Crescentic, proliferative IgA nephropathy: clinical and histological response to methylprednisolone and intravenous cyclophosphamide

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Abstract

Background. IgA nephropathy is an immune-complex glomerulopathy that can result in capillary or extracapillary proliferation. Previous attempts to correlate specific histological findings including cellular crescents or endocapillary proliferation, with clinical outcomes, have produced conflicting results.

Methods. We conducted a prospective open-labelled trial of 12 patients with crescentic, proliferative IgA nephropathy and clinically progressive disease and treated them with pulse steroids and intravenous cyclophosphamide. Therapy included pulse solumedrol at 15 mg kg⁻¹ day for 3 days, followed by monthly intravenous cyclophosphamide at 0.5 g m⁻² body surface area for 6 months. Clinically significant proteinuria (>1.0 g 24 h) was present in all patients, while nephrotic-range proteinuria (>3.0 g 24 h) was observed in eight of 12 patients. All patients were hypertensive (BP >140/90 mmHg).

Results. After 6 months of treatment, the mean serum creatinine was reduced from a maximum of 2.65 ± 0.39 to 1.51 ± 0.10 mg/dl (P < 0.03), while proteinuria was reduced from 4.04 to 1.35 g 24 h (P < 0.01). The mean slope of 1/serum creatinine increased from −0.0398 ± 0.02 to 0.0076 ± 0.01 after 6 months of therapy, but this trend did not reach statistical significance (P < 0.08).

A repeat kidney biopsy was performed in all treated patients. Endocapillary proliferation, cellular crescents and karyorrhexis were eliminated in all 12 patients after 6 months of therapy, while interstitial fibrosis and tubule dropout remained unchanged. To determine the long-term efficacy of the treatment, treated patients were compared to 12 historical controls matched for severity of IgA on initial biopsy. After 36 months, the rate of end-stage renal disease in the treated group was lower (1/12) than in the historical controls (5/12).

Conclusions. We conclude that steroids and intravenous cyclophosphamide reduce proliferative lesions, reduce proteinuria and stabilize renal function in patients with crescentic IgA nephropathy.

Keywords: crescents; endocapillary proliferation; end-stage renal disease; hypertension; IgA nephropathy; proteinuria

Introduction

IgA nephropathy is one of the most common causes of glomerulonephritis in the world and is characterized histologically by the deposition of polymeric forms of IgA within the mesangium and along glomerular capillary walls [1]. The binding of IgA to putative Fc receptors on the surface of mesangial cells leads to mesangial hypercellularity and production of proinflammatory cytokines. In addition, IgA complexes can indirectly stimulate cell proliferation and mesangial matrix deposition through the activation of complement via the alternative pathway [2].

While mesangial cell hypercellularity and matrix expansion are common in IgA nephropathy, additional glomerular pathology can include endocapillary proliferation, karyorrhexis and cellular crescents [3–6]. The incidence and clinical significance of these lesions are unknown. In a clinical pathological review of 218 paediatric patients, Hogg et al. [7] observed that 20% of patients with IgA nephropathy had crescents on the initial biopsy, and that crescents were often associated with focal endocapillary proliferation or capillary-wall necrosis, suggesting intense glomerular inflammation. Several studies have documented a higher incidence of hypertension and nephrotic-range proteinuria in patients with the crescentic form of IgA nephropathy, suggesting that patients with this variant of the disease may have a worse prognosis [8–10]. For example, Abe et al. [3] studied the clinicopathological outcome of 205 patients with IgA nephropathy and noted that patients with >25% crescents on initial biopsy had <50% renal survival after 4 years. D’Amico et al. [11] found that the presence of crescents in IgA nephropathy increased...
the risk of renal failure almost 1.5-fold and that 50% of patients with crescents and diffuse mesangial proliferation reached end-stage renal disease (ESRD) within 5 years. In an attempt to correlate histopathology with clinical outcome, Haas [4] divided IgA nephropathy into five different grades based upon histological activity. The presence of crescents in patients with grade III or grade IV IgA nephropathy was associated with a worse overall outcome and a greater than 70% chance of ESRD at 5 years.

In the present study, we prospectively treated 12 patients with IgA nephropathy and at least 10% cellular crescents or endocapillary proliferation with pulse solumedrol, oral steroids and intravenous cyclophosphamide. To determine the efficacy of cyclophosphamide therapy in patients with crescentic IgA nephropathy, all 12 patients underwent repeat kidney biopsies after 6 months of therapy. The clinical and histopathological changes, as assessed by a histological activity and chronicity index score, are presented.

**Subjects and methods**

**Study criteria and patient population**

Twelve consecutive patients with crescentic, proliferative IgA nephropathy referred to Emory University Hospital were enrolled in a prospective, open-labelled study of pulse solumedrol, oral prednisone and monthly intravenous cyclophosphamide after signing informed consent. Histological criteria for study enrolment included the presence of incipient to fulminant cellular crescents, with or without segmental endocapillary proliferation, in $\geq 10\%$ of glomeruli. Clinical entry criteria included the presence of hypertension ($\geq 140/90$ mmHg) and $>1.0$ g proteinuria per 24 h. Patients were also considered eligible for enrolment if IgA nephropathy was associated with clinical signs of Henoch–Schönlein purpura (HSP). All drugs, including antihypertensive medications, but with the exception of alternative immunosuppressive agents, were allowed to continue throughout the study. Unless clinically contraindicated, all patients received ACE inhibitors as part of their anti-hypertensive regimen.

**Study protocol**

Patients enrolled in the study received intravenous methylprednisolone (15 mg/kg/day) for 3 days in conjunction with oral prednisone (1 mg/kg/day) for 60 days. Patients were then tapered to 0.6 mg/kg/day for 60 days followed by 0.3 mg/kg/day prednisone for 60 days and 0.15 mg/kg/day for an additional 60 days. At the time of repeat biopsy, all patients were maintained on 10 mg prednisone per day. Intravenous cyclophosphamide was given at 0.5–0.75 g/m² body surface area (BSA) monthly for 6 months. Cyclophosphamide dosages were titrated to achieve a nadir while blood cell count was between 2500 and 3000 cells/ml [3]. All patients enrolled in the study underwent a repeat kidney biopsy 1 month after completion of six courses of cyclophosphamide. Omega-3 fatty acid fish oil supplementation was then initiated at 12.0 g/day. During the follow-up period, oral prednisone was maintained at 0.15 mg/kg/day and systolic and diastolic blood pressures were maintained at 120–130 and 60–70 mm Hg, respectively. Unless clinically contraindicated, all patients received ACE inhibitors as part of their anti-hypertensive regimen.

**Historical controls**

To determine the long-term clinical response to therapy, changes in the slope of the reciprocal of the serum creatinine (1/serum Cr), 24-h proteinuria and incidence of ESRD in the treated patients were compared to 12 untreated patients with similar degrees of histological activity. The surgical tissue archives of The Department of Pathology and Laboratory Medicine, Emory University Hospital, Atlanta, GA, USA were searched by computerized SnoMed codes for a diagnosis of IgA nephropathy. Approximately 4500 biopsies dating from 1992 to mid-2001 were screened. A total of 331 cases were found where the diagnosis of IgA nephropathy was confirmed or considered. Of the 331 cases of IgA nephropathy, 28 were identified with histologically active disease as defined by the presence of incipient-to-fulminant cellular crescents with or without endocapillary proliferation in 10% or more of glomeruli. The incidence of crescentic/proliferative IgA nephropathy at Emory University Hospital was $\sim 8.5\%$. Of the 28 patients with crescentic proliferative IgA nephropathy, 12 patients matched for age, baseline creatinine, proteinuria and incidence of hypertension but managed without immunosuppressive therapy were analysed and compared to the treatment group. Biopsies from renal allografts were excluded.

**Histology**

To determine whether intravenous cyclophosphamide improves glomerular histopathology, patients underwent repeated renal biopsies and the level of cellular proliferation and cortical scarring determined using a modified SLE disease activity/chronicity scoring system. Tissue for light-microscopic examination was prepared in the conventional manner. An experienced renal pathologist (RAH) reviewed the glass slides and electron photomicrographs in blinded fashion. Each biopsy was graded in terms of histological activity and chronicity (Table 1). Basic grading criteria for histological activity included degree of (i) mesangial proliferation, (ii) glomerular endocapillary proliferation, (iii) glomerular endocapillary proliferation, (iv) glomerular endocapillary proliferation, and (v) mesangial hypercellularity. Each tissue sample was divided into five different grades based upon histological activity. Each biopsy was graded in terms of histological activity and chronicity (Table 1). Basic grading criteria for histological activity included degree of (i) mesangial proliferation, (ii) glomerular endocapillary proliferation, (iii) glomerular endocapillary proliferation, and (iv) mesangial hypercellularity.

**Table 1. Clinical data**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 12)</th>
<th>Steroids/CTX (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>43</td>
<td>44</td>
</tr>
<tr>
<td>% Male</td>
<td>66 (8/12)</td>
<td>33 (4/12)</td>
</tr>
<tr>
<td>% Hypertension (&gt; 140/90)</td>
<td>42 (5/12)</td>
<td>100 (12/12)</td>
</tr>
<tr>
<td>% Proteinuria (&gt; 1.0 g/24 h)</td>
<td>92 (11/12)</td>
<td>100 (12/12)</td>
</tr>
<tr>
<td>% Nephrotic (&gt; 3.0 g/24 h)</td>
<td>58 (7/12)</td>
<td>66 (8/12)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.72 ± 0.3</td>
<td>1.49 ± 0.2</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>3.4 ± 0.2</td>
<td>3.2 ± 0.2</td>
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Despite the rapid loss of renal function, treatment with steroids and intravenous cyclophosphamide stabilized renal function and increased the mean slope to 0.0076 ± 0.02 mg/dl/month after 6 months of therapy. As shown in Figure 2, reciprocal 1/serum Cr plots improved or stabilized in 10 of 12 patients after 6 months of treatment. Arrows indicate the point of treatment for each patient.

All patients in the treatment group underwent a repeat biopsy at 6 months to determine (i) the effectiveness of combined corticosteroids and cyclophosphamide in reducing histological activity, and (ii) to delay the progression of chronicity. We found that pulse solumedrol and intravenous cyclophosphamide significantly reduced the number of crescents and degree of endocapillary proliferation without significantly increasing chronicity. Figure 3A, C and E shows representative light-microscope biopsies of three patients with increasing histological severity. As shown in Figure 3A, endocapillary proliferation (large arrow) or Figure 3B circumferential crescents (large arrow) could be seen alone or in combination (Figure 3C). To determine whether treatment with cyclophosphamide reduces cellular proliferation and histological activity, all patients underwent repeat renal biopsies. Figure 3B, D and F shows representative biopsy samples taken after 6 months of steroids and intravenous cyclophosphamide therapy in the same patients as in Figure 3A, C and E. After 6 months of cyclophosphamide and steroids, endocapillary proliferation (Figure 3B) and crescents (Figure 3D) were almost eliminated. Residual activity in follow-up biopsies was manifested primarily as ongoing mesangial proliferation and interstitial inflammation. Glomerulosclerosis was present in some biopsies despite aggressive immunosuppression (Figure 3F).

Clinical data and statistical analyses

A detailed chart review for patients in the control and treatment groups was performed and the following clinical data determined: (i) time of kidney biopsy, (ii) age, (iii) sex, (iv) race, (v) basal and peak serum creatinine, (vi) basal and nadir albumin, (vii) systolic and diastolic blood pressures, (viii) presence of microscopic or gross haematuria, (ix) 24-h proteinuria, (x) and time to renal replacement therapy. Data was obtained on all 24 patients included in the study. Data of aggregate basal and peak serum creatinine (Cr), slope of 1/serum Cr, proteinuria, and pre- and post-activity chronicity scores were included in the statistical analyses for the study group and historical controls. Data are expressed as mean ± SEM for continuous variables or number (percentage) for dichotomous variables unless otherwise stated. Differences within the treatment group were calculated using Student’s t-test and a two-sample paired analysis. The incidence of ESRD at 36 months was calculated using Kaplan–Meier survival curves. Statistical calculations were conducted using GB Stat for Windows, Version 5.0. A P-value of <0.05 was considered to be statistically significant.

Results

To determine the efficacy of corticosteroids and cyclophosphamide therapy on the progression of crescentic/proliferative IgA nephropathy, patients with evidence of crescents or endocapillary proliferation in 10% or more glomeruli were treated with pulse solumedrol and cyclophosphamide for 6 months. As shown in Figure 1, the mean serum creatinine at baseline was 1.49 ± 0.84 mg/dl rising significantly during the course of therapy to a peak value of 2.69 ± 1.47 (P<0.03 vs baseline). After 6 months of solumedrol and intravenous cyclophosphamide, the mean serum creatinine fell to 1.51 ± 0.38 mg/dl. At 36 months, the serum creatinine had increased to 1.85 ± 1.54 mg/dl, but this value was statistically not different from baseline levels. Proteinuria at baseline was 3.70 ± 2.70 g/24 h, increasing to a peak of 4.25 ± 2.32 g/24 h. Treatment with solumedrol and cyclophosphamide significantly reduced proteinuria at 6 and 36 months to 1.35 ± 1.43 and 1.46 ± 2.26 g of protein per 24 h, respectively. All data are reported as means ± SD.

To determine the effect of intensive immunosuppression upon proliferative IgA nephropathy, 1/serum Cr plots were calculated for all patients before and after treatment with steroids and intravenous cyclophosphamide. Prior to therapy, the mean slope of the 1/serum Cr plot was −0.0398 ± 0.07 mg/dl/month. Despite the rapid loss of renal function, treatment...
To determine whether corticosteroids and intravenous cyclophosphamide globally reduced the level of crescents and endocapillary proliferation, a modified SLE disease activity and chronicity scoring system was applied to all 12 patients. As shown in Figure 4, an analysis of the histological activity in the pre-compared to post-treatment biopsies demonstrated a significant \( P < 0.004 \) decrease in activity. Activity in follow-up biopsies decreased in all patients (except patient 5) and fell to one-half or more of original values in 50% of patients. Renal scarring, as indicated by chronicity scoring, did not increase after 6 months for patients receiving steroids and intravenous cyclophosphamide.

To determine the effect of steroids and intravenous cyclophosphamide on long-term renal function, we compared the levels of proteinuria and serum creatinine in treated patients to those in 12 historical controls matched for age, gender, baseline Cr, proteinuria and histological severity. The clinical characteristics of the patients in both groups are listed in Table 1. There were no statistically significant differences between the two groups in age, plasma creatinine or serum albumin. Male patients were more frequent in the control group, but this trend did not reach statistical significance. While five of 12 patients in the control group had systolic and diastolic blood pressures greater than 140.90, all patients (12/12) in the treatment group were hypertensive. This difference was not statistically significant. Gross haematuria was the presenting symptom in 25% of the patients. Serum complement levels were normal in 11 of 12 patients and screening for C-ANCA antibodies was negative in all patients. The baseline Cr in the control group was higher (1.72 ± 1.01 mg/dl) than the treatment group (1.49 ± 0.22 mg/dl) but this difference was not statistically significant. Clinically significant proteinuria (> 1.0 g/24 h) was present in 82 and 100% of the control and treatment groups, respectively, while nephrotic-range proteinuria (> 3.0 g/24 h) was observed in 45 and 66%, respectively.

As shown in Figure 5, baseline creatinine in the historical control group was 1.72 ± 1.01 mg/dl, rising to a peak level of 5.15 ± 3.18 mg/dl. After 36 months of follow-up, serum creatinine remained elevated at 4.33 ± 3.35 mg/dl. Among the historical controls, baseline proteinuria was in the nephrotic range at 4.73 ± 3.76 g/24 h and remained elevated at 4.33 ± 2.50 after 36 months of follow-up. The 24-h proteinuria in the control group was significantly \( P < 0.05 \) higher than the treatment group at 36 months (4.33 ± 2.50 vs 1.46 ± 2.26 g/24 h). Reciprocal 1/serum Cr plots demonstrated a negative slope of 0.0168 ± 0.0163 mg/dl/month, which was significantly less negative than...
Fig. 3. Histological response to intravenous cyclophosphamide in crescentic/proliferative IgA nephropathy. Representative lesions of crescentic/proliferative IgA nephropathy before and after treatment with 6 months steroid and intravenous cyclophosphamide are shown. (A and B) Early extracapillary proliferation is manifest as incipient cellular crescent (large arrow) accompanied by segmental endocapillary proliferation (small arrows) in patient 1 (Jones' methenamine silver with PAS counterstain, ×400). (C and D) The post-treatment biopsy results where extra- and endocapillary proliferation are absent from glomeruli (PAS ×400). (E and F) A fulminant cellular crescent (arrow) and acute necrotizing glomerulonephritis are present in patient 12 prior to treatment (PAS, ×400). The post-treatment biopsy is shown in (B), where crescents and endocapillary proliferation are absent from glomeruli (PAS ×400). (E and F) A fulminant cellular crescent (arrow) and acute necrotizing glomerulonephritis are present in patient 12 prior to treatment (PAS, ×400). The post-treatment biopsy is shown in (F). There is an absence of extra- and endocapillary proliferative lesions with scattered obsolete glomeruli (PAS, ×200).

Fig. 4. Steroids and cyclophosphamide reduce glomerular activity and minimize cortical scarring. A modified NIH SLE histological activity/chronicity index was applied to baseline renal biopsies in the treatment group and historical controls. There were no significant differences in the average activity and chronicity scores between the two groups. After 6 months of cyclophosphamide, the mean activity score in the treatment group was significantly lower than pre-treatment levels (P < 0.004). Mean chronicity scores were not significantly different between baseline levels in the treatment group or baseline levels among the historical controls. Data are presented as means ± SD.

Fig. 5. Progressive renal insufficiency and nephrotic-range proteinuria in untreated crescentic/proliferative IgA nephropathy. Serum creatinine and 24-h proteinuria levels were averaged for 12 patients with crescentic proliferative IgA nephropathy who did not receive immunosuppressive therapy at baseline and after 6 and 36 months of follow-up. Serum Cr increased significantly (P < 0.03) from 1.72 to a maximum of 5.18 mg/dl, falling to 4.31 mg/dl after 36 months of follow-up. Proteinuria was 4.73 g/24 h at baseline, remaining in the nephrotic range (4.33 g/24 h) after 36 months of follow-up. Data are presented as means ± SD.
that in patients receiving intravenous cyclophosphamide ($P<0.001$). The slope of reciprocal plot was negative in 10 of 12 patients in the historical control group (Figure 6).

To determine the efficacy of corticosteroids and intravenous cyclophosphamide upon the incidence of ESRD, a Kaplan–Meier survival plot was calculated for both the treatment group and historical controls. Figure 7 demonstrates that after 36 months of follow-up, 1 of 12 (8.3%) patients in the treatment group reached ESRD compared to 5 of 12 (42%) in the historical controls. This value did not reach statistical significance. Recurrence of proliferative IgA disease, as evidenced by the appearance of endocapillary proliferation or crescents, occurred in two patients. Patient 2 developed endocapillary proliferation while patient 3 developed cellular crescents at respectively 20 and 26 months after completion of initial cyclophosphamide therapy. Both patients were re-induced with cyclophosphamide therapy. Renal function stabilized in patient 3 following re-treatment, but patient 2 did not respond and ultimately reached ESRD ~26 months after diagnosis. Therapy with steroids and cyclophosphamide was well tolerated in the majority of patients. Patient 1 developed compression fracture of the first lumbar vertebra 12 months after initiating therapy, while patient 2 developed severe pneumonia during a second induction for disease relapse.

**Discussion**

We conducted a prospective open-label trial of 6 months of corticosteroid and intravenous cyclophosphamide therapy on glomerular histopathology and disease progression in 12 patients with biopsy-proven crescentic proliferative IgA nephropathy. We find that
short-term cyclophosphamide therapy (i) significantly reduces proteinuria and stabilizes serum Cr after 6 months, (ii) reduces the level cellular crescents, karyorrhexis and endocapillary proliferation, and (iii) minimizes cortical scarring and tubule drop-out. To determine whether these clinical improvements correlate with improved long-term renal survival, we compared the dialysis-free survival at 36 months of patients receiving cyclophosphamide and steroid therapy with 12 untreated patients matched for histopathology.

The clinical significance of glomerular crescents and endocapillary proliferation in IgA nephropathy is unknown because of the absence of a clinically meaningful definition for proliferative subsets of the disease. The lack of a uniform nomenclature for specific histopathology has blocked investigations into the natural history of disease subsets and impairs the design of prospective trials for more effective therapies. Early case series indicate that the presence of cellular crescents and endocapillary proliferation in association with hypertension or proteinuria are poor prognostic signs [4,5,9–11]. Welch et al. [9] reported that patients with proliferative IgA nephropathy were frequently hypertensive at the time of biopsy, while accelerated hypertension (MAP >150) was the presenting symptom in 20% of patients with IgA nephropathy. In a similar study, Subias et al. [10] examined 66 patients with IgA nephropathy and noted that 24/66 (36%) were hypertensive (MAP >114 mmHg) at the time of initial presentation, while 15% had malignant or accelerated hypertension (MAP >163 mmHg). Moreover, these authors noted that crescents or endocapillary proliferation were present in 70% of the patients presenting with accelerated hypertension. Abe et al. [3] studied 203 patients with IgA disease and correlated the percentage of cellular or fibrocellular crescents with clinical risk factors and long-term prognosis. Patients with crescents in >25% glomeruli had a higher incidence of hypertension (MAP >107) and proteinuria (>1.0 g/24 h). We studied 12 patients with 10% cellular crescents with or without the presence of endocapillary proliferation and found that hypertension (MAP >107) was present in all patients at the time of biopsy. While none of our patients had accelerated hypertension, non-nephrotic-range (>1.0 g/24 h) and nephrotic-range (>3.0 g/24 h) proteinuria were present in 100 and 66% of patients, respectively. We found no correlation between the presence of nephrotic-range proteinuria and the response to therapy or development of progressive renal disease.

Early reports on the natural history of IgA nephropathy demonstrated an overall benign course, with only 10% of patients reaching ESRD within 10 years [11]. More recently, D’Amico [12] examined the renal survival rates in 3620 patients compiled from 18 different studies and found an average of 19% ESRD after a follow-up of 10 years. However, subsequent analysis of histological subgroups demonstrated that patients with extracapillary proliferation had a 1.5-fold higher risk of developing ESRD [11]. These initial observations have been corroborated with numerous additional studies. For example, Nicholls et al. [8] reported a case series of three patients with an average of 22% crescents on initial biopsy (range 4–50%) and noted that all patients reached ESRD within an average of 27 months of initial presentation. In a prospective study of 80 children with IgA nephropathy, Hogg et al. [7] noted that 12 of 80 patients (15%) reached ESRD within 4 years. Of the patients reaching ESRD, light microscopy demonstrated that 42% had crescents at the time of presentation while 93% had evidence of focal or diffuse endocapillary proliferation. Abe et al. [3] demonstrated that the risk of ESRD increased with rising percentage of crescents on initial biopsy. After 3 years, 10% of patients with 25–30% crescents on initial biopsy reached ESRD, while 45% of patients with >50% crescent required dialysis within 3 years. Lastly, Roccatello et al. [13] prospectively followed eight patients with IgA nephropathy and cellular crescents in 10–40% of glomeruli and noted that after 5 years >62% of patients reached ESRD. To determine whether 10% cellular crescents in our population was clinically significant, we calculated the slopes of 1/serum Cr in the treatment group and historical controls out to 36 months. Prior to therapy, both the treatment group and historical controls demonstrated a negative slope of 1/serum Cr, indicating a progressive loss of renal function. Despite a comparatively lower percentage of crescents, 5 of 12 patients in the historical controls reached ESRD within 36 months. These rates of renal failure are comparable with the results of Haas [4] who demonstrated that 35% of patients with >50% endocapillary proliferation on light microscopy (class IV IgA nephropathy) reached ESRD within 3 years. These observations suggest that the presence of even minor proliferative lesions on initial biopsy portend a poor prognosis.

The lack of uniform definitions for specific subpopulations of IgA nephropathy has slowed the development of effective treatments for proliferative forms of IgA nephropathy. Early trials using pulse steroid therapy have given conflicting results. In a prospective trial of 86 patients with IgA nephropathy and moderate to severe proteinuria, Pozzi et al. [14] demonstrated that pulse corticosteroids for 6 months slowed the loss of renal function compared to controls matched for clinical severity. A recent review of trials assessing the efficacy of glucocorticoids in the treatment of IgA nephropathy concluded that for patients with preserved renal function (CrCl > 70 ml/min), prolonged therapy (>2 years) effectively slows the loss of renal function [15]. However, in the majority of these studies patients were not classified by pathological changes or histological severity; thus the efficacy of glucocorticoids in patients with more severe pathological changes was not assessed. In an attempt to address this question, Lai et al. [16] divided 34 patients with IgA nephropathy into three groups based upon the degree of mesangial proliferation, glomerulosclerosis and percentage of crescents, and
prospectively studied the efficacy of short-term steroid therapy. In patients randomized to oral prednisone, 4 months of treatment stabilized renal function and reduced proteinuria, but only in those patients with >20% crescents on initial biopsy.

Several small trials have studied whether the addition of oral cyclophosphamide to steroid treatment improves renal survival. For example, Ballardie and Roberts [17] treated 38 progressive IgA nephropathy patients with a combination of steroids and oral cyclophosphamide for 34 months followed by two additional years of prednisone and azathioprine. Kaplan–Meier analysis of renal survival showed a 72% 5-year survival compared to 6% for matched controls. While histological changes including mesangial hypercellularity, interstitial fibrosis and tubular atrophy were similar between groups, patients were not controlled for presence of crescents or endocapillary proliferation [17]. Ferrario et al. [5] treated six patients who had focal glomerular necrosis and ≥20% cellular crescents with steroids and oral cyclophosphamide, and demonstrated that when compared to eight historical controls, 6 months of combination therapy significantly prolonged renal survival.

We examined the effect of intense immunosuppression in 12 patients with progressive IgA nephropathy and histological evidence of ≥10% cellular crescents. In our hands, prednisone and intravenous cyclophosphamide reduced proteinuria and stabilized renal function after 6 months of therapy. Both proteinuria and serum creatinine reduced to near baseline levels within 6 months. Long-term follow-up in the treatment group demonstrated that proteinuria and renal function remained stable over 36 months. To investigate the response of treatment to glomerular histopathology, the percentage of crescents and endocapillary proliferation in the initial biopsy was compared to repeat biopsies performed at the end of the induction therapy. We found that 6 months of steroids and intravenous cyclophosphamide almost eliminated all active cellular crescents and endocapillary proliferation while minimizing cortical scarring and tubular drop-out in the majority of patients. Numerous studies have documented the poor prognosis with crescentic forms of IgA nephropathy, but few had utilized follow-up biopsies to prospectively assess a response to treatment. In a similar study, McIntyre et al. [18] treated nine patients suffering from severe crescentic IgA nephropathy (cellular crescents involving 20–70% of glomeruli) with prednisone and oral cyclophosphamide for up to 6 months, followed by 2 years with prednisone and oral azathioprine. Long-term follow-up demonstrated that steroids in conjunction with alkylating agents reduced proteinuria and improved creatinine clearance. To determine whether steroids and cyclophosphamide reduced the percentage of crescents and histological activity, eight of the nine patients underwent repeat biopsy at the completion of cyclophosphamide therapy. Repeat biopsies demonstrated a partial or complete reduction in disease activity while three of eight patients showed an increase in glomerulosclerosis [18]. To determine the long-term effect of this therapy, we calculated the rate of ESRD in the treated patients compared to 12 historical controls matched for histological severity. In 12 historical controls receiving conventional medical therapy but no immunosuppression, 42% reached ESRD within 36 months compared to 8.5% in the treatment group.

In conclusion, our data suggests that the presence of even small concentrations (10%) of crescents in patients with IgA nephropathy is associated with a poor clinical outcome and a rapid decline toward ESRD. In our hands, 6 months of steroids and intravenous cyclophosphamide stabilizes renal function and reduces proliferative lesions in the glomerulus. Larger, randomized, prospective trials in histologically defined subsets of IgA nephropathy will be needed to ultimately determine the efficacy of cyclophosphamide in patients with crescentic IgA nephropathy.

Conflict of interest statement. None declared.

References


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