Mycophenolate Mofetil therapy in IgA Nephropathy: Histological changes after treatment.

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Abstract

Background: Endocapillary hypercellularity independently predicts renal outcome in IgA nephropathy (IgAN). Mycophenolate mofetil (MMF) treatment is offered to patients presenting to the Imperial College Renal and Transplant Centre with IgAN and histological evidence of endocapillary hypercellularity. Clinical trials of MMF in IgAN have been inconclusive and have been limited by a lack of specific histological inclusion and exclusion criteria when recruiting patients. Evidence of histological improvement following MMF treatment would support its therapeutic use. We therefore reviewed histological changes after MMF therapy in a cohort of IgAN patients.

Method: Eighteen IgAN patients with native renal biopsies before and repeated after MMF treatment were identified. Patients were excluded if they had received any other immunosuppressive therapy, including corticosteroids. Based on the Oxford classification of IgAN, we reviewed histological changes after MMF treatment.

Results: Nine patients (50%) were male. At diagnostic renal biopsy, median age was 35 years (IQR 30-41), serum creatinine was 97μmol/L (IQR 79-153), and urine protein creatinine ratio (UPCR) was 146mg/mmol (IQR 98-212). The median time between biopsies was 24 months (range 9-41). Following MMF treatment, repeat biopsy demonstrated statistically significant improvement in the mean percentage of glomeruli showing endocapillary hypercellularity and cellular/fibrocellular crescents. There was no change in mesangial hypercellularity, segmental sclerosis or tubular atrophy scores. Mesangial IgA deposition was also significantly reduced. Histopathological improvement persisted after cessation of MMF therapy, suggesting that two years of treatment is adequate for benefit. Median serum creatinine remained stable at 3 years follow-up at 104μmol/L (IQR 79-147).

Conclusion: MMF treatment is associated with histopathological improvement in IgAN.

Key words: Mycophenolate mofetil, IgA Nephropathy, Oxford Classification
Introduction

IgA nephropathy (IgAN) is the most common form of glomerulonephritis worldwide and is characterised histologically by the presence of IgA-dominant or co-dominant immune deposits within glomeruli, as shown by immunohistochemistry or immunofluorescence [1]. There is a wide range of clinical presentations and histological findings, but despite extensive research the underlying pathophysiology of the disease is not yet fully understood [2,3]. Consequently treatment is non-specific and IgAN remains the main cause of end-stage renal disease (ESRD) in patients with primary glomerular disease. Predicting outcome for individual patients remains a challenge, but poorer prognosis is associated with proteinuria, hypertension, obesity and certain histological lesions [1].

Current research has produced conflicting data about the benefit of mycophenolate mofetil (MMF) therapy in IgAN [4-10]. Four small randomised controlled trials have been performed, with a range of results reported. Some have demonstrated no benefit from MMF therapy [4,5,7], particularly in advanced fibrotic disease [5], while others have described a reduction in proteinuria and long term renoprotection following treatment with MMF [6,11]. Previous studies looking at outcomes in IgAN have been limited by a lack of specific histological inclusion and exclusion criteria. To date, no study has examined histopathological outcomes following MMF therapy.

Endocapillary hypercellularity independently predicts renal outcome in IgAN, particularly in patients not given immunosuppression [1, 12]; therefore evidence of histopathological improvement following MMF therapy would support its use. To determine the effects of MMF therapy on histological features in patients with IgAN, we retrospectively reviewed all renal biopsies from patients with IgAN who had been treated with MMF monotherapy at our centre. We analysed clinical characteristics and histopathological findings within this cohort to assess the impact of MMF therapy on patient outcomes.
Materials and Methods

Study design

The reports of all renal biopsies referred to the Imperial College Renal and Transplant Centre between 1997 and 2016 were reviewed. Patients satisfying pathologic criteria for a diagnosis of IgAN were identified. Patients were included if they demonstrated the presence of IgA-dominant or co-dominant immune deposits within glomeruli, as shown by immunohistochemistry or immunofluorescence on biopsy, with characteristic findings on electron microscopy, and had been treated with MMF monotherapy. Since 2006, MMF treatment has been offered to patients presenting with IgAN and histological evidence of endocapillary hypercellularity with less than 50% tubular atrophy, if treatment with renin-angiotensin blockade has not resulted in a urine protein creatinine ratio of <100 after three months. MMF is then uptitrated as tolerated to achieve trough mycophenolic acid (MPA) levels of 1.2-2.4 mg/L. Patients aged <16 years were excluded from the study. Patients suspected of having IgA-dominant post-infectious glomerulonephritis, lupus nephritis with predominant IgA deposition, ANCA-associated vasculitis, Henoch-Schonlein purpura, chronic liver disease, history of a significant gastrointestinal disorder, human immunodeficiency virus, or those on immunosuppressive agents in addition to mycophenolate mofetil were also excluded. This study was a retrospective cohort analysis, so ethical approval was not required.

Study end points

Light microscopy (LM), immunohistology, and electron microscopy (EM) findings were reviewed by one of two expert renal pathologists (H.T.C. or C.R) at the time of the original reporting. Recorded LM findings included the following: total number of glomeruli; number of sclerosed glomeruli; number of glomeruli with segmental necrosis; number of cellular, fibrocellular, or fibrous crescents; extent of mesangial and endocapillary hypercellularity; presence of capillary wall double contours; percentage of cortical involvement by interstitial fibrosis and/or tubular atrophy; and the extent of arteriolar sclerosis. Recorded immunohistology findings included the strength of staining for C3, IgG, IgA, and IgM (graded 0–3+ on a semi quantitative scale), as well as the location and pattern of
staining (linear, granular). Recorded EM findings included the location and morphology of electron dense deposits. Crescentic GN was defined as GN with $\geq 50\%$ of viable glomeruli containing crescents. Included biopsies were then re-reviewed by one renal pathologist (H.T.C). Renal histopathologic lesions were evaluated and scored using the Oxford Classification [1]. M score quantifies mesangial hypercellularity: M0, 4 or more mesangial cells per mesangial area in $< 50\%$ of glomeruli; M1, 4 or more mesangial cells per mesangial area in $\geq 50\%$ of glomeruli. E score describes the presence or absence of endocapillary hypercellularity (due to increased numbers of cells within glomerular capillary lumina causing narrowing of the lumina). S score describes the presence or absence of segmental glomerulosclerosis (sclerosis involves any amount of the tuft, but not the entire tuft) or the presence of an adhesion. Finally, T score quantifies the percentage of cortical area with tubular atrophy or interstitial fibrosis, whichever is greatest, where T0 is 0-25%, T1 26-50% and T2 $>50\%$.

Covariates

Demographic, clinical, and laboratory data at the time of the first renal biopsy were manually obtained from patient medical records and included age, sex, blood pressure, haematuria, proteinuria, treatment, family history of renal disease, serum creatinine, serum albumin, and serum C3 and C4 levels. Microscopic haematuria was defined as $> 5$ red cells per high-power field on microscopic examination or positive blood at least 1+ by urine dipstick. Nephrotic range proteinuria was defined as $>3.5$ g of protein in a 24-hour urine collection or a urine protein creatinine ratio $>350$ mg/mmol.

Statistical analyses

Data were analysed using GraphPad Prism (version 6) and IBM SPSS Statistics (Version 22). Categorical variables were expressed as means and SD or SEM, and compared using a two-tailed Fisher’s exact test. Continuous non-parametric variables were expressed as the median and interquartile range and compared with Wilcoxon signed rank test. When comparing pre-, post- and off- MMF patient groups, a repeated measures one-way ANOVA was performed. A P value $<0.05$ was considered statistically significant.
Results

644 patients with IgA Nephropathy were identified. 73 patients had more than one native renal biopsy. Of these 22 were on MMF monotherapy. Two patients were unable to tolerate MMF or non-adherent with therapy, so were excluded from analysis. Two patients were started on MMF without the presence of E1, so were also excluded from analysis as they were outside protocol (Figure 1). Median length of follow up was 60 months (IQR 42-88) and patients were treated with MMF monotherapy for a median duration of 28 months (IQR 16-39).

During the study period, 65 patients with IgAN were treated with MMF therapy (with or without a second agent). In addition to the 18 patients included in this study, 25 patients were treated with MMF monotherapy, but have not yet been re-biopsied.

Baseline characteristics (Table 1).

Demographic details of our cohort are shown in Table 1. The median time between biopsies was 24 months (range 9-41). All patients were on renin-angiotensin aldosterone system (RAAS) blockade unless contraindicated- in two patients hypotension precluded their use. Fourteen patients were on RAAS blockade prior to initiation of MMF therapy; two patients had RAAS blockade and MMF therapy started simultaneously.

Histopathological outcomes (Table 2)

Following MMF treatment, repeat biopsy demonstrated statistically significant improvement in the mean percentage of glomeruli showing endocapillary hypercellularity (p<0.0001) (Figure 2). The mean percentage of glomeruli with cellular/fibrocellular crescents also improved significantly, from 6.82% to 1.30% (p= 0.0017). There was no change in mesangial hypercellularity, segmental sclerosis or tubular atrophy scores. Mesangial IgA, IgG and IgM deposition were significantly reduced after treatment (Table 3). There was no statistically significant difference in capillary wall IgA deposition before and after treatment. Outside our cohort, three patients with E1 were treated with both MMF
and prednisolone. Following treatment, there was resolution of endocapillary hypercellularity in all patients. In this small group, MMF and steroids had a similar effect to that observed with MMF alone.

Clinical Outcomes.

Median serum creatinine remained stable at 3 years follow-up at 104umol/L (IQR 79-147). Urinary protein creatinine ratio had improved at 3 years follow-up, from 146mg/mmol (IQR 98-212) at baseline to 115mg/mmol (IQR 35-223), although this difference was not statistically significant. Two patients received corticosteroid treatment after repeat renal biopsy showed ongoing active disease. Three patients doubled their serum creatinine levels over the course of follow up at 35, 44 and 69 months respectively. One of these patients has undergone a pre-emptive live-related renal transplant; the others have not reached ESRD.

Of the three patients who showed doubling of their serum creatinine, one became pregnant, stopped MMF and was lost to follow up. The other two patients had repeat biopsies which showed persistence of E1 lesions after MMF therapy, suggesting a repeat biopsy is of predictive value in assessing risk of developing progressive disease.

There were no serious complications as a result of MMF therapy; no infections requiring admission, no hyperkalaemic episodes and no patients required treatment for leucopenia. One patient had diarrhoea, with a trough MPA level of 4.

Serial biopsies

Six patients subsequently had a further repeat renal biopsy off MMF therapy (separate to those included in Table 2). A repeated measures ANOVA with a Greenhouse-Geisser correction confirmed a statistically significant difference in endocapillary hypercellularity following MMF treatment (p=0.08) but no statistical differences between M, S and T scores. Post hoc tests using the Bonferroni correction demonstrated a significant difference in endocapillary hypercellularity between pre-treatment and post-treatment or off-treatment biopsies, but no significant difference between post-
treatment biopsies and off-treatment biopsies. This suggests that histopathological improvement persists after cessation of MMF therapy and that two years of treatment (as is standard at our centre) may be adequate for prolonged benefit.
Discussion

The use of MMF in treatment of IgAN is controversial. To date only four RCTs have compared MMF with placebo [4-7, 11] and results have been conflicting. All studies have been small (between 17 and 22 patients receiving MMF monotherapy) and have utilised different inclusion criteria, ethnic populations and durations of follow up. Early studies from Belgium [4] and North America [5,7] showed no benefit from MMF therapy in treating IgAN. In contrast, Tang and colleagues found MMF significantly increased the likelihood of remission from proteinuria in a cohort of Chinese patients and lowered the risk of progression to end stage kidney disease compared to RAAS alone [6, 11].

Previous data looking at outcomes in IgAN has been limited by a lack of specific histological inclusion and exclusion criteria when recruiting patients to studies. This study is the first to examine histopathological outcomes, incorporating the Oxford-MEST score, following MMF monotherapy in an ethnically diverse population.

The role of immunosuppression in IgA nephropathy is contentious. Current KDIGO guidelines recommend a six month course of corticosteroids following 3-6 months of optimized supportive care (including RAAS blockade and blood pressure control) for patients with persistent proteinuria over one gram per day, if their GFR is >50ml/min [13]. This follows work by Pozzi et al [14] and Manno et al [15] who demonstrated that corticosteroid treatment improves rates of clinical disease remission and long term renal survival. Recent work by Rauen and colleagues has suggested that maximising supportive care alone, with aggressive blood pressure control, RAAS blockade and sodium restriction, may have equal effects to supportive care plus immunosuppression (the STOP-IgAN trial) [16].

Unfortunately, the follow up period in the STOP-IgAN trial was short (three years), and some early studies have reported renal survival as poor as 57% at 10 years in IgAN [17], suggesting that a longer follow up period may be required to adequately detect differences in long-term renal outcomes [18]. Indeed, the long term data from both Tang [11] and Pozzi [19] highlight significant differences in renal survival between the treatment groups and controls at ten years; yet these differences were not visible at three years. Rauen and colleagues [16] also excluded patients with over 3.5g proteinuria a day: arguably the patients who would benefit the most from intensive immunosuppression.
Consequently, many nephrologists would be nervous leaving a patient with evidence of active disease on renal biopsy off all immunosuppressive therapy. A large retrospective review of 1147 patients who were part of the European Validation Study of the Oxford Classification of IgAN (VALIGA) cohort identified 184 subjects with greater risk of progression, and propensity matched them to 184 subjects who received RAAS blockade alone. They found that immunosuppression (corticosteroids) in this targeted cohort of patients reduced proteinuria and the rate of renal function decline, and increased renal survival [20]. This suggests that for certain patients at greater risk of progression, immunosuppressive therapy may in fact be indicated.

Heavy proteinuria, hypertension and impaired renal function at the time of diagnosis are well-established clinical risk factors for the progression of IgAN [21-24]. The Oxford Classification of IgAN also identified four histological lesions associated with poor outcome: mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis and tubular atrophy/interstitial fibrosis [1]. Glomerular endocapillary hypercellularity has been shown to be associated with a higher degree of proteinuria and impaired renal function at the time of biopsy, as well as a more rapid loss of kidney function, particularly in those patients who do not receive immunosuppressive therapy [17, 25-27]. Serial biopsies in patients who were treated with immunomodulatory treatment showed improvement in endocapillary proliferation [28,29] implying that this lesion may be amenable to immunosuppressive therapy.

Mycophenolate mofetil (MMF) treatment is offered to patients presenting to our centre with IgAN and histological evidence of endocapillary inflammation. In determining which patients to treat, we wanted to include patients with histological findings predictive of worse outcome, but also with the potential to respond to immunosuppression. Consequently, patients with endocapillary hypercellularity on biopsy were included, but those with >50 % tubular atrophy were excluded, as this suggests a chronic lesion with limited reversibility.

Evidence to support the treatment of endocapillary hypercellularity (E1 score) in IgAN has previously been reported. In 2012, Rocatello and colleagues demonstrated a significant improvement in outcome
(proteinuria, haematuria and serum creatinine) in eight patients with IgAN following six months treatment with MMF [30]. They hypothesised that in order for treatment with MMF to be effective, there needed to be evidence of “florid inflammatory processes” in the glomeruli. This was supported by recent work from Hogg et al [7], who also found that the five patients enrolled in their study with E1 endocapillary hypercellularity scores had improvement in their urinary protein creatinine ratio following MMF therapy.

The present study has demonstrated that MMF treatment is associated with histopathological improvement in IgAN, with a statistically significant improvement in endocapillary hypercellularity following MMF therapy. It has also shown a statistically significant improvement in the mean percentage of glomeruli showing cellular/fibrocellular crescents. In a recent cohort of IgAN receiving no immunosuppression, endocapillary hypercellularity emerged as an independent predictor of rate of loss of renal function, providing further evidence to support immunosuppressive treatment of an endocapillary pattern of IgAN [12]. Uniquely, our study has also provided the opportunity to examine the histopathology of six patients who underwent repeat renal biopsies both whilst on MMF therapy and after cessation of treatment. No differences in histological lesions were found between post treatment and off-treatment biopsies, suggesting that histopathological improvement persisted after therapy. This study also provided the opportunity to examine renal biopsies from a multi-ethnic population, with a prolonged follow-up period, supporting the strength of its findings.

At our centre, the standard protocol is to complete a two year course of MMF prior to a repeat biopsy to aid decision-making regarding further treatment, but repeat biopsy may be performed earlier if clinically indicated. If bias is present in those having a repeat biopsy, this would be towards a less favourable outcome. Given the prolonged follow up period of this study (all biopsies between 1997 and 2016 were reviewed), we do not feel this will significantly affect our data. If on repeat biopsy, there is ongoing evidence of persistent disease, then patients are switched to corticosteroid therapy.

Two patients in this study received a course of corticosteroid treatment and one patient developed end-stage renal disease, requiring transplantation. Analysis from the VALIGA study showed that
7/184 (3.8%) patients who had received any form of immunosuppression developed ESRD compared to 20/184 (10.8%) of propensity matched patients receiving RAAS blockade alone after mean follow up of 4.7 years [20]. Acknowledging the limitations of a small sample size, observed rates of development of ESRD (5%) in our study could suggest that MMF provides some long-term renal protection. Despite a significant improvement in endocapillary hypercellularity, no significant improvement in renal function was observed in participants in our study. This may reflect irreversible nephron loss prior to treatment instigation. We therefore suggest early treatment initiation before irreparable damage has occurred.

Our study has a number of limitations. It is retrospective in nature and from a single treatment centre with limited sample size. It is a cohort study and there is no control group, as all patients with similar disease characteristics were offered MMF. It is also uncertain whether the histopathological changes seen resulted directly from MMF treatment, or could be due to RAAS blockade, or whether they represent the natural history of the disease. However, taken together with the other observations described above, we propose that MMF treatment is associated with histopathological improvement in IgAN.

Since endocapillary hypercellularity independently predicts renal outcome in patients with IgAN not receiving immunosuppressive therapy, the histopathological improvement demonstrated in this study would support a randomised controlled trial in such patients. In an era where there is increasing need for steroid sparing therapies, MMF represents an attractive therapeutic option in a selected cohort of individuals at greater risk for progression.

**Acknowledgements**

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Conflicts of Interest

None to declare.

The results presented in this paper have not been published previously in whole or part, except in abstract format.
References


Figure 1: Study Flow Diagram

644 patients with IgAN on native renal biopsy identified

- 571 patients excluded as single biopsy

- 73 patients had two or more native renal biopsies

- 51 patients excluded as not treated with MMF monotherapy

- 22 patients on MMF monotherapy

- 2 patients non-compliant/unable to tolerate MMF

- 20 patients identified

- 2 patients treated off-protocol (without presence E1)

- 18 patients included in study
### Table 1: Baseline characteristics of patient cohort

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<td>Age (years)</td>
<td>35 (30-41)</td>
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</tr>
<tr>
<td>Male: Female</td>
<td>9: 9</td>
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<tr>
<td>Caucasian/Asian/Indian/Other</td>
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<td>Blood Pressure (mm Hg)</td>
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<td>Systolic</td>
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<tr>
<td>Diastolic</td>
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<td>Serum creatinine (umol/L)</td>
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<td>Serum albumin (g/L)</td>
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<td>Urinary protein creatinine ratio (mg/dL)</td>
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Table 2: Histopathological Outcomes

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<th>P value</th>
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<td>M Post</td>
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<td>13/18</td>
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<td>0.402 (NS)</td>
</tr>
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<td>E Pre</td>
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<td>18/18</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>E Post</td>
<td>15/18</td>
<td>3/18</td>
<td>n/a</td>
<td>&lt;0.0001*</td>
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<td>S Pre</td>
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<td>17/18</td>
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<tr>
<td>T Pre</td>
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<td>3/18</td>
<td>2/18</td>
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Abbreviations

M score quantifies mesangial hypercellularity: M0, 4 or more mesangial cells per mesangial area in <50% of glomeruli; M1, 4 or more mesangial cells per mesangial area in ≥ 50% of glomeruli. E score describes the presence or absence of endocapillary hypercellularity (due to increased numbers of cells within glomerular capillary lumina causing narrowing of the lumina). S score describes the presence or absence of segmental glomerulosclerosis (sclerosis involves any amount of the tuft, but not the entire tuft) or the presence of an adhesion. Finally, T score quantifies the percentage of cortical area with tubular atrophy or interstitial fibrosis, whichever is greatest, where T0 is 0-25%, T1 26-50% and T2 >50% [1].
Figure 2: Histopathological findings before and after treatment with MMF

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<th>Immune Reactants</th>
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<td>IgM Post</td>
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