Application of MPA in glomerulonephritis

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Primary FSGS

- For patients with presumed primary FSGS who present with nephrotic syndrome (ie, proteinuria >3.5 g/day and serum albumin <3.5 g/dL), we suggest initial treatment with glucocorticoids.

- In patients who have a high risk for glucocorticoid-induced toxicity (eg, patients with obesity, diabetes, severe osteoporosis, or age >70 years), a CNI (cyclosporine or tacrolimus), with or without low-dose glucocorticoids, is an alternative option for initial therapy.

- However, we avoid using CNIs in patients with significantly reduced kidney function (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m2) because of the potential nephrotoxicity of these drugs.

- Patients who cannot be treated with either glucocorticoids or a CNI are rare. In such cases, alternative options might include mycophenolate mofetil (MMF)/enteric-coated mycophenolate sodium (EC-MPS), rituximab, and adrenocorticotropic hormone (ACTH) gel, although there is no evidence to support the use of these agents as initial therapy.

- If, at any time after a complete or partial remission is attained, proteinuria increases while the prednisone is being tapered, we stop the taper and temporarily maintain the current prednisone dose while adding a CNI or, if the eGFR is <30 mL/min/1.73 m2, MMF/EC-MPS.

- Although the use of MMF/EC-MPS is not supported by evidence, some authors and editors use it in this setting based on its potential role as a glucocorticoid-sparing agent, its safe use in patients with low eGFR, and its role as maintenance therapy in other glomerular diseases such as minimal change disease and lupus nephritis.

- Adult patients who have little or no reduction in proteinuria after 16 weeks of daily prednisone are presumed to be glucocorticoid resistant. In such patients, we prefer to add a CNI (or MMF if the eGFR is low) and switch to alternate-day prednisone with a progressive taper in prednisone therapy, reducing the dose by approximately one-third every week.

Patients who achieve a remission and then develop a relapse at least several months after discontinuation of therapy are considered to have a late relapse.

- Treatment of late relapse in primary FSGS has not been evaluated in controlled trials; the suggestions below are based upon personal experience and limited observational data.

- The approach to this problem varies with the response to initial therapy and the time to relapse:

- If the patient had significant glucocorticoid-induced toxicity during initial therapy, has developed a condition that increases the risk of glucocorticoid-induced toxicity, or has had multiple relapses, then we usually treat with a CNI, with or without low-dose glucocorticoids. In such patients who have substantially reduced (eGFR); eg, <30 mL/min per 1.73 m2), we prefer mycophenolate mofetil (MMF)/enteric-coated mycophenolate sodium (EC-MPS) combined with low-dose glucocorticoids rather than a CNI, although evidence to support this approach is weak.

- If the patient previously had a complete or partial remission with a CNI, and cannot receive a CNI because of prior toxicity or reduced eGFR (<30 mL/min per 1.73 m2), MMF/EC-MPS or rituximab is a possible alternative.

glucocorticoid-dependent or glucocorticoid-resistant FSGS :

- Patients who attain a remission but who relapse while still on therapy or within two weeks of discontinuing therapy are considered glucocorticoid dependent.

- Adult patients with little or no reduction in proteinuria at 16 weeks are considered glucocorticoid resistant.

Calcineurin inhibitors as preferred second-line therapy

- Other therapies for patients resistant or intolerant to a calcineurin inhibitor:
  - ➢There is no high-quality evidence to guide the optimal therapy
- Those with glucocorticoid-dependent FSGS may be alternatively treated with mycophenolate mofetil (MMF)/enteric-coated mycophenolate sodium (EC-MPS), rituximab, or cytotoxic therapy (cyclophosphamide).
- For those with glucocorticoid-resistant FSGS, commonly used alternative options to a CNI include MMF/EC-MPS and rituximab; cyclophosphamide, ACTH, plasmapheresis, and low-density lipoprotein (LDL) apheresis are infrequently used but may be beneficial in some patients.

- MMF/EC-MPS in combination with low-dose glucocorticoids is an alternative option for patients with glucocorticoid-dependent or glucocorticoid-resistant primary FSGS who have either not responded to or should not be exposed to CNIs, or who have had a partial response to prednisone and/or CNIs but developed signs of toxicity to these drugs.

- If MMF is used, we give 750 to 1000 mg twice daily for six months. If EC-MPS is used, we give 540 to 720 mg twice daily for six months.

- MMF/EC-MPS should be administered with low-dose glucocorticoid therapy.

primary IgA nephropathy

- In general, the management of primary IgAN focuses on optimized supportive care, including blood pressure control to optimal targets, reduction of proteinuria with renin-angiotensin system inhibition, and lifestyle modifications as appropriate.

- Immunosuppressive therapy, which has been shown to improve outcomes in patients with IgAN but has significant toxicity, should be reserved only for patients who remain at high risk for progression to end-stage kidney disease (ESKD) despite maximal supportive care.

❖Immunosuppressive therapy in high-risk patients

➢high-risk patients :

✓proteinuria ≥1 g/day despite at least three months of optimized supportive care

❖We inform patients that immunosuppressive therapy likely improves kidney outcomes among patients with IgAN but has the potential for significant toxicity.

- we do not give immunosuppressive therapy to patients if they have evidence of severe and irreversible kidney damage (eGFR <30 mL/min/1.73 m2 for >3 months, small echogenic kidneys on kidney ultrasound, or evidence of severe interstitial fibrosis, tubular atrophy, or glomerulosclerosis on kidney biopsy), since immunosuppressive therapy is unlikely to be effective in such patients

✓First step: Glucocorticoid therapy

✓For patients who cannot tolerate or who do not wish to receive glucocorticoids, MMF is our preferred alternative option.

- Some contributors use MMF in high-risk patients who continue to have disease progression despite treatment with glucocorticoids, while others use MMF as initial therapy in high-risk patients who have both proteinuria and microscopic hematuria.

- If MMF is used, we start with 500 mg twice daily and titrate the dose to 1000 mg twice daily over several weeks as tolerated.

- We treat initially for four to six months.

- If eGFR or proteinuria worsen during this time, we discontinue treatment.

- If eGFR and proteinuria remain stable or improve, we continue treatment for one year and then taper the dose to discontinuation.

- There are limited data concerning the efficacy of MMF in the primary treatment of progressive IgAN.

- Three small, prospective, placebo-controlled randomized trials evaluated the efficacy of MMF therapy; the patients were also treated with ACE inhibitors.

- The trials had conflicting results, ranging from no benefit ,particularly in patients with advanced fibrotic disease, to a reduction in proteinuria and a decrease in rate of decline in GFR

- Another trial that compared the combination of MMF and lower-dose prednisone (0.4 to 0.6 mg/kg/day) with full-dose prednisone (0.8 to 1 mg/kg/day) in Chinese patients with clinically and histologically active IgAN found no difference in complete remission rates at 6 and 12 months, suggesting a glucocorticoid-sparing effect of MMF .

lupus membranous nephropathy

- There is a lack of consensus on the indications for immunosuppressive therapy in patients with pure lupus membranous nephropathy (LMN):

- most experts agree that immunosuppressive drugs should be administered to patients with pure LMN who have nephrotic syndrome or, in the absence of nephrotic syndrome, persistent proteinuria >3.5 g/day despite nonimmunosuppressive therapy; a progressive rise in serum creatinine above baseline; or mixed membranous and proliferative lesions on kidney biopsy.

- Some experts suggest that patients with LMN and proteinuria >1 g/day without evidence of extensive chronic damage (eg, glomerulosclerosis, interstitial fibrosis and tubular atrophy) on kidney biopsy should receive immunosuppressive therapy.

- Some experts suggest that all patients with LMN, regardless of the degree of proteinuria, should receive immunosuppressive therapy, given that patients with LMN often do not spontaneously remit.

Choice of immunosuppressive therapy

- Patients who have concurrent LMN and focal or diffuse lupus nephritis (LN) are treated according to the same approach as used for those with focal or diffuse LN alone.

- In patients with pure LMN selected for immunosuppression, we suggest mycophenolate mofetil (MMF), in combination with glucocorticoids, rather than intravenous (IV) cyclophosphamide or a calcineurin inhibitor (CNI).

- cyclophosphamide or CNIs in combination with glucocorticoids are a reasonable alternative, particularly among patients who have a contraindication or cannot tolerate MMF.

- There are no trials comparing MMF with cyclosporine in patients with LMN.

- A randomized trial (Aspreva Lupus Management Study [ALMS]) compared MMF with cyclophosphamide in 370 patients with LN, including 60 with pure LMN; all patients also received oral prednisone . The primary outcome was a prespecified reduction in the urine protein-to-creatinine ratio to less than 3 or by at least 50 percent. Secondary outcomes included stabilization or improvement of the serum creatinine, reduction of protein excretion to less than 0.5 g/day, and attainment of inactive urinary sediment. At 24 weeks, the percentage of patients who achieved the primary and secondary outcomes were similar between the two treatment groups.

- A second randomized trial compared MMF with IV cyclophosphamide in 140 patients with LN, 27 of whom had LMN. Complete and partial renal responses were attained by 7 of 14 patients treated with MMF, and 4 of 13 treated with cyclophosphamide.

- A pooled analysis of patients from the last two trials included 65 patients with pure LMN: 33 patients on MMF and 32 patients on cyclophosphamide completed 24 weeks of treatment. Both the percent reduction in proteinuria (including among 40 patients with nephrotic-range proteinuria) and the rate of partial response were similar between the treatment groups. The rates of adverse events were also similar between the groups.

- If a mycophenolate-based regimen is used, we give 0.5 g of MMF twice daily for the first week, then 1 g twice daily for the second week, and thereafter increase the dose as tolerated to between 1 and 1.5 g twice daily.

- For patients who are unable to tolerate adequate doses of MMF due to gastrointestinal side effects (eg, nausea, abdominal pain, or diarrhea), enteric-coated mycophenolate sodium (EC-MPS) can be substituted for MMF (1 g of MMF is equivalent to 720 mg of EC-MPS).

- We usually continue MMF at these doses for six months. At six months, the dose may be reduced to 1 g twice daily, which is continued for two to three years and then slowly tapered.

- Voclosporin is a next-generation CNI that is structurally similar to cyclosporine but is more potent and does not require monitoring of drug levels.
- Voclosporin is US Food and Drug Administration (FDA) approved for the treatment of LN in combination with mycophenolate and glucocorticoids.

resistant and relapsing disease

- Patients require modification of immunosuppressive therapy if they have persistent heavy proteinuria (over 3 g daily) despite 6 to 12 months of adequate therapy (ie, are nonresponders) or

- have an initial response but then develop worsening proteinuria, a new active urinary sediment, or worsening kidney function (ie, have relapsing disease).

- For patients who do not respond to initial treatment with mycophenolate mofetil (MMF) in combination with glucocorticoids, we typically switch to cyclophosphamide therapy, a calcineurin inhibitor (CNI), or rituximab.

- For patients who initially respond to MMF but then subsequently relapse, modification of immunosuppression depends upon when the relapse occurs:
  - If the relapse occurs during long-term therapy (when the MMF dose is being tapered) or after MMF has been discontinued, we resume the original dose of MMF (usually with a goal between 1 and 1.5 g twice daily).
  - If the relapse occurs during the first six months of MMF treatment, we typically continue MMF and add either a CNI or rituximab.

Membranous nephropathy

- Our approach to initial therapy in patients at moderate risk of progression varies depending upon the course of disease during an initial three-to-six-month observation period with maximal general supportive measures .

- In moderate-risk patients who show a progressive increase in proteinuria over the observation period, we recommend treatment with immunosuppressive therapy and continued general supportive measures.

- In moderate-risk patients who show stable proteinuria over the observation period, we suggest immunosuppressive therapy and continued general supportive measures.

- some clinicians would continue to withhold immunosuppressive therapy beyond six months in such patients if they are doing well, especially if serum albumin is increasing, anti-PLA2R antibody levels (if initially positive) are low or decreasing, or if the patients are at high risk of having an adverse event with immunosuppressive therapy.

- In moderate-risk patients who show a progressive decline in proteinuria over the observation period, we withhold immunosuppression and continue general supportive measures.

- Preferred first-line immunosuppressive therapies for moderate-risk patients with primary MN include rituximab, combination therapy with glucocorticoids plus a cytotoxic agent (preferably cyclophosphamide), or a CNI (cyclosporine or tacrolimus).

- We do not routinely use mycophenolate mofetil (MMF), as initial therapy in moderate-risk patients.

- such agents may be considered in patients who do not respond to all of the first-line therapies.

Treatment of resistant disease

- Patients with primary MN who do not respond to initial therapy with rituximab, cyclophosphamide plus glucocorticoids, or a calcineurin inhibitor (CNI) should be given an alternative regimen of one of these first-line therapies.
- Patients who do not achieve a complete or partial remission after all of the first-line therapies have been tried are considered to have resistant disease.
- Among patients who are anti-phospholipase A2 receptor (PLA2R) antibody positive, persistence of serum anti-PLA2R antibodies in spite of immunosuppressive therapy is also indicative of resistant disease.

- The optimal approach to patients with resistant disease is not known.

- Mycophenolate mofetil (MMF) ,natural adrenocorticotropic hormone (ACTH) gel ,and plasma exchange are reasonable therapeutic options, although high-quality data demonstrating their efficacy are lacking.

- In patients who are refractory to multiple immunosuppressive regimens, it may be difficult to distinguish between resistant disease and chronic, irreversible damage to the glomerular filtration barrier or the development of glomerulosclerosis.

- In such patients, a repeat kidney biopsy may be helpful to inform therapeutic decisions.


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