Lupus Nephritis—Should MMF Be Considered the Drug of Choice?

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Summary

Severe lupus nephritis is an aggressive disease that requires an aggressive approach to treatment. Recent randomized clinical trials showed that mycophenolate mofetil compared favorably with cyclophosphamide (traditional approach) for remission induction. Consequently, mycophenolate mofetil is now commonly recommended as first-line therapy. Nevertheless, the role of mycophenolate mofetil in treating severe lupus nephritis is unclear, because such patients were excluded from these trials. With this limitation as background, this work addresses the question of mycophenolate mofetil for induction therapy for severe lupus nephritis. We performed a systematic review of the outcomes of treating severe lupus nephritis with mycophenolate mofetil or cyclophosphamide. Because no studies directly addressed this question, these data were extracted from the published literature or obtained by personal communications from investigators. There is no universally accepted definition, and therefore, severe lupus nephritis was arbitrarily defined by renal histology, resistance to therapy, or level of kidney function at presentation. For each trial analyzed, we determined the partial and complete remission rates. Long-term outcomes were compared when available. The pooled results suggest that mycophenolate mofetil and cyclophosphamide are equally effective in inducing remission of severe lupus nephritis. However, relapse rates and risk of developing ESRD were higher for mycophenolate mofetil compared with cyclophosphamide. In conclusion, in the short term, mycophenolate mofetil and cyclophosphamide are about equal in inducing remission. However, long-term outcomes suggest better preservation of kidney function and fewer relapses with cyclophosphamide therapy. Therefore, mycophenolate mofetil should not yet be considered the induction drug of choice for severe lupus nephritis.


Introduction

Two transformative events have modified the treatment of lupus nephritis (LN) since corticosteroids became routinely used for this manifestation of systemic lupus erythematosus. The first event occurred in 1986 with publication of the National Institutes of Health study showing that kidney function in patients with LN was better preserved if cyclophosphamide was used in conjunction with corticosteroids compared with corticosteroids alone, especially in patients considered high risk for renal failure because of histologic findings of glomerulosclerosis and interstitial fibrosis (1). Importantly, this beneficial effect of cyclophosphamide did not become evident for 5 years after beginning therapy. Before 5 years, corticosteroids, azathioprine, and cyclophosphamide each performed equally well in inducing remission of the LN. This pattern of late but not early benefit of cyclophosphamide compared with other therapies was confirmed in additional studies (2,3). Long-term follow-up also showed that cyclophosphamide therapy was better for preventing LN flares (4). The long-term benefits of cyclophosphamide were found to be applicable to patients with normal or elevated serum creatinine at the start of treatment (5).

The second transformative event occurred as investigators tried to find an alternative approach to LN therapy that was associated with fewer severe adverse effects than the National Institutes of Health cyclophosphamide regimen. Landmark studies showed that shortening the duration and/or cumulative dose of cyclophosphamide was as effective as longer courses with higher doses, at least in mild to moderate proliferative LN in a cohort of mainly Caucasian subjects (6–8).

At the same time, efforts were underway to determine if cyclophosphamide could be replaced as the drug of choice for LN. Several prospective trials showed that mycophenolate mofetil (MMF) was as effective as cyclophosphamide in inducing remission of LN during the initial phase of therapy (9,10). Nonwhite, non-Asian patients tended to respond better to MMF than intravenous cyclophosphamide (10). Interestingly, although not statistically significant, in the largest of these studies, almost two times as many patients in the MMF group withdrew because of adverse effects than the cyclophosphamide group, and there were more deaths in the MMF group (10). Long-term preservation of kidney function, ostensibly the
What Is Severe LN?

As investigators began using MMF for lupus erythematosus-related kidney disease, reports considered severe LN to be class III, IV, or V LN. However, patients with serum creatinine levels above 2.3 mg/dl were routinely excluded from these trials (14–16). Thus, patients with an elevated serum creatinine at study entry were relatively few in number, and they were pooled with patients who had normal serum creatinine values. Now that MMF has been shown to be as effective as cyclophosphamide for induction of proliferative LN in general (10), attention can be focused on specific subgroups of LN.

After reviewing the data available in the published literature, it is clear that a single definition of severe LN is not applicable to all of the relevant studies. Accordingly, we have arbitrarily defined severity of LN in three distinct ways. (1) Class IV LN with more than 15% crescents and/or glomerular capillary necrosis (this degree of kidney injury is often accompanied by an elevated serum creatinine). (2) Persistent or relapsing disease despite administration of cyclophosphamide (persistent disease is often associated with elevated serum creatinine). (3) Proliferative LN (class III or IV) with impaired renal function at initiation of therapy defined as an elevated serum creatinine. This criterion is particularly important, because an abnormal creatinine at the time of diagnosis or initiation of therapy for LN seems to be the strongest risk factor for progressive renal failure during long-term follow-up (17–19). However, it must be pointed out that, for this review, because so few patients with significantly impaired kidney function have been studied in published trials, we included patients with any increase in serum creatinine above the normal range. One could argue that severe LN should be defined as disease presenting with a GFR below a prespecified cutoff level. Such data, had they been available, might have revealed differences between MMF and cyclophosphamide (see below).

These definitions of severity are arbitrary. Having a standard, widely accepted definition would be desirable and likely based on a combination of clinical and histologic parameters that would allow a prognosis label to be attached to the severity label. For example, diffuse kidney injury from inflammation accompanied by moderate or markedly impaired kidney function can be considered severe but with a good prognosis if treated appropriately as opposed to kidney injury that healed with diffuse sclerosis/fibrosis accompanied by moderate or markedly impaired kidney function.

Histologic Severity

Two studies directly compared MMF with cyclophosphamide as the initial treatment of class IV LN with extensive glomerular and interstitial injury (20,21). As shown in Table 1, rows 1 and 2, the number of complete remissions within 6–12 months of starting therapy was higher in the MMF-treated patients than the patients treated with intravenous cyclophosphamide, whereas partial responses were the same or higher in the cyclophosphamide patients. One of these studies had long-term follow-up, and relapses were found to be more frequent in the cyclophosphamide group (20). Based on the 69 patients studied, MMF seems at least as effective as intravenous cyclophosphamide for remission induction in severe crescentic/necrotic LN.

Persistent/Relapsing Disease

Another way to evaluate MMF for remission induction in severe LN is to determine its success in rescuing patients who have failed induction therapy with cyclophosphamide. Table 1, rows 3 and 4, highlights two studies (22,23) that examined eight patients. MMF was unable to rescue any of three African-American children with refractory LN, but it did lead to complete or partial response in 60% of Hispanic adults over 4–16 months. A third study did not define complete or partial responses but did list serum creatinine levels before and after rescue therapy with MMF (24). These 11 class IV LN patients were European-American, African-American, and Hispanic, and 9 patients had elevated serum creatinine when MMF was started. For all 11 patients, the average initial creatinine was 1.76±0.87 mg/dl. After 3–24 months of MMF, the group’s average creatinine decreased to 1.46±0.75 mg/dl, with eight patients showing an improvement in creatinine (but not to normal levels in seven patients; one patient deteriorated). Taken together, the results from all 19 patients suggest that MMF can rescue or stabilize at least some cyclophosphamide failures, even in the face of significant impairment of kidney function. A caveat to this conclusion is the difficulty in excluding a delayed effect of cyclophosphamide in some of these patients.

Elevated Serum Creatinine at Presentation

Two approaches were used to evaluate the response to MMF or cyclophosphamide in patients with impaired kidney function at the time of treatment initiation. As shown in Table 1, rows 5–8, data on patients with elevated serum creatinine were extracted directly from publications of studies using either MMF or cyclophosphamide to treat proliferative LN (25–28) or data provided by the studies’ investigators through personal communications. Although pooling these data is not statistically valid, for the purposes of this discussion, the combined partial remission rate was around 30% for both cyclophosphamide and MMF, and complete remissions were around 40% for MMF and 50% for cyclophosphamide.
<table>
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<tr>
<th>Row</th>
<th>Measure of Severity&lt;sup&gt;a&lt;/sup&gt;</th>
<th>R/E&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Definition of Response&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Cytotoxic Treatment&lt;sup&gt;d&lt;/sup&gt;</th>
<th>N</th>
<th>PR&lt;sup&gt;e&lt;/sup&gt; (%)</th>
<th>CR&lt;sup&gt;e&lt;/sup&gt; (%)</th>
<th>Time Response Assessed (Months)</th>
<th>Reference</th>
<th>Study Type&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Histologic severity</td>
<td>CH</td>
<td>CR: SCr &lt; 1.24 mg/dl;</td>
<td>MMF: 750–1000 mg two times/d</td>
<td>26</td>
<td>19</td>
<td>54</td>
<td>12</td>
<td>20</td>
<td>Retro</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PR: Up &lt; 1 g/d</td>
<td>IVCY: 0.5–0.75 g/m²/monthly×6</td>
<td>23</td>
<td>44</td>
<td>26</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Persistent/relapsing disease</td>
<td></td>
<td>CR: SCr nl;</td>
<td>MMF: 750–1000 mg two times/d</td>
<td>9</td>
<td>22</td>
<td>44</td>
<td>6</td>
<td>21</td>
<td>RCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Up &lt; 0.4 g/d</td>
<td>IVCY: 0.5–0.75 g/m²/monthly×6</td>
<td>11</td>
<td>27</td>
<td>0</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Elevated SCR at presentation</td>
<td>AA&lt;sup&gt;h&lt;/sup&gt;</td>
<td>R: SCr &lt; 0.2 mg/dl; Up ≥ 0.5 g/d</td>
<td>MMF: 1000 mg two times/d</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3–15</td>
<td>22</td>
<td>CS</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>H</td>
<td>CR: SCr within 15% of entry;</td>
<td>MMF: 500–1000 mg two times/d</td>
<td>5</td>
<td>20</td>
<td>40</td>
<td>4–16</td>
<td>23</td>
<td>CS</td>
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<td></td>
<td></td>
<td></td>
<td>Up &lt; 300 mg/d</td>
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<tr>
<td>5</td>
<td></td>
<td>C, B, H, A</td>
<td>CR: SCr nl; Up &lt; 0.5&lt;sup&gt;i&lt;/sup&gt;</td>
<td>MMF: Up to 3000 mg/d</td>
<td>29</td>
<td>34</td>
<td>17</td>
<td>12</td>
<td>25, 26, 27 and PC&lt;sup&gt;k&lt;/sup&gt;</td>
<td>RCT</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>CH</td>
<td>CR: SCr stable or improved;</td>
<td>IVCY: 0.5–0.75 g/m²/monthly×6</td>
<td>22</td>
<td>14</td>
<td>59</td>
<td>24</td>
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<td></td>
<td></td>
<td></td>
<td>Up &lt; 1g/d</td>
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<td>7</td>
<td></td>
<td>CH</td>
<td>CR: SCr stable or improved;</td>
<td>POCY: 50–100 mg/d ×6 for 9 months</td>
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<td>21</td>
<td>57</td>
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<td></td>
<td>Up ≥ 50% and &lt; 3 g/d</td>
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<tr>
<td>8</td>
<td>proliferative LN;</td>
<td>CH</td>
<td>CR: SCr stable or improved;</td>
<td>IVCY: 0.5–1.0 g/m²/monthly×6</td>
<td>78</td>
<td>46</td>
<td>40</td>
<td>6</td>
<td>28 and PC&lt;sup&gt;k&lt;/sup&gt;</td>
<td>Retro</td>
</tr>
<tr>
<td></td>
<td>SCr ≥ 1.1.4 mg/dl</td>
<td></td>
<td>Up &lt; 1g/d</td>
<td></td>
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<td></td>
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<tr>
<td>9</td>
<td>class III/IV LN; mean</td>
<td>CH</td>
<td>CR: SCr normal;</td>
<td>MMF: 1000 mg two times/d</td>
<td>11</td>
<td>55</td>
<td>9</td>
<td>6</td>
<td>9 and PC&lt;sup&gt;i&lt;/sup&gt;</td>
<td>RCT</td>
</tr>
<tr>
<td></td>
<td>SCR = 1.52 mg/dl in MMF–treated patients and 1.46 mg/dl in PO CY–treated patients</td>
<td></td>
<td>Up &lt; 0.3g/d</td>
<td></td>
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<sup>a</sup> Measure of severity includes class IV; 50% crescents; SCr ≥ 1.24 mg/dl; class IV; 60% capillary necrosis; 20% crescents; mean SCr = 1.51 mg/dl; 100% noninflammatory necrotizing vasculopathy.

<sup>b</sup> R/E = Reference/Evaluation.

<sup>c</sup> Definition of response includes CR: SCr < 1.24 mg/dl; PR: Up < 1 g/d.

<sup>d</sup> Cytotoxic treatment includes MMF: 750–1000 mg two times/d; IVCY: 0.5–0.75 g/m²/monthly×6.

<sup>e</sup> Reference and Study Type includes Reference Study Type.

<sup>i</sup> Includes 100% noninflammatory necrotizing vasculopathy.

<sup>h</sup> Includes persistent relapsing disease.

<sup>g</sup> Includes persistent relapsing LN despite IVCY or PO CY.

<sup>l</sup> Includes persistent relapsing disease.

<sup>u</sup> Includes persistent relapsing LN despite cyclophosphamide.

<sup>k</sup> Includes persistent relapsing disease.

<sup>l</sup> Includes persistent relapsing LN despite cyclophosphamide.

<sup>o</sup> Includes persistent relapsing disease.

<sup>j</sup> Includes persistent relapsing disease.

<sup>p</sup> Includes persistent relapsing disease.

<sup>q</sup> Includes persistent relapsing disease.

<sup>r</sup> Includes persistent relapsing disease.

<sup>s</sup> Includes persistent relapsing disease.

<sup>t</sup> Includes persistent relapsing disease.

<sup>u</sup> Includes persistent relapsing disease.

<sup>v</sup> Includes persistent relapsing disease.

<sup>w</sup> Includes persistent relapsing disease.

<sup>x</sup> Includes persistent relapsing disease.

<sup>y</sup> Includes persistent relapsing disease.
<table>
<thead>
<tr>
<th>Row</th>
<th>Measure of Severity</th>
<th>R/E</th>
<th>Definition of Response</th>
<th>Cytotoxic Treatment</th>
<th>N</th>
<th>PR (%)</th>
<th>CR (%)</th>
<th>Time Response Assessed (Months)</th>
<th>Reference</th>
<th>Study Type</th>
</tr>
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<tbody>
<tr>
<td>10</td>
<td>proliferative LN; mean SCr=1.48 mg/dl in MMF-treated patients and 1.69 mg/dl in IVCY-treated patients</td>
<td>C, AA, H, A</td>
<td>CR: ↓ SCr, Up to within 10% of normal; PR: ↓ SCr, Up by 50% without a worsening &gt;10% in any single measurement</td>
<td>MMF: titrated to 3000 mg/d; IVCY: titrated to 1 g/m² monthly ×6</td>
<td>13</td>
<td>50</td>
<td>8</td>
<td>6</td>
<td>29 and PC</td>
<td>RCT</td>
</tr>
<tr>
<td>11</td>
<td>proliferative LN with creatinine clearance&lt;60 ml/min</td>
<td>A</td>
<td>CR: SCr normal; Up&lt;0.3g/d; PR: SCr stable or improved; Up ↓ 50% and &lt;3 g/d</td>
<td>MMF: 1000 mg two times/d; IVCY: 0.5–1 g/m² monthly ×6</td>
<td>8</td>
<td>33</td>
<td>0</td>
<td>6</td>
<td>15 and PC</td>
<td>RCT</td>
</tr>
<tr>
<td>12</td>
<td>proliferative LN; mean SCr=1.8 mg/dl in MMF-treated patients and 1.7 mg/dl in IVCY-treated patients</td>
<td>C, B, H, A</td>
<td>CR: SCr normal; Up&lt;0.3g/d; PR: SCr stable or improved; Up ↓ 50% and &lt;3 g/d</td>
<td>MMF: 1500 mg two times/d; IVCY: 0.5–1 g/m² monthly ×6</td>
<td>38</td>
<td>53</td>
<td>13</td>
<td>6</td>
<td>30 and PC</td>
<td>RC</td>
</tr>
</tbody>
</table>

R/E, race/ethnicity; PR, partial response; CR, complete response; SCr, serum creatinine; CH, Chinese; Up, urine protein; MMF, mycophenolate mofetil; Retro, retrospective observational; IVCY, intravenous cyclophosphamide; RCT, randomized controlled trial; AA, African-American; R, response; CS, case study or case series; LN, lupus nephritis; POCY, oral cyclophosphamide; H, Hispanic; C, Caucasian; B, black; A, Asian; Upcr, urine protein to creatinine ratio; PC, personal communication; Pros, prospective open label.

aCriteria/rationale for labeling LN as severe.
bRace/ethnicity: CH, Chinese; AA, African-American; H, Hispanic; C, Caucasian; B, black; A, Asian.
cCriteria for CR, PR, and R. The proteinuria and renal functional criteria for response are shown. The parent studies often included urine sediment and other clinical parameters in their definitions of response. These criteria are not shown for data extracted directly from publications or when summary data but not individual data were provided (rows 1–8 and 10). When raw data were provided for each individual patient (rows 9, 11, and 12), response rates were calculated based only on the proteinuria and renal functional criteria shown.

dOnly MMF and cyclophosphamide are listed. For IVCY, X6 indicates six monthly doses. All induction regimens also included oral corticosteroids and in some cases, initial high-dose intravenous methylprednisolone. After the induction period, most of these trials used MMF or azathioprine for maintenance therapy.
eStudy type is presented to assess the strength of the data. In descending order of quality/clinical strength: RCT (could be open label), Pros, Retro, and CS. In addition to study type, the number of patients should be considered when evaluating data strength.
fSerum creatinine.
gUrine protein.
hPediatric cohort.
iUrine protein to creatinine ratio.

kC.C. Mok, personal communication, 2012.
mE.M. Ginzler, personal communication, 2012.
oN. Solomons, personal communication, 2012.
Alternatively and perhaps more relevantly, similar data on patients with impaired renal function at the time of presentation were extracted from publications or original datasets of studies that compared MMF to cyclophosphamide for treatment of proliferative LN (Table 1, rows 9–12) (9,10,15,29). All of these studies had a few patients with an increased serum creatinine in each treatment group, although most targeted less severe LN and excluded patients with markedly elevated serum creatinine. After 6 months of treatment, the average partial (48% MMF; 51% cyclophosphamide) and complete (9% MMF; 6% cyclophosphamide) remission rates were comparable for both drugs in 139 patients. The definitions of complete and partial remissions were also comparable, and in some cases, they were modified by us from the original studies to be comparable and thus, facilitate comparisons for this discussion (Table 1, footnote c).

The original datasets were also examined to compare the response rates of patients with impaired or normal presenting serum creatinine values to MMF or cyclophosphamide (Table 2). Although these results are highly variable and the total number of patients is small, there is some suggestion that complete remissions may be less frequent in patients who present with an elevated serum creatinine, regardless of induction therapy. This suggestion raises the possibility that stratifying patients by kidney function at presentation could determine a cutoff (above which the usual therapies are less effective), and add-on therapy with a novel agent may prove useful, especially if chronicity parameters are not high.

Relapse data were available for the study represented in Table 1, row 9. Approximately 50% of the patients relapsed, but the average time to relapse in the MMF group was significantly shorter than the cyclophosphamide group (35±19 versus 62±26.7 months, P=0.01). It should be noted that, in this study, azathioprine was used for maintenance in both groups, and it may have affected relapse rates (30).

**Long-Term Kidney Function**

The ultimate goal of treating LN is not only to achieve a remission after induction therapy but also, long-term preservation of kidney function to avoid the need for renal replacement therapy. Additionally, it is important to prevent CKD and its risks of cardiovascular morbidity. This goal likely means minimizing additional renal injury by reducing flares of LN. Whether MMF is comparable with cyclophosphamide in long-term preservation of kidney function remains an unresolved question.

A retrospective analysis of Korean LN patients treated with either intravenous cyclophosphamide (n=51) or MMF (n=20) examined the endpoints of death or ESRD, and it found that, although there were no differences in the rate of remission between induction drugs, mortality and ESRD were significantly higher in the MMF group (31). This cohort consisted mainly of patients with proliferative LN, with more class IV patients in the cyclophosphamide group. Patients treated with MMF had average baseline serum creatinine and urine protein to creatinine ratios of 1.6±21. mg/dl and 1.8±1.5, respectively, and those patients treated with cyclophosphamide had baseline levels of 1.3±0.7 mg/dl and 4.3±3.1. Baseline serum creatinine was not statistically different between groups. Complete and partial remissions were comparable in both groups: 39% complete and 18% partial remissions over an average of 33 months in cyclophosphamide-treated patients compared with 47% complete and 5% partial remissions in the MMF-treated patients over 42 months. Relapse rate was 4% in the cyclophosphamide group and 15% in the MMF group. The relative risk for the composite endpoint of death or ESRD was 0.25 for cyclophosphamide versus MMF (P=0.04), and the probability of ESRD-free survival was 100% for cyclophosphamide treatment compared with 81% for MMF treatment over 5 years. The only prognostic risk factor for ESRD by multivariate analysis was the level of serum creatinine at diagnosis.

Long-term results suggesting better outcomes with cyclophosphamide than MMF have also been seen in other studies. In a cohort of Chinese patients with class IV LN, MMF and oral cyclophosphamide induced similar rates of complete and partial remissions (>70%), generally within 4–5 months, and this finding was not dependent on baseline serum creatinine (32). Over a median follow-up of 63 months, there were no significant differences in proteinuria, serum creatinine, or ESRD between MMF and cyclophosphamide induction. However, there was a trend to higher residual proteinuria in the MMF group, possibly explained by more (although not significantly more) baseline proteinuria in the MMF-treated patients. Furthermore, the hazard ratio for relapse was 1.5 in the MMF group compared with the cyclophosphamide group, but this ratio did not reach statistical significance.

Finally, the Aspreva Lupus Management Study trial comparing MMF and cyclophosphamide for induction therapy in LN (10) was continued for 3 years in patients who had responded to either MMF or intravenous cyclophosphamide to compare MMF and azathioprine as maintenance drugs for LN (30). This study showed superiority of MMF for LN maintenance therapy in a racially and ethnically diverse population. However, the study also showed a trend to more treatment failures in the patients who received MMF as opposed to cyclophosphamide for induction therapy (30). Treatment failure was defined as death, ESRD, sustained doubling of serum creatinine, LN flare, or need for rescue medications. Patients who were induced with intravenous cyclophosphamide followed by MMF had a 4.7% failure rate per 100 person-years compared with a 10.1% failure rate per 100 person-years in patients induced with MMF and maintained with MMF. Similarly, cyclophosphamide-induced patients who were maintained with azathioprine had a 14.5% failure rate per 100 person-years compared with a 20.1% failure rate per 100 person-years for those patients induced with MMF. These results did not reach statistical significance, but the study was not designed to examine this question.

Although these results must be interpreted cautiously, because the parent studies were retrospective, not adequately powered to assess long-term renal function outcomes, or restricted to very homogenous ethnic groups, they do raise a concern that the type of induction therapy may influence long-term outcome of the kidney, despite equivalent early, short-term remissions. Except for the Korean cohort described above, which had fairly severe disease (31), the other studies had a mix of severe and (mostly) less severe...
This finding may account for some of these observations being trends and not significant differences. It is conceivable that, for patients with severe LN, the choice of induction therapy is more critical for long-term outcomes than less severe LN.

Conclusions

The bulk of the existing data suggests that, in the short term, MMF and intravenous or oral cyclophosphamide are equally effective induction therapies for severe LN, with severity defined histologically or as impaired kidney function. However, these definitions of severity are imperfect, and a more explicit definition, including levels of kidney function and histologic injury, may reveal short-term differences. Long-term kidney outcome data, while limited, suggest that cyclophosphamide may preserve renal function better than MMF. On this basis, we suggest that MMF cannot yet be considered the drug of choice for induction therapy of severe LN. Studies to examine this question are warranted, and in fact, this question should be considered for all novel induction therapies of proliferative LN that are, or will be, in clinical trial.

Disclosures

B.H.R. is a consultant for Genetech, Teva, Questcor, centacor, and Biogen idec and a member of data safety and monitoring boards for Lilly and Celtic. P.B. and R.M. are employees of Genetech. N.S. is an employee of Vifor Pharamceuticals.

References

7. Houssiau FA, Vasconcelos C, D’Cruz D, Sebastiani GD, Garrido Ed ER, Danieli MG, Abramovicz D, Blockmans D, Mathieu A, Table 2. Comparison of response rates for induction therapy stratified by initial serum creatinine

<table>
<thead>
<tr>
<th>Reference</th>
<th>Corresponding Row in Table 1</th>
<th>MMF or CYC for Induction</th>
<th>SCr&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CR&lt;sup&gt;b&lt;/sup&gt; (%)</th>
<th>CR or PR&lt;sup&gt;c&lt;/sup&gt; (%)</th>
<th>Time Response Assessed (Months)</th>
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<tr>
<td>25, 26, and PC&lt;sup&gt;d&lt;/sup&gt;</td>
<td>5</td>
<td>MMF</td>
<td>Normal</td>
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<td></td>
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<td>Increased (1.69 mg/dl)</td>
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<td>76</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Normal (&lt;1.02 mg/dl)</td>
<td>57</td>
<td>86</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Increased (&gt;1.02 mg/dl)</td>
<td>33</td>
<td>83</td>
<td>6</td>
</tr>
<tr>
<td>9 and PC&lt;sup&gt;f&lt;/sup&gt;</td>
<td>9</td>
<td>MMF</td>
<td>Normal (0.81 mg/dl)</td>
<td>9</td>
<td>64</td>
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</tr>
<tr>
<td></td>
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<td></td>
<td>Increased (1.52 mg/dl)</td>
<td>67</td>
<td>86</td>
<td>6</td>
</tr>
<tr>
<td>28 and PC&lt;sup&gt;e&lt;/sup&gt;</td>
<td>7</td>
<td>CYC</td>
<td>Normal (&lt;1.2 mg/dl)</td>
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<td>86</td>
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<td></td>
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<td>57</td>
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<tr>
<td>9 and PC&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>CYC</td>
<td>Normal (0.79 mg/dl)</td>
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<td>60</td>
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<td>Increased (1.46 mg/dl)</td>
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<td>80</td>
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MMF, mycophenolate mofetil; CYC, cyclophosphamide; SCr, serum creatinine; CR, complete response; PR, partial response; PC, personal communication.
<sup>a</sup>Mean SCr for the group or SCr level designated as normal or increased.
<sup>b</sup>Complete renal response.
<sup>c</sup>Partial renal response.
<sup>d</sup>P. Brunetta and R. Maciuca, personal communication, 2012.
<sup>e</sup>C.C. Mok, personal communication, 2012.
<sup>f</sup>T.M. Chan, personal communication, 2012.