Severe pneumonia in mycophenolate mofetil combined with low-dose corticosteroids-treated patients with immunoglobulin A nephropathy

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Pneumocystis pneumonia;
Severe pneumonia

Abstract The tolerance of mycophenolate mofetil (MMF; Shanghai Roche, China) in Lee Classes III, IV, and V immunoglobulin A nephropathy (IgAN) remains unclear. This article reports nine cases of severe pneumonia (SP), including pneumocystis pneumonia (PCP) and cytomegalovirus (CMV) pneumonia, and its risk factors in MMF plus low-dose corticosteroid-treated patients with Lee Classes III, IV, and V IgAN. Fifty-three patients with IgAN were included in this single-center study. The treatment regimen was MMF (1–1.5 g/d) plus low-dose corticosteroids (0.5 mg/kg/d). SP was defined as diffuse bilateral lung infiltrate with respiratory failure. PCP was diagnosed by detecting the organisms in the sputum and bronchoalveolar lavage. CMV infection was diagnosed through serum screening for CMV-IgG and IgM antibodies and CMV-DNA testing by a real-time polymerase chain reaction assay. The risk factors of SP were analyzed. Nine cases (16.9%) of SP occurred in this study. All SP developed at approximately the 10th–14th week after the initiation of the regimen: PCP was diagnosed in four cases and CMV infection in two cases. Renal function impairing was more serious in patients with SP than in those without SP, as evidenced by estimated glomerular filtration rate ($p = 0.019$) and serum creatinine level ($p = 0.016$). Six of the nine SPs occurred in MMP plus low-dose methylprednisolone group, which was statistically higher than that in the MMF plus low-dose prednisone group ($p = 0.000$). The incidence of SP in this study was 16.9%. Chronically impaired renal function and the use of methylprednisolone may be the risk factors for SP.

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Introduction

Mycophenolate mofetil (MMF; Shanghai Roche, China) has selective inhibitory effects on proliferative T- and B-lymphocytes [1]. Several prospective, randomized, controlled trials have proven the effectiveness of MMF in immunoglobulin A nephropathy (IgAN) [2,3]. Most clinical trials have shown that MMF is well tolerated and possesses potent activity against pneumocystis pneumonia (PCP) [4]. Until this study, although one study [5] concerning the fact that severe infections, especially PCP, could occur following MMF administration has been reported, the tolerance of MMF combined with low-dose corticosteroids in Lee Classes III, IV, and V IgAN still remains unknown. To further evaluate the occurrence of severe pneumonia (SP) and the clinical characteristics in Chinese patients classified as having Lee Classes III, IV, and V IgAN and treated with MMF, this retrospective cohort study was performed in patients with IgAN who received either MMF plus low-dose methylprednisolone (MP) or MMF combined with low-dose prednisone during the same follow-up period from 2006 to 2012.

Materials and methods

Patients and data

This retrospective study evaluated 53 primary Chinese patients with IgAN, as determined by biopsy, who were registered for a follow-up examination in our renal center. Eighteen patients received MMF plus low-dose MP (0.5 mg/kg/d), whereas the remaining 35 patients received MMF plus low-dose prednisone (0.5 mg/kg/d). MMF was initiated with 0.5 mg/kg/d for 2 months, then slowly tapered by 5 mg every 2 weeks until discontinuation (the usage of MP was the same as that of prednisone in the current study). The records of the patients were reviewed from the start of the treatment through the time when the chart was reviewed, and until the drug was discontinued or severe infection appeared (final time point). Baseline characteristics including age, sex, 24-hour urine protein excretion, serum creatinine, and estimated glomerular filtration rate (eGFR; according to the modified Modification of Diet in Renal Disease (MDRD) equation for Chinese [6]) were recorded. SP was defined as diffused bilateral lung infiltrate with respiratory failure (PO2 < 60 mmHg). PCP was diagnosed by detecting the organism in the sputum and bronchoalveolar lavage (BAL) [7]. CMV infection was diagnosed through serum screening for CMV-IgG and IgM antibodies. CMV-DNA testing was carried out by a real-time polymerase chain reaction assay. This study was conducted in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of Shenzhen Second People’s Hospital, Guangdong, China. Written informed consent was obtained from all participants.

Statistical analysis

The clinical characteristics and occurrence of SP were compared between the MMF plus MP group and the MMF plus prednisone group. The results are given as mean ± standard deviation for descriptive statistics. The baseline clinical variables were compared using the Student t test between groups, and the Chi-square test was used for the comparison of stratified data. SPSS version 13.0 software (SPSS Inc., Chicago, IL, USA) was used in all analyses. A p value < 0.05 was considered significant.

Results

Baseline characteristics

Fifty-three patients with IgAN were registered in our renal center, and received follow-up examinations from 2006 to 2012. Among these patients, 18 (34%) were treated with MMF plus low-dose MP, whereas 35 (66%) were treated with MMF combined with low-dose prednisone. The two groups did not differ in terms of their distribution of age, sex, serum creatinine, eGFR, and urine protein excretion at the baseline (Table 1).

Table 1 Demographic and clinical data for patients with Lee Classes III, IV, V IgAN in the mycophenolate mofetil plus low-dose methylprednisolone and mycophenolate mofetil combined with low-dose prednisone groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MMF + MP group (n = 18)</th>
<th>MMF + prednisone group (n = 35)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>38.3 ± 11.9</td>
<td>36.9 ± 11.6</td>
<td>0.433</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>11:7</td>
<td>19:16</td>
<td>0.767</td>
</tr>
<tr>
<td>SCR (µmol/L)</td>
<td>232.16 ± 103.9</td>
<td>228.6 ± 101.8</td>
<td>0.338</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>39.93 ± 11.63</td>
<td>43.06 ± 12.16</td>
<td>0.381</td>
</tr>
<tr>
<td>Urine protein excretion (g/d)</td>
<td>3.14 ± 1.72</td>
<td>3.30 ± 1.66</td>
<td>0.631</td>
</tr>
</tbody>
</table>

Values expressed as mean ± standard deviation. There were no significant differences in baseline characteristics between the groups.

eGFR = estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; MMF = mycophenolate mofetil; MP = methylprednisolone; SCR = serum creatinine.

Treatment efficacy

MMF plus low-dose MP or MMF combined with low-dose prednisone reduced the urine protein excretion and preserved the renal function in the present study. At the 12th month of follow-up, urine protein excretion decreased greatly from 3.14 ± 1.72 g/d to 0.96 ± 0.32 g/day (p = 0.000), and the renal function remained stable (serum creatinine was 232.16 ± 103.9 µmol/L and 206.33 ± 79.5 µmol/L prior to and after the treatment, respectively, p = 0.245) in the MMF plus MP group. Meanwhile, urine protein excretion decreased greatly from 3.30 ± 1.66 g/day to 0.31 ± 0.23 g/d (p = 0.000), and renal function remained stable (serum creatinine was 228.6 ± 101.8 µmol/L and 201.3 ± 99.3 µmol/L prior to and after the treatment, respectively, p = 0.035) in the MMF plus prednisone group.
Occurrence, clinical characteristics, and prognosis

Among the 53 patients treated with MMF and low-dose corticosteroids, nine developed SP around the 3rd month (10th–14th week) after treatment. Six of these nine patients with SP occurred in the MMP plus low-dose MP group, which was statistically higher than that in the MMF plus low-dose prednisone group (33.3% vs. 8.6%, \( p = 0.000 \)). The nine patients that developed delayed SP after MMF plus low-dose corticosteroid treatment had fevers > 38°C, dry cough, and progressive dyspnea, as outlined in (Table 2). Chest radiography and computed tomography demonstrated diffuse, bilateral interstitial, and alveolar infiltrates. All the nine patients had acute onset and progressed respiratory failure in 4–7 days. All patients had hypoxemia with arterial PO\(_2\) < 60 mmHg (range: 41–56 mmHg). Two patients died of respiratory failure after 7–10 days of fever, dry cough, and progressive dyspnea. The other seven patients recovered.

Clinical characteristics

Renal function impairing was more serious in patients with SP than in those without SP, as evidenced by eGFR (41.3 ± 14.2 mL/min/1.73 m\(^2\) vs. 65.3 ± 30.6 mL/min/1.73 m\(^2\), respectively, \( p = 0.019 \)) and serum creatinine (263.36 ± 112.3 vs. 112.77 ± 63.1, respectively, \( p = 0.016 \); Table 3). The other index did not exhibit statistical difference.

Microbial etiology

Human immunodeficiency virus screening was negative in all the nine patients. Six of the nine patients with SP were transferred to Guangzhou Institute of Respiratory Disease, Guangzhou, China for further treatment. PCP was diagnosed in four patients through PCP screening of sputum, induced by hypertonic sodium chloride and BAL. BAL revealed an abundance of inflammatory cells, with a predominance of neutrophils (49–66%). CMV infection was diagnosed in two patients with serum screening for CMV-IgG and IgM antibodies and CMV-DNA testing by real-time polymerase chain reaction assay. The microbial etiology of the other three patients with SP was unclear.

Table 3 Clinical characteristics of patients with and without severe pneumonia.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients with SP (n = 9)</th>
<th>Patients without SP (n = 44)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>41.7 ± 166</td>
<td>39.7 ± 11.6</td>
<td>0.073</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>5:4</td>
<td>26:18</td>
<td>0.903</td>
</tr>
<tr>
<td>SCr (( \mu \text{mol/L} ))</td>
<td>263.36 ± 112.3</td>
<td>112.77 ± 63.1</td>
<td>0.016</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m(^2))</td>
<td>41.3 ± 14.2</td>
<td>65.3 ± 30.6</td>
<td>0.019</td>
</tr>
<tr>
<td>MMF dosage (g/d)</td>
<td>1.33 ± 0.21</td>
<td>1.38 ± 0.19</td>
<td>0.283</td>
</tr>
</tbody>
</table>

Discussion

IgAN is the most common type of glomerulonephritis in the world [8]. The course of IgAN is variable, and 15–40% of patients progress to end-stage renal disease over 10–20 years [9]. However, the effectiveness, especially the safety therapy, for IgAN remains uncertain and curative therapy is still unavailable [10]. MMF was introduced into clinical practice 10 years ago [11,12]. Until this report, SP, including PCP and MCV, followed with MMF, had rarely been reported in the treatment of primary renal diseases [13,14]. Many randomized, controlled studies of lupus glomerulonephritis have shown that MMF had a good tolerance compared with other immunosuppressants [15]. In four controlled human trials, none of the 1068 renal transplant recipients that received MMF developed PCP [16]. In a retrospective study, PCP and MCV did not occur in 272 renal transplant recipients treated with MMF [4]. MMF was first used to treat IgAN in 1997 [17]. To date, four randomized controlled trials have shown good safety profile in patients with IgAN [2,3,18,19]. However, in a retrospective study [5], six patients had SP in 32 MMF-treated patients with IgAN, (3 patients with PCP and 2 patients suspected of having PCP), compared with those.

Table 2 Clinical data of patients with severe pneumonia.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (y)</th>
<th>Sex</th>
<th>eGFR (mL/min/1.73 m(^2))</th>
<th>MMF (g/d)</th>
<th>Time for SP after MMF (wk)</th>
<th>Onset</th>
<th>Cause of SP</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>Male</td>
<td>29.9</td>
<td>1.5</td>
<td>11</td>
<td>Acute</td>
<td>PCP</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>Male</td>
<td>43.1</td>
<td>1.0</td>
<td>10</td>
<td>Acute</td>
<td>PCP</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>Male</td>
<td>41.7</td>
<td>1.5</td>
<td>14</td>
<td>Acute</td>
<td>not clear</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>Female</td>
<td>39.4</td>
<td>1.0</td>
<td>13</td>
<td>Acute</td>
<td>CMV</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>Female</td>
<td>49.0</td>
<td>1.5</td>
<td>12</td>
<td>Acute</td>
<td>CMV</td>
<td>Survived</td>
</tr>
<tr>
<td>6</td>
<td>49</td>
<td>Female</td>
<td>51.3</td>
<td>1.5</td>
<td>13</td>
<td>Acute</td>
<td>not clear</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>36</td>
<td>Male</td>
<td>38.6</td>
<td>1.5</td>
<td>11</td>
<td>Acute</td>
<td>not clear</td>
<td>Survived</td>
</tr>
<tr>
<td>8</td>
<td>39</td>
<td>Female</td>
<td>41.6</td>
<td>1.5</td>
<td>12</td>
<td>Acute</td>
<td>PCP</td>
<td>Survived</td>
</tr>
<tr>
<td>9</td>
<td>61</td>
<td>Male</td>
<td>38.2</td>
<td>1.5</td>
<td>13</td>
<td>Acute</td>
<td>PCP</td>
<td>Died</td>
</tr>
</tbody>
</table>

CMV = cytomegalovirus; eGFR = estimated glomerular filtration rate; MMF = mycophenolate mofetil; PCP = pneumocystis pneumonia; SP = severe pneumonia.
treated with cyclophosphamide and low-dose prednisone. Moreover, the patients with SP had a very poor prognosis; five of six patients presented with an abrupt onset that rapidly progressed to respiratory failure; three patients died despite receiving intensive trimethoprim-sulfamethoxazole therapy. The authors of this retrospective study thought that the chronically impaired renal function may be a risk factor for SP in their patients with IgAN [5].

However, the safety of MMF combined with low-dose prednisone in IgAN remains unclear. In this study, the incidence of SP in patients with IgAN treated with MMF combined with low-dose corticosteroids was 16.9%, similar to that reported in the literature [5]. The microbial etiology of SP included PCP and CMV, which was a bit different from the article reported previously [5]. All the nine patients presented with an abrupt onset of symptoms that rapidly progressed to respiratory failure; Two patients died (mortality rate was 22.2%). The prognosis was even worse than that of AIDS patients with PCP [7].

To date, the related factors of SP in MMF combined with low-dose prednisone regimen in IgAN are still not well known. Reduced renal function has been strongly associated with the occurrence of SP [5]. In the current study, renal function impairment was also found to be more statistically serious in patients with SP than in those without SP, as evidenced by eGFR and serum creatinine. This finding may be due to the pharmacokinetic characteristics of MMF. The pharmacokinetics of MMF in patients with end-stage renal disease indicated that renal failure prolongs the half-life of glucuronide, causing the accumulation of the mycophenolic acid glucuronide (MPAG) and increasing the free non-protein-bound fraction of mycophenolic acid (MPA) (fMPA) [18–21]. All of the instances of SP occurred on the 10th–14th week of MMF treatment, suggesting that fMPA and MPAG accumulated in patients when renal function was damaged. Thus, pharmacokinetic analysis in different stages of renal damage deserves further evaluation in future studies. MMF may be prescribed by adjusting the dosage according to the renal function.

The incidence of SP in MMF plus low-dose MP group was statistically higher than that in the MMF combined with low-dose prednisone group, which has not been previously reported. According to the literature [22], in vitro, the relative immunosuppressive potency of prednisone is zero, whereas the MP’s immunosuppressive function is 11. Thus, patients treated with MMF plus MP may be more susceptible to infection than patients treated with MMF combined with prednisone. Given the number of patients with SP is only nine in this study, the further analysis of the relationship between SP and prednisone or MP is needed. The immunosuppressive mechanisms of glucocorticoids are currently unclear, but the high T-cell sensitivity may indicate that glucocorticoids interact with the proliferation of activated T-lymphocytes [22]. According to the previous study [7], the decreased numbers of CD4+ T cells is a strong risk factor for PCP infection and lymphopenia is associated with the susceptibility for PCP [5], so, the immune status should be monitored by testing lymphocytes and CD4+ T cells.

This retrospective study showed that chronically impaired renal function and MP are probably the two risk factors for SP. The microbial etiology mainly was PCP and CMV. Based on this preliminary result, we recommended that caution should be taken in the administration of MMF combined with a steroid, especially with MP, in IgAN patients with renal insufficiencies. If needed, MMF plus prednisone is safer than MMF plus MP in Lee Class III-V IgAN patients.

References


