to favour the intervention. Provided that the risk of ESRD is 30% over 20 years, the very high event rate in the available published trials indicates that enrolled patients were ‘high risk’ ones, which is atypical. Therefore, applicability to patients with less severe disease is problematic and the advantages of long-term treatment of patients in the early stages of IgA nephropathy are less clear. Additionally, the use of steroid/immunosuppressive treatment in low-risk populations may be questionable, because of uncertainties about the natural history of the disease; this is slowly progressive and in many cases, a silent disease, therefore, the use of immunosuppressive agents may be questionable unless efficacy is strongly proven.

Implications for clinical practice and research

The results of this meta-analysis are promising because the outcomes consistently favour the use of immunosuppressive interventions. Of the interventions tested in the available trials, steroids seem the most beneficial. Further research, in the form of well-designed randomized trials, is necessary to ascertain whether immunosuppressive treatments work in patients with IgAN and what benefit they confer. Promising interventions should be tested, including steroids alone (e.g. prednisolone 40 mg/day for 4 weeks, tapering to 20 mg/day in the subsequent 8 weeks and maintenance dose of 15 mg/day subsequently) or their combination with cytotoxic agents such as cyclophosphamide (e.g. as outlined in the study by Ballardie and Roberts). A factorial trial design could be used (steroids vs cytotoxic agents vs combined steroid plus cytotoxic agents). However, given the uncertainty of these interventions and the potential for serious side-effects, a placebo control arm should also be included in these trials. Mycophenolate mofetil should also be evaluated, because small sample sizes in the currently ongoing trial may have led to non-statistically significant findings in preliminary analyses.

Outcomes of interest should be simple measures of clinical relevance. Composite outcomes should generally be avoided, but in this case, a study examining the composite of ESRD and doubling of serum creatinine seems the most feasible. The occurrence of ESRD is low in patients with IgA nephropathy and its detection would require large sample sizes and unfeasible follow-up periods. Only 15–20% of IgA nephropathy patients reach ESRD in 10 years from the time of apparent onset, therefore, treatment of 270 patients in each intervention arm of a trial (total of 810 patients for a three arm intervention trial) over a follow-up period of 10 years would be necessary to detect a 10% significant reduction of this outcome with the intervention (using a two-sided significance test at the 5% level and a power of 80%). This is logistically and economically untenable, so enrolment of high-risk patients and use of a composite outcome (such as ESRD and doubling of serum creatinine) are suggested. In any future trial, the side-effects of treatment should be evaluated.

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