Overview of Current and Alternative Therapies for Idiopathic Membranous Nephropathy

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Membranous nephropathy is one of the leading causes of nephrotic syndrome in adults, which is characterized by edema, hypoalbuminemia, hyperlipidemia, lipiduria, and proteinuria. Determination of idiopathic membranous nephropathy (IMN) disease progression risk is important for guiding initial therapy, with immunosuppressive therapy being reserved for high-risk patients. Because IMN may spontaneously remit in approximately 30% of patients, it is important to carefully select which patients should begin immunosuppressive therapy so as to maximize clinical benefit while limiting toxicity. An observation period of at least 6 months with conservative management that includes the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is recommended. Initial treatment in high-risk IMN is a 6-month course of alternating steroids and alkylating agents. Calcineurin inhibitors (CNIs) represent an alternative first-line therapeutic option for high-risk patients who refuse treatment with steroid or alkylating agent therapy or for whom these treatments are contraindicated. Additional options are essential for patients with IMN who fail to adequately respond to initial therapies or who cannot use recommended therapies due to contraindications or intolerance, risks associated with repetitive dosing with alkylating agents, or potential exacerbation of impaired renal function with CNIs. While evidence for the use of alternative therapies in IMN is modest at best, our review summarizes the available literature for rituximab, mycophenolate mofetil, adrenocorticotropic hormone, intravenous immunoglobulin, and azathioprine. Rituximab has generally demonstrated beneficial outcomes with limited toxicity. Evidence supports a role for mycophenolate mofetil, although the evidence is of low quality and limited duration. Results from ongoing studies are required before adrenocorticotropic hormone can be recommended as therapy for treatment-resistant patients. Intravenous immunoglobulin and azathioprine are unlikely to have a role in IMN. With the advent of new tools and biomarkers measuring disease activity combined with new data regarding possible treatment options, the management and prognosis of IMN are likely to improve.

Key Words idiopathic membranous nephropathy, membranous, rituximab, mycophenolate mofetil, adrenocorticotropic hormone, intravenous immunoglobulin, azathioprine.


In adults, membranous nephropathy is one of the leading causes of nephrotic syndrome, which is characterized by edema, hypoalbuminemia, hyperlipidemia, lipiduria, and proteinuria. To aid in prognosis and to determine management, membranous nephropathy is distinguished as either idiopathic or secondary.

In a groundbreaking study published in 2009, the M-type phospholipase A2 receptor (M-type PLA2R) was identified in the serum of 70% of patients with idiopathic membranous nephropathy (IMN), while none was identified in patients with secondary membranous nephropathy (e.g.,
that due to lupus membranous nephropathy or hepatitis B–associated membranous nephropathy) or normal controls. While not yet fully elucidated, knowledge regarding the pathogenesis of IMN has progressed in recent years. Deposits found in the subepithelial layer of the glomerular basement membrane were initially thought to be due to antibody–antigen complexes formed in circulation. There is now evidence suggesting that these deposits are formed in situ by antibodies binding to antigens on specialized glomerular epithelial cells called podocytes. While antigens have been identified in these deposits, only the M-type PLA2R has been correlated with disease severity and degree of proteinuria.

After a diagnosis of IMN is confirmed by renal biopsy, patients should undergo a 6-month observation period during which they should receive supportive therapy, including angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), or both. Use of immunosuppressive therapy should be restricted to high-risk patients with persistent proteinuria or evidence of disease progression so as not to unnecessarily expose lower-risk patients to the potential toxicities of immunosuppressive agents. A careful selection of eligible patients is important to maximize clinical benefit while limiting toxicity. Such a restrictive treatment approach is supported by a recently published cohort study of 254 patients, of whom 130 received supportive therapy only and 124 were treated with immunosuppression due to persistent or worsening disease. Renal survival over 10 years among all patients was 86%, and 83% of patients achieved remission. The overall evidence base for therapeutic agent selection in IMN is limited.

Overview of Current Standard Immunosuppressive Therapies for IMN

Immunosuppressant medications are an important option for the 70% of patients with IMN that does not spontaneously remit with supportive therapy. Recommendations made within the published treatment guidelines from the Kidney Disease: Improving Global Outcomes (KDIGO) organization for the initial treatment of IMN and the treatment of patients who are at high-risk for disease progression, fail to respond to, or who relapse following successful initial treatment are summarized in Figure 1. The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (KDOQI) broadly supported the KDIGO recommendations with regard to the immunosuppressive treatment of IMN, except where noted here later. The following review discusses the use of immunosuppressant therapy in these high-risk IMN patients.

Alkylating Agents

Because steroid monotherapy is ineffective in IMN, the initial treatment for high-risk patients is a 6-month course of alternating steroids and alkylating agents. Several randomized controlled trials (RCTs) have demonstrated superiority of alternating steroids and cyclophosphamide compared with supportive treatment, with statistical equivalence of cyclophosphamide and chlorambucil on the end points of complete remission (CR) and partial remission (PR) of proteinuria and change in renal function. Cyclophosphamide is a broad immunosuppressant, inhibiting T- and B-cell function and reducing expression of proinflammatory cytokines, and may also increase Th2-type responses and stimulate production of anti-inflammatory cytokines such as interleukin-10. The recommended dosing regimen for steroids plus alkylating agents is 1 month of steroids (methylprednisolone 1 g/day intravenously for three doses and then 0.5 mg/kg/day orally for 27 days) followed by 1 month of oral alkylating agents (cyclophosphamide 2 mg/kg/day or chlorambucil 0.15 to 0.2 mg/kg/day for 30 days). This should then be repeated twice for a total treatment period of 6 months. Cyclophosphamide may be preferable to chlorambucil in patients with renal insufficiency due to a higher remission rate, more durable improvement in renal function, better tolerability, and a reduced discontinuation rate. For patients with serum creatinine greater than 2 mg/dl, cyclophosphamide dosage should not exceed 1.5 mg/kg/day.

Though there are potentially serious side effects associated with the use of alkylating agents, clinical trials have largely reported this treatment regimen to be well tolerated. Side effects reported in clinical trials have included increased risk of serious opportunistic infections, thrombotic episodes, nausea and vomiting, gonadal damage, neoplasia, leukopenia, and bone marrow hypoplasia. A recently published cohort study, however, reported a threefold increase in cancer risk associated with cyclophosphamide therapy. Additional concerns associated with corticosteroid use include infection, glucose intolerance, Cushingoid features, and osteoporosis.
Calcineurin Inhibitors

Although the evidence to support the use of calcineurin inhibitors (CNIs) is of low to moderate quality, they are an alternative first-line therapeutic option for high-risk patients who refuse treatment or have contraindications to steroid/alkylating agent therapy. Multiple individual studies have reported a benefit of cyclosporine in IMN; however, a recent meta-analysis of six studies (N=202) failed to demonstrate statistical superiority of cyclosporine with or without concomitant steroids compared with no treatment, ACEIs, or steroids in combination with alkylating agents/azathioprine. This study’s primary end point was all-cause mortality and/or risk of end-stage kidney disease (ESKD). The secondary end point was CR or PR at the end of follow-up. The authors acknowledged, however, that the follow-up time in the analyzed studies might have been too short to adequately assess some of these end points.

CNIs block T-cell–mediated responses through inhibition of calcineurin-dependent nuclear factor of activated T cells (NFAT) signaling. CNIs also have hemodynamic effects and have been shown to be cytoprotective in podocytes through inhibition of synaptopodin degradation and stabilization of the podocyte actin cytoskeleton. While studies have demonstrated efficacy of cyclosporine and tacrolimus administered alone or with steroids, safety concerns include a potential risk of nephrotoxicity and high relapse rates following treatment discontinuation (15% to 80% within several months following treatment discontinuation).

Because of the increased frequency of relapse, treatment is recommended for at least 6 months with CNIs. Cyclosporine should be dosed at 3.5 to 5 mg/kg/day orally in two divided doses along with a single daily dose of prednisone (0.15 mg/kg/day), whereas tacrolimus should be dosed at 0.05 to 0.075 mg/kg/day orally in two divided doses without prednisone. There is uncertainty regarding the need for concomitant prednisone, as early studies of cyclosporine used the combination, while later ones with tacrolimus did not. It is recommended that both agents be

Figure 1. Guideline-based recommendations for immunosuppressive therapy in patients with IMN.
initiated at the lower end of the dosing range with the dose increased as necessary to minimize the risk of acute nephrotoxicity. Serum concentrations of calcineurin inhibitor and creatinine should be checked regularly, and patients should be monitored for evidence of nephrotoxicity.5, 6

In the absence of at least a PR by 6 months, KDIGO recommends discontinuation of CNI therapy.5 KDOQI recommends considering discontinuation only in the absence of substantial (30% to 50%) reduction of proteinuria after 4 to 6 months of treatment with CNI trough levels within the target range (125 to 175 ng/ml for cyclosporine5 and of 8 to 10 ng/ml or less for tacrolimus).6 In patients who do achieve at least a PR, the dose of CNI should be reduced every 4 to 8 weeks to 50% of the starting dose (as long as remission is maintained and treatment is tolerated) and continued for at least 12 months.5, 6 Prolonged maintenance treatment with low-dose cyclosporine (1.5 mg/kg/day) may be considered, especially for patients with a high risk of relapse and who show no evidence of cyclosporine-induced nephrotoxicity, as long-term therapy may more effectively maintain remission.4

Importantly, both cyclosporine and tacrolimus carry a U.S. Food and Drug Administration (FDA) black box warning indicating that they may increase the susceptibility for infection and the development of neoplasia. In clinical trials of patients with IMN, treatment with CNI was well tolerated with side effects that included hypertension, glucose intolerance, and infection.16–19 In two retrospective studies, however, 19% and 70% of patients treated with cyclosporine and prednisone developed complications that included hirsutism, diabetes mellitus, hypertension, renal impairment/nephrotoxicity, hyperlipidemia, gingival hyperplasia, and interaction between cyclosporine and statins requiring temporary hemodialysis.12, 20

Nonresponders to Initial Therapy

While a majority of patients tend to respond to initial therapy with steroids/alkylating agents or CNI s, 10% to 40% of patients may fail to respond.7–9, 16–18 Treatment with the alternative initial regimen is recommended as second-line therapy (Figure 1), using the same dosing regimens discussed here earlier.5 Failure to respond to one regimen does not predict failure to respond to another, but risk of renal injury is a concern as these agents share similar toxicity profiles.5, 6 In addition, as treatment-resistant patients tend to experience disease progression, dose adjustments or the use of alternative agents may be necessary because renal impairment can be worsened by CNIs and alkylating agents.21

Relapse Management

Relapse following successful initial therapy is common, with up to 30% of patients relapsing within 5 years following treatment with alkylating agents; 15% to 80% of patients relapse within 1 year following treatment with CNIs.5, 9, 16–18 Patients who relapse should be treated with the same initial regimen, unless proteinuria is subnephrotic, in which case conservative management is advised as the relapse may be transient and may spontaneously resolve.5 Therapy with steroids and alkylating agents should be repeated only once due to an increased risk of neoplasia induction, opportunistic infections, and gonadal damage.5

Alternative Agents

Literature Search

There are significant numbers of patients for whom conventional therapies are insufficient due to inadequate responses, frequent relapses, contraindications, or intolerance. Alternative options are needed to address this unmet need. At present, the best-studied alternative agents are rituximab, mycophenolate mofetil (MMF), and adrenocorticotropic hormone (ACTH). There are also trials of intravenous immunoglobulin (IVIG) and azathioprine. We reviewed the available literature for these agents to delineate their potential role in the treatment paradigm for patients with IMN requiring alternatives to conventional therapies.

We performed a MEDLINE search from inception to April 30, 2014, for English-language studies reporting treatment of IMN in patients older than 18 years with rituximab, MMF, ACTH, IVIG, and azathioprine using the search term “membranous” with each of the aforementioned drugs. Search results were also compared to the references of all identified publications. If prospective or retrospective studies and case series existed for a particular drug, case reports were excluded from our review. We defined CR as most recent proteinuria of 0.3 g/24 hours or less with eGFR of 60 ml/minute or greater and PR as 50% or greater reduction in proteinuria with proteinuria greater than 0.3 and less
than 3.5 g/24 hours at last follow-up. When proteinuria data for individual patients were not available, we noted results based on the author’s definitions of remission.

Rituximab

Rituximab is a monoclonal antibody against the cell surface CD20 antigen present on immature and mature B cells (but not on plasma cells) that depletes the B-cell population through the induction of complement-dependent and -independent apoptosis. Injurious autoantibodies deposited in the glomerular subepithelial space in patients with IMN are B-cell products, thus making rituximab a rational and specific treatment option. Further, depletion of specific B-cell subsets may produce additional immunomodulatory effects through alterations in the interaction between B cells and other cells within the adaptive and innate immune systems. Rituximab-induced B-cell depletion is complete and usually persists for 6 to 9 months, though this may vary widely between patients.

The initial trials of rituximab treatment in IMN, which were not RCTs, used a dosing strategy of 375 mg/m² once weekly for four doses, similar to the dosage used for the treatment of lymphoma. In three observational studies of patients with persistent proteinuria despite full-dose ACEI and optimized conservative therapy, this four-dose protocol led to CR plus PR in 52% to 75% of patients at 1 year with a significant reduction in proteinuria (Table 1). After recognizing that complete depletion of B cells is seen after the first rituximab dose in most patients, the research group compared the standard four-dose regimen of rituximab to an adjusted B-cell–driven protocol of rituximab given once, followed by a second rituximab dose if more than five circulating B cells/mm³ were detected the morning after the first dose. Their results demonstrated statistically equivalent efficacy of the four-dose and B-cell–driven protocols, and the latter approach became their standard. With fewer doses per patient in those receiving the B-cell–driven protocol, the authors estimated a potential cost savings of $11,000 per treatment course and a hospital stay that was almost 6 days shorter than that for those receiving the four-dose protocol.

Using the rituximab dosing for rheumatoid arthritis (1 g on day 1 and day 15), another study also showed favorable results in 15 severely nephrotic patients with IMN, seven of who had failed prior immunosuppressive therapy. At 6 months, 27% of patients achieved PR and were not retreated. Two of these patients subsequently achieved CR by 12 months. Ten patients received a second course of rituximab, of whom two achieved PR 6 months later. Mean reduction in proteinuria in this study closely resembled outcomes described here earlier with the standard four-dose regimen.

Improvement of proteinuria tends to be gradual; although remission has been reported as early as 1 month after rituximab administration, improvement may continue up to 2 years. It is unclear why in some patients the reduction of proteinuria so closely mirrors the depletion of the B-cell population and in others with similar B-cell depletion, reduction is much more protracted. This does suggest, however, that there should be a waiting period after administration before a patient is considered a treatment failure. In addition, a second course of rituximab may lead to improved response in patients with an absence of early response. Such a strategy was shown to lead to remission in six of eight patients with insufficient initial response (less than 50% reduction in proteinuria) by 6 months. Additional insight regarding the efficacy of a second treatment course will be obtained by the ongoing MENTOR trial (NCT01180036), comparing rituximab and cyclosporine in patients with IMN. Patients randomized to receive rituximab will receive 1 g intravenously on days 1 and 15 and patients failing to achieve CR by month 6, but who achieve a minimum of 25% reduction in proteinuria from baseline, will receive a second course of rituximab.

The effect of rituximab treatment appears to be sustained, as low incidences of relapse have been reported. A 2010 publication reported that of 18 patients followed for 2 years, only 1 relapsed (5.6%). A retrospective study of 100 patients reported that 18 (28%) of 65 patients who achieved CR or PR relapsed at 7 to 116 months posttreatment (median 42 months). The reason for these low relapse rates despite recovery of B-cell populations is unknown but supports the notion that the reconstituted B-cell population may be more self-tolerant. For those patients who do relapse, a repeated course of rituximab may be effective as witnessed by the fact that 4 and 7 of the aforementioned 18 patients achieved CR or PR, respectively, following a second course.
Table 1. Studies of Alternative Therapies for Idiopathic Membranous Nephropathy

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Therapy and Duration</th>
<th>Concomitant Immunosuppression</th>
<th>Patients (N)</th>
<th>Prior Immunosuppressive Therapy</th>
<th>Outcomes; Number of patients with CR (%)/PR (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Mean reduction in proteinuria</th>
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<tr>
<td>Ruggenenti et al. 24</td>
<td>Rituximab 375 mg/m&lt;sup&gt;2&lt;/sup&gt; once weekly for four doses</td>
<td>No</td>
<td>8 adult patients with IMN and persistent nephrotic syndrome and CrCl &gt; 20 ml/min per 1.73 m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>No previous remissions or treatment with steroids or immuno-suppressive drugs within 1 year</td>
<td>CR 1 (12.5%)/PR 4 (50%) at 5 mo&lt;sup&gt;23&lt;/sup&gt;</td>
<td>57%; p&lt;0.0001 at 5 mo&lt;sup&gt;23&lt;/sup&gt;, 66%; p&lt;0.005 at 12 mo&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ruggenenti et al. 25</td>
<td>Rituximab 375 mg/m&lt;sup&gt;2&lt;/sup&gt; once weekly for four doses</td>
<td>No</td>
<td>14 patients (retrospective) + 9 patients (prospective) with IMN, persistent nephrotic syndrome and CrCl &gt; 20 ml/min per 1.73 m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>No previous remissions or treatment with steroids or immuno-suppressive drugs within 1 year</td>
<td>CR 6 (26%)/PR 6 (20%) at 12 mo&lt;sup&gt;26&lt;/sup&gt;</td>
<td>71% at 12 mo&lt;sup&gt;26&lt;/sup&gt;</td>
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<tr>
<td>Cravedi et al. 26</td>
<td>Group A: 375 mg/m&lt;sup&gt;2&lt;/sup&gt; once weekly for four doses; Group B: Rituximab 375 mg/m&lt;sup&gt;2&lt;/sup&gt; once then 2nd rituximab dose administered if &gt; 5 circulating B cells per mm&lt;sup&gt;3&lt;/sup&gt; were detected the morning after first dose</td>
<td>No</td>
<td>24 patients with IMN and persistent nephrotic syndrome matched by age (± 5 yrs), gender, and proteinuria (± 1 g/24 hrs)</td>
<td>No prior remissions or treatment with steroids or immuno-suppressive drugs during the past year</td>
<td>Group A CR 2 (8%)/PR 14 (58%)&lt;sup&gt;3&lt;/sup&gt; at 1 yr&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Group A: 58% vs Group B: 60%; p=0.10</td>
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<tr>
<td>Ruggenenti et al. 27</td>
<td>April 2001–October 2005; Rituximab 375 mg/m&lt;sup&gt;2&lt;/sup&gt; once weekly for four doses; after Oct 2005: Rituximab 375 mg/m&lt;sup&gt;2&lt;/sup&gt; once and 2nd rituximab infusion administered if &gt; 5 circulating B cells per mm&lt;sup&gt;3&lt;/sup&gt; were detected the morning after first dose</td>
<td>No</td>
<td>100 patients with IMN and persistent nephrotic syndrome, and CrCl &gt; 20 ml/min per 1.73 m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>32 patients previously treated with steroids alone or in combination with alkylating agents, calcineurin inhibitors, or other immuno-suppressants</td>
<td>CR 27 (27%)/PR 38 (38%) at 29 mo follow up&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Proteinuria significantly (p&lt;0.001) progressively decreased by month 1 after rituximab, and up to last available follow-up in study group as a whole</td>
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<sup>a</sup>Proteinuria significantly (p<0.001) progressively decreased by month 1 after rituximab, and up to last available follow-up in study group as a whole.
<table>
<thead>
<tr>
<th>Study Design</th>
<th>Therapy Dose and Duration</th>
<th>Concomitant Immunosuppression</th>
<th>Prior Immunosuppressive Therapy</th>
<th>Outcomes; Number of patients with CR (%)/PR (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Mean reduction in proteinuria</th>
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<tbody>
<tr>
<td>Cravegl&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Matched-cohort study Group A: 2nd line rituximab Group B: 1st line rituximab April 2001–October 2005: Rituximab 375 mg/m² once weekly for four doses; after Oct 2005: Rituximab 375 mg/m² once and 2nd rituximab infusion administered if &gt; 5 circulating B cells per mm&lt;sup&gt;3&lt;/sup&gt; were detected the morning after first dose</td>
<td>No</td>
<td>Group A: Steroids alone (n=2); cyclosporine ± steroids (n=3); alkylating agents with steroids (n=6)</td>
<td>Group A: CR 3 (27%); PR 5 (45%); at 2 yrs Group B: CR 2 (18%); PR 5 (49%) at 2 yrs</td>
<td>Group A: 50.5 ± 23.1%, p&lt;0.01 at 1 yr and 60.9 ± 17.4%, p&lt;0.01 at 2 yrs</td>
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<tr>
<td>Fervenza&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Open-label, nonrandomized, pilot trial 2 infusions of rituximab 1000 mg on day 1 and day 15. At 6 mo, second course of rituximab given if proteinuria &gt; 3 g/24 hrs and CD19+ B cell count &gt; 15 cells/μl</td>
<td>No</td>
<td>No</td>
<td>CR 0 (0%); PR 4 (27%); at 6 mo&lt;sup&gt;d&lt;/sup&gt;</td>
<td>48%; p=0.0003 at 12 mo</td>
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<tr>
<td>Fervenza&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Prospective, open label Rituximab 375 mg/m² once weekly for four doses; repeated at 6 mo</td>
<td>No</td>
<td>11 patients previously failed on steroids alone or in combination with alkylating agents, calcineurin inhibitors, or other immunosuppressants</td>
<td>CR 0 (0%); PR 8 (40%); at 6 mo&lt;sup&gt;d&lt;/sup&gt;</td>
<td>86% at 2 yrs</td>
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<tr>
<td>Segarra&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Prospective pilot study Rituximab 375 mg/m² once weekly for four doses; 2nd course of rituximab 650 mg/m² once, dosed to achieve depletion of CD19+ cells</td>
<td>No</td>
<td>Alkylating agents and steroids before CNI (cyclosporine or tacrolimus) and GFR &gt; 60 ml/min in PR</td>
<td>At 6 mo, CNI, MMF, and steroids in all patients withdrawn without relapse. At 12 mo 46% (44%) remained in remission.&lt;sup&gt;e&lt;/sup&gt; 3 patients relapsed at 19, 24, and 28 mo</td>
<td>At 6 mo, CNI, MMF, and steroids in all patients withdrawn without relapse. At 12 mo 46% (44%) remained in remission.&lt;sup&gt;e&lt;/sup&gt; 3 patients relapsed at 19, 24, and 28 mo</td>
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<td>Study Design</td>
<td>Therapy Dose and Duration</td>
<td>Concomitant Immunosuppression</td>
<td>Patients (N)</td>
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<td>Outcomes: Number of patients with CR (%)/PR (%)</td>
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<tr>
<td>MMF Studies Chan et al.33</td>
<td>Prospective, randomized, open-label, multicenter Group A: MMF 1 g BID + prednisolone 10 mg/day for 6 mo Group B: modified Ponticelli regimen for 6 mo</td>
<td>Yes</td>
<td>Group A: 11 patients Group B: 9 patients Patients with biopsy proven IMN and proteinuria ≥ 3 g/24 hrs</td>
<td>No cytotoxic or cyclosporine treatment within the previous 12 mo, or prednisolone at ≥ 20 mg/day for 4 wks or more within the past 6 mo</td>
<td>Group A: CR 5 (27%) PR 4 (36%) at 15 mo^2 Group B: CR 3 (33%) PR 3 (33%) at 15 mo^2</td>
</tr>
<tr>
<td>Senthil Nayagam et al.34</td>
<td>Randomized, open-label, pilot study Group A: MMF 1 g BID for 6 mo with prednisolone 0.5 mg/kg/day for 8–12 wks Group B: steroids + cyclophosphamide for 6 mo</td>
<td>Yes</td>
<td>Group A: 11 patients Group B: 10 patients Patients with biopsy-proven IMN, urine-protein-to-creatinine ratio &gt; 3.5, or &gt; 2.5 along with serum albumin &lt; 2.2 g/dl, edema and hyperlipidemia, and eGFR of &gt; 60 ml/min</td>
<td>No</td>
<td>Group A: CR 5 (45.5%) PR 2 (18.2%) at 6 mo^2 Group B: CR 3 (30%) PR 5 (50%) at 6 mo^2</td>
</tr>
<tr>
<td>Branten et al.35</td>
<td>Clinical trial, using historic controls MMF group: 1 g BID + steroids for 12 mo^5 Control: steroids + cyclophosphamide PO 1.5 mg/kg/day for 12 mo^6</td>
<td>Yes</td>
<td>MMF: 32 patients Patients with biopsy proven IMN and CrCl ≤ 70 ml/min per 1.73 m^2, proteinuria &gt; 2.0 g/10 mmol creatinine^8</td>
<td>MMF: Prednisone alone (n=3) prednisone plus cytotoxic (n=6) Cyclophosphamide group: Prednisone alone (n=5), prednisone plus cytotoxic (n=6)</td>
<td>MMF: CR 0 (0%) PR 21 (66%) at 12 mo^1 Control: CR 0 (0%) PR 27 (84%) at 12 mo^1</td>
</tr>
<tr>
<td>Dullos et al.36</td>
<td>Prospective, randomized MMF group: 1 g BID + conservative therapy^9 for 12 mo Control: conservative therapy^10 for 12 mo</td>
<td>No</td>
<td>MMF: 19 Patients with biopsy proven IMN and proteinuria ≥ 3 g/24 hrs, albumin &lt; 3 g/dl, Scr &lt; 2.26 mg/dl</td>
<td>No</td>
<td>MMF: CR 1 (5%) PR 6 (32%) at 12 mo^1 Control: CR 2 (12%) PR 5 (29%) at 12 mo^1</td>
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IDIOPTPATHIC MEMBRANOUS NEPHROPATHY THERAPIES Tran et al.
Table 1. (continued)

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Therapy Dose and Duration</th>
<th>Concomitant Immunosuppression</th>
<th>Patients (N)</th>
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<th>Outcomes; Number of patients with CR (%)/PR (%)</th>
<th>Mean reduction in proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller et al.37</td>
<td>Prospective case series</td>
<td>MMF 0.5–2 g/day for approximately 8 mo</td>
<td>Yes</td>
<td>16 patients with persistent nephrotic range proteinuria 3 patients received concomitant steroids</td>
<td>Steroid-resistant (n=15); prior cytotoxic agents (n=6) prior cyclosporine therapy (n=3) Steroid-dependent (n=11), cyclosporine-dependent (4)</td>
<td>CR 0 (0%); PR 2 (13%) at 4 mo&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Choi et al.38</td>
<td>Retrospective</td>
<td>MMF 1 g BID + variable doses of steroids (3 patients received MMF monotherapy)</td>
<td>Yes</td>
<td>17 patients with biopsy proven IMN with nephrotic syndrome and renal insufficiency 11 patients received concomitant steroids, 4 patients received other concomitant immunosuppressants</td>
<td>CR 2 (13.3%); PR 8 (53.3%) at varying follow up times&lt;sup&gt;9&lt;/sup&gt;</td>
<td>61% (p=0.001)</td>
</tr>
<tr>
<td>ACTH Studies Ponticelli et al.43</td>
<td>Randomized, controlled trial</td>
<td>Group A: methylprednisolone + cytotoxic agent for 6 mo&lt;sup&gt;9&lt;/sup&gt; Group B: Synthetic ACTH 1 mg twice weekly for 12 mo</td>
<td>Yes</td>
<td>Group A: 16 patients Group B: 16 patients Patients had biopsy-proven IMN, proteinuria &gt; 3.5 g/day, albumin &lt; 2.5 g/dl, and Scr &lt; 1.9 mg/dl</td>
<td>No</td>
<td>CR 0 (0%), p=0.004 Group B: 59%, p=0.049</td>
</tr>
<tr>
<td>Bomback et al.44</td>
<td>Retrospective case series in nonresearch setting (i.e., by prescription)</td>
<td>ACTH gel mostly 80 IU twice weekly for 5–12 mo</td>
<td>No</td>
<td>11 patients with IMN and nephrotic syndrome</td>
<td>CR 3 (27%); PR 6 (55%) at varying follow up times&lt;sup&gt;9&lt;/sup&gt;</td>
<td>58%</td>
</tr>
<tr>
<td>Bomback et al.45</td>
<td>Prospective, open-label</td>
<td>ACTH gel 80 IU twice weekly for 6 mo</td>
<td>No</td>
<td>5 patients with IMN and nephrotic syndrome</td>
<td>All failed to achieve sustained remission with at least 2 prior immunosuppressive regimens</td>
<td>CR 0 (0%); PR 2 (40%) at 6 mo</td>
</tr>
<tr>
<td>Hladunewich et al.46</td>
<td>Nonblinded, dose finding, randomized</td>
<td>Group A: ACTH gel 40 IU twice weekly for 12 wks Group B: ACTH gel 80 IU sc twice weekly for 24 wks</td>
<td>No</td>
<td>Group A: 4 patients Group B: 16 patients Patients had biopsy-proven IMN, proteinuria &gt; 4.0 g/dl and eGFR ≥ 40 ml/min/1.73 m&lt;sup&gt;2&lt;/sup&gt; Patients were treatment-naive (n=13) or intolerant or partially responsive (n=7) to other treatment regimens</td>
<td>CR 0 (0%) Low dose CR 2 (13%) at 6 mo High dose CR 9 (56%) at 6 mo&lt;sup&gt;3&lt;/sup&gt;</td>
<td>57% for both groups combined, p&lt;0.001</td>
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<table>
<thead>
<tr>
<th>Study Design</th>
<th>Therapy Dose and Duration</th>
<th>Concomitant Immunosuppression</th>
<th>Patients (N)</th>
<th>Outcomes; Number of patients with CR (%)/PR (%)</th>
<th>Mean reduction in proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IVIG studies</strong></td>
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<tr>
<td>Palla et al.49</td>
<td>Prospective, nonrandomized</td>
<td>IVIG at three doses at 1.2 g/kg every 3 wks followed by 0.4 g/kg every 3 wks for 10 mo</td>
<td>No</td>
<td>Group A: 5 patients with IMN, proteinuria ≥ 4 g/24 hrs and normal pretreatment renal function</td>
<td>Group A: 1 patient previously on cyclophosphamide and steroids at 10 mo before CR of 80% and PR of 20%</td>
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<tr>
<td>Monova et al.50</td>
<td>Prospective, observational</td>
<td>IVIG 85 mg/kg/day 3 times every other day, repeated after 1–3 mo if proteinuria &gt; 1 g/24 hrs after CR or &gt; 1 g/24 hrs in excess of baseline in PR</td>
<td>No</td>
<td>18 patients with IMN and severe nephrotic syndrome (proteinuria &gt; 6 g/24 hr)</td>
<td>4 patients were treatment-naive</td>
</tr>
<tr>
<td>Yokoyama et al.51</td>
<td>Retrospective, nonblind, nonrandomized</td>
<td>Group A: 1–3 courses of IVIG 0.1–0.15 g/kg/day for six consecutive days</td>
<td>No</td>
<td>Group A: 30 patients with IMN (70% had nephrotic syndrome [proteinuria &gt; 3.5 g/24 hrs]) Group B: 56 patients with IMN (68% with nephrotic syndrome)</td>
<td>Group A: 25 patients treatment-naive Group B: 17 patients treatment-naive</td>
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<tr>
<td><strong>Azathioprine studies</strong></td>
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<td></td>
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<tr>
<td>Naumovic et al.52</td>
<td>Randomized, prospective</td>
<td>Group A: cyclosporine 3 mg/kg/day for 6 mo then adjusted to achieve trough levels of 80–100 ng/ml for 24 mo Group B: azathioprine 1.5–2 mg/kg/day for 6 mo, then 50 mg daily for 24 mo</td>
<td>Yes, prednisone 0.5 mg/kg/day × 8 wks, then reduced to 5–10 mg/day</td>
<td>Group A: 10 Group B: 13</td>
<td>Yes</td>
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<tr>
<th>Study Design</th>
<th>Therapy Dose and Duration</th>
<th>Concomitant Immunosuppression</th>
<th>Patients (N)</th>
<th>Prior Immunosuppressive Therapy</th>
<th>Outcomes; Number of patients with CR (%)/PR (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Mean reduction in proteinuria</th>
</tr>
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<tbody>
<tr>
<td><strong>Goumenos et al.</strong>&lt;sup&gt;53&lt;/sup&gt;</td>
<td><strong>Prospective</strong></td>
<td>Group A: azathioprine 2 mg/kg/day + prednisolone 60 mg/day for 26 ± 9 mo Group B: no treatment</td>
<td>No for Group B</td>
<td>Group A: 33 patients Group B: 17 patients</td>
<td>Not reported</td>
<td>Scr doubling: Group A: 42% vs Group B: 35%, <em>p</em> = NS at 10 yrs ESKD: Group A: 21% vs Group B: 18%, <em>p</em> = NS at 10 yrs</td>
</tr>
<tr>
<td><strong>Ahuja et al.</strong>&lt;sup&gt;54&lt;/sup&gt;</td>
<td><strong>Retrospective</strong></td>
<td>Group A: azathioprine 2 mg/kg/day + prednisolone 1 mg/kg/day for 26 mo (range 6–48 mo) Group B: no treatment</td>
<td>No for Group B</td>
<td>Group A: 58 patients Group B: 20 patients</td>
<td>IMN with nephrotic range proteinuria</td>
<td>Not reported</td>
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<sup>a</sup>CR as proteinuria ≤ 0.3 g/24 hrs with eGFR ≥ 60 ml/min and PR as ≥ 50% reduction in proteinuria with proteinuria > 0.3 g/24 hrs and < 3.5 g/24 hrs.

<sup>b</sup>Persistent nephrotic syndrome defined as proteinuria > 3.5 g/24 hrs for ≥ 6 mo. [while on ramipril 5–10 mg/day for at least 6 months].<sup>25</sup>–<sup>37</sup>

<sup>c</sup>Eight patients included in the retrospective review were previously described in reports by Remuzzi et al. (2002)<sup>33</sup> and Ruggenenti et al. (2003).<sup>34</sup>

<sup>d</sup>CR as proteinuria < 1 g/24 hrs and PR as ≥ 40% reduction in proteinuria and proteinuria < 3 g/24 hrs.

<sup>e</sup>CR/PR definitions not reported; Relapse defined as proteinuria > 3.5 g/24 hrs.

<sup>f</sup>Methylprednisolone i.v. 1 g daily for 3 days, followed by prednisolone 0.4 mg/kg per day p.o. for 3 wks, then 0.2 mg/kg per day until the end of the month, alternating with chlorambucil 0.2 mg/kg per day for 1 mo, for a total duration of 6 mo.

<sup>g</sup>CR as ≤ 0.3 g/24 hrs and PR as 0.3–2 g/24 hrs or < 50% of baseline, whichever was lower.

<sup>h</sup>iV methylprednisolone 1 g/day for 3 consecutive days followed by oral prednisolone 0.5 mg/kg/day for 27 days alternating with oral cyclophosphamide at 2 mg/kg/day for 30 days.

<sup>i</sup>ACEIs, statins, low-salt and protein diet, and loop diuretic.

<sup>j</sup>Methylprednisolone, 1 g, t.i.d. daily for 3 days at the beginning of months 1, 3, and 5 and prednisone, PO 0.5 mg/kg every other day, for 6 mo with tapering.

<sup>k</sup>A protein-creatinine index (grams per gram of creatinine [grams per 10 mmol of creatinine]) was used to quantitate proteinuria to correct for improper 24 hrs collections.

<sup>l</sup>CR as ≤ 0.2 g/10 mmol creatinine and PR as 0.21–2.0 g/10 mmol creatinine.

<sup>m</sup>CR and PR were not defined in original study.

<sup>n</sup>Three cycles of treatment with methylprednisolone, 1 g, administered i.v. on 3 consecutive days, then 0.4 mg/kg/d for 27 days, administered orally in a single morning dose. Each cycle was followed by 1 mo of treatment with either chlorambucil (0.2 mg/kg/d orally) or cyclophosphamide (2.5 mg/kg/day orally). This 2-mo treatment was repeated 3 times.

<sup>o</sup>CR as proteinuria < 0.2 g/24 hrs and PR as proteinuria > 0.2 to < 3.5 g/24 hrs.

<sup>p</sup>CR as proteinuria < 0.5 g/24 hrs and PR as proteinuria > 0.5 and < 1.5 g/24 hrs.
Concerns regarding the safety profile of rituximab include infectious complications, infusion reactions, and development of immunity. Indeed, rituximab does carry black box warnings for fatal infusion reactions within 24 hours of infusion, severe mucocutaneous reactions, hepatitis B virus reactivation, and progressive multifocal leukoencephalopathy. Among the studies we reviewed, however, rituximab was generally reported to be well tolerated with a favorable side effect profile. Acute infusion reactions—chills, itching, larynx spasm, and cutaneous rash—were reported most frequently in IMN studies with rituximab for four doses and B-cell-driven protocols in the range of 0% to 37.5%. For the most part, temporary interruption of rituximab infusion alleviated nonserious adverse reactions, and methylprednisolone injection resolved a few cases of rash and larynx spasm. Additional adverse events such as angioedema, muscle pain, fatigue, voice loss, and hair loss and thinning were also reported. There were only two infectious complications: one patient developed pneumonia 3 months after receiving treatment, and the other patient experienced viral reactivation of herpes zoster. Serious adverse events were also rare, and included one patient with serum sickness-like syndrome and one patient with a history of immunosuppressant treatment diagnosed with adenocarcinoma 3 months after receiving rituximab. The latter patient consequently died after withdrawing from the study.

The studies reported thus far for rituximab in the treatment of patients with IMN suggest that it may be a viable alternative to conventional immunosuppressants. Rituximab has demonstrated efficacy in treatment-naive patients, treatment-resistant patients, and CNI-dependent patients. Barriers to its use as a first-line agent include high cost, lack of FDA approval for treatment of patients with nephrotic syndrome, and lack of RCTs. In addition, the safety and efficacy of rituximab use in patients with reduced renal function require further study. Thus, at present, rituximab should be reserved for patients who are resistant or intolerant to conventional agents with preserved renal function. Additional ongoing studies with rituximab include a prospective multicenter open-label study comparing rituximab 375 mg/m² on days 1 and 8 to nonimmunosuppressive symptomatic treatment (NCT01508468) and a pilot study with rituximab plus cyclosporine versus cyclosporine alone (NCT00977977).

Mycophenolate Mofetil

As with rituximab, MMF has not been approved by the FDA for use in IMN. The mechanism of action (MOA) for MMF in IMN is thought to be related to immunosuppression, partially through inhibitory effects on T- and B-lymphocyte proliferation (Table 1). MMF in conjunction with steroids as a first-line therapy is supported by two randomized trials that found no statistically significant differences in remission rates or relapses between MMF plus steroids compared with cyclical alkylating agents with steroids in treatment-naive patients. Although a historical matched-control study comparing combination MMF and steroids with cyclophosphamide and steroids also found similar rates of remission, the MMF plus steroids arm in this study had a higher rate of relapse and a lower incidence of proteinuria reduction. Due to this conflicting evidence, better-designed trials are warranted before MMF in conjunction with steroids can be considered as first-line therapy.

When used as monotherapy, MMF appears to show no benefit compared with conservative therapy in treatment-naive IMN patients. One RCT showed that MMF monotherapy failed to improve remission rates or to impact mean proteinuria-to-creatinine ratio. Thus, MMF monotherapy should be avoided as first-line therapy for the treatment of IMN.

In treatment-resistant patients who have previously failed alkylating agents or CNIs, MMF plus steroids may be a reasonable alternative option. A modest reduction in proteinuria and increased remission with MMF (plus variable use of steroids) was demonstrated in two nonrandomized studies in patients who were resistant to or dependent on conventional therapies. In one study, all 14 patients deemed steroid or cyclosporine dependent were able to discontinue treatment with the dependent drug following therapy with MMF. Interestingly, of those successfully withdrawn off cyclosporine, three had received MMF as monotherapy. As it stands, the role of MMF role in treatment-resistant patients previously failing alkylating agents or CNIs is largely unknown, although short-term benefits have been reported. Long-term use with MMF and its effect on hard renal outcomes have not been studied. MMF at a dose of 1 g twice/day for 6 to 12 months with adjunct steroids may be reasonably considered in patients who are resistant or intolerant to
conventional therapy. Current data in this population, however, are limited to anecdotal and observational clinical experience. Side effects associated with MMF in these trials include gastrointestinal symptoms, malaise, and anemia. Serious side effects included malignancy and infection. MMF has FDA-issued black box warnings, which include increased risk of infection, lymphoma, skin malignancy, and congenital malformations, as well as risk of pregnancy loss during the first trimester. An additional FDA boxed warning states that MMF should be given by a health care provider who has experience using immunosuppressant therapy. Significant adverse drug reactions (defined as an incidence of greater than 20%) include cardiovascular, hematologic, and hepatic effects. It is recommended that patients be monitored for complete blood counts and liver function, among other parameters, during therapy. Despite these serious adverse drug reactions, MMF was reported to be well tolerated in the studies just described; however, caution should be properly exercised with its use.

MMF monotherapy or in combination with steroids is not currently recommended as first-line therapy for IMN. While MMF may be considered in treatment-resistant patients and CNI-dependent patients, more-robust studies will help back up the available data, which is of low quality and limited in duration. The lack of well-designed prospective RCTs, the need for concomitant steroids, and a relatively high incidence of relapse following its discontinuation represent barriers to more widespread use of MMF. Of note, there is currently an ongoing trial investigating the use of MMF in combination with tacrolimus versus tacrolimus monotherapy to learn whether combination therapy will result in decreased renal progression and number of relapses on discontinuation of therapy (NCT00843856).

Adrenocorticotropic Hormone

ACTH injections were used in the 1950s for nephrotic syndrome in both adults and children but became obsolete with the advent of oral prednisone shortly thereafter. Recently, however, there has been a renewed interest with its use in nephrotic syndrome and IMN partly due to its potential steroid-independent effects. This hypothesized MOA differs from that of the historically presumed MOA of purely steroid-dependent effects of adrenal cortex stimulation. It is proposed that ACTH, a known agonist of all five melanocortin receptors that have been cloned and characterized to date, may directly alter podocyte function and lead to amelioration of proteinuria. Furthermore, the steroid-independent effects of ACTH are supported by the fact that glucocorticoid monotherapy is not effective in IMN and studies have demonstrated efficacy of ACTH in patients who did not respond to steroid treatment.

Presently, there are two available long-acting ACTH products. The first is a natural highly purified gel available only in the United States, and the second is a synthetic, truncated analog that is not available in the United States. There is currently insufficient evidence to comment on the pharmacokinetic and pharmacodynamic similarities between these products, but preliminary data suggest differences in the degree of adrenal stimulation. Additionally, differences in pharmacologic activity have been suggested, credited to the C-terminal portion of the gel, which is lacking in the synthetic form.

In treatment-naive patients, one prospective RCT found that synthetic ACTH could achieve comparable rates of remission and sustained remission at 2 years compared with methylprednisolone and a cytotoxic agent. In treatment-resistant patients, two nonrandomized studies have reported that ACTH gel promoted remission in patients who had previously received a mean of 2.4 immunosuppressive therapies. Patients responding to ACTH in these trials also included patients who had not responded to prior steroid treatment.

A recently published prospective, randomized, open-label pilot study found a statistically significant association between larger cumulative doses of ACTH gel and better proteinuria outcomes. Based on the existing data for ACTH gel, the most commonly reported dosing regimen has been 80 IU twice/week for 6 months in patients not responding to or tolerating conventional therapies. Although ACTH gel does not carry an FDA-issued boxed warning, patients should be monitored for steroid-like side effects, as these have been the most common side effects reported. Table 1 outlines the evidence for ACTH.
nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus," there is an absence of high-quality data to support its broader use. In addition, ACTH gel is expensive. RCTs are needed to support a more widespread role of ACTH gel in IMN patients. Currently, there is one company-sponsored, randomized, placebo-controlled trial of ACTH gel in treatment-resistant IMN patients. Results of this study may further shed light on the efficacy of this agent in these hard-to-treat patients (NCT01386554).

Intravenous Immune Globulin

Since 1991, there has been scant evidence evaluating the use of IVIG in patients with IMN (Table 1). A prospective, nonrandomized trial reported that IVIG may have benefit in IMN through dissolution of glomerular subepithelial immune deposits and indirect interference with the immune processes of IMN. Treatment was reported to be well tolerated with only minor side effects; these were prevented by slow infusion of IVIG. A prospective, observational trial from 2002 reported that IVIG led to CR plus PR in 14 of 18 patients with IMN. Five patients received only one treatment course whereas 13 received two or more courses due to insufficient response or relapse. Two of the four nonresponders developed ESKD on hemodialysis and two died; the deaths were not attributed to treatment. The largest IVIG study in IMN patients to date is a retrospective study showing the benefit of IVIG for 6 consecutive days in 30 patients, 25 of whom were treatment naive. All patients achieved PR or CR except for three patients who maintained their pretreatment serum creatinine and nephrotic syndrome status and three who developed ESKD. In this study, IVIG was well tolerated with no reported adverse events and was deemed beneficial compared with 56 historical controls after a 5-year follow-up.

Currently, there is insufficient evidence to support the use of IVIG in IMN. One study reported that the cost for one course of IVIG is $7,600, and many patients require multiple courses. IVIG was reported to be well tolerated in these small nonrandomized studies with only minimal adverse effects, which could be managed or prevented with slow infusion. However, IVIG is known to cause anaphylactic reactions, thrombosis, and acute renal failure. Thus, larger RCTs with longer follow-up times are necessary before deeming IVIG safe in this patient population.

Azathioprine

Several small studies have compared azathioprine as a treatment for IMN versus placebo or active comparators (Table 1). Overall, the rate and extent of deterioration of serum creatinine and reduction of proteinuria were not markedly favorable for azathioprine. Because of this, there is no role for azathioprine with or without corticosteroids in altering the course of this disease. With the promising potential of newer agents such as rituximab and MMF, there are not likely to be future studies with azathioprine.

Conclusions

Conventional immunosuppressive therapies carry important risks and are ineffective for a large percentage of patients. Unremitted disease is associated with loss of renal function and mortality and, thus, advancement in the treatment of IMN and development of alternative therapies is necessary. There is definite promise demonstrated by the trials discussed in this review; with the exception of azathioprine, these alternative therapies have the potential to address this need. These trials have shown benefit in treatment-naive, resistant, and intolerant patients, a population that would benefit from more alternative options. Additionally, the safety profiles reported in the reviewed studies are favorable. Further experience with their use and comparator studies will be necessary, however, before any claims can be made as to their improved safety to supplant conventional therapies.

There are important limitations of the trials published to date for the agents discussed here. The most glaring is the absence of large RCTs, which, together with the high cost of some of these agents, represents significant barriers to their adoption in routine clinical practice. Indeed, KDIGO suggests that until there are data from large RCTs, no recommendations can be made for the use of these agents. Ongoing RCTs for both rituximab and ACTH, the results of which are expected within the next several years, will address this need and their results will aid in the determination of the place of
these agents in the treatment armamentarium. Studies with longer follow-up are also needed to more accurately predict relapse rates, to determine the impact on disease progression, and to assess long-term safety. We believe, however, that the absence of such studies should not negate these agents to the status of experimental therapies to be used only within the confines of the research setting. Rather, the available data, as well as clinical experience surrounding the use of these agents, demonstrate that they are viable options for difficult to treat, high-risk patients unresponsive to or intolerant of conventional therapies for whom there is large unmet need. To eschew these potentially life-saving therapies due to an absence of RCTs would be detrimental to these patients and their families.

Acknowledgments
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