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14

Lupus Glomerulonephritis

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1. Introduction

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease of unknown etiology. The onset of SLE is believed to be triggered by ill-defined environmental factors in genetically susceptible individuals (Mok, 2003a). Although the exact pathogenetic mechanisms have yet to be elucidated, recent works have revealed a myriad of immunological abnormalities in patients with SLE. These include aberrant apoptosis and defective clearance of apoptotic materials such as nuclear autoantigens and nucleosomes, and immune complexes by macrophages and the complement system (Katsiari, 2010), increased maturation of myeloid dendritic cells which drive the development of the proinflammatory Th17 cells (Fransen, 2010), and defective functions of the regulatory T cells (Tregs) leading to hyperactivity of the helper T cells and autoreactive B cells causing production of autoantibodies (Tucci, 2010).

Of the numerous clinical manifestations of SLE, renal disease is one of the commonest and most serious. Lupus renal disease appears to be more prevalent in certain ethnic groups such as the African and Hispanic Americans, as well as the Asians (Mok, 2005a). Renal involvement in SLE adversely affects its ultimate prognosis as reflected by the rates of patient survival and renal survival (survival without the need for renal replacement therapy), and is a major determinant for morbidity and impairment of quality of life (Mok, 1999).

The glomerulus is the commonest site of kidney involvement by lupus. However, the renal interstitium and tubules, as well as the vessels may also be affected (Cross, 2005). The presentation of renal disease in SLE is variable, ranging from no symptoms, trace proteinuria or urinary sediments to frank nephrotic syndrome, chronic renal insufficiency, and nephritic syndrome with rapid progression leading to acute renal failure. Early recognition of renal disease and close monitoring of renal parameters for progress after treatment is an essential part of the management. Conventional serological markers and clinical renal parameters for active lupus nephritis are not sensitive or specific enough, and novel biomarkers for early detection of renal disease and prediction of renal prognosis are under ongoing evaluation. It is believed that a combination of conventional parameters with one or more serological or urine biomarkers may yield better sensitivity and specificity for predicting renal activity or flare of nephritis in patients with SLE. This may help to abate the need for more invasive investigations such as renal biopsy in the assessment of renal activity and allow early institution of therapy (Mok, 2010a).

Therapy of lupus nephritis should target at symptomatic control, preservation of renal function, reduction of renal flares, prevention of treatment-related complications, and ultimately reduction in mortality (Mok, 2003b). The treatment schedule of lupus nephritis is now divided into an induction phase and a maintenance phase. Induction treatment aims at controlling inflammation and minimizing glomerular injury, whereas maintenance therapy is to reduce the risk of renal flares and renal function decline in the long-run. A combination of glucocorticoids with a non-glucocorticoid immunosuppressive agent has been shown to be more effective than glucocorticoid monotherapy in reducing the risk of progression into end stage renal failure in lupus nephritis (Austin, 1986). Of the many non-glucocorticoid immunomodulating agents, mycophenolate mofetil (MMF) has emerged to be the first-line treatment of lupus nephritis around the world because studies have shown that it is associated with fewer adverse effects than cyclophosphamide, particularly on the ovarian functions (Ginzler, 2005). Recent evidence also reveals that maintenance therapy with MMF is more effective than azathioprine in reducing the composite endpoint of renal flare and deterioration of renal function (Wolfsy, 2010).

In this chapter, the prevalence, presentation and significance of renal involvement in patients with SLE is discussed. An update on the current therapies of lupus nephritis is also presented based on the results of recent randomized controlled trials. Finally, promising biomarkers for the detection and monitoring of lupus nephritis is briefly reviewed.

2. Prevalence of renal disease in SLE

Lupus renal disease appears to be more prevalent in certain ethnic groups such as the African and Hispanic Americans, as well as the Asians (Mok, 2005a; Dooley, 1997). In a comparative study of the clinical manifestations of SLE in three ethnic groups, it was reported that renal disease, as defined by the American College of Rheumatology (ACR) criteria, namely persistent daily proteinuria of more than 500mg, presence of cellular casts or biopsy evidence of lupus nephritis, occurred in 45% of African American, 42% of Chinese and 30% of Caucasian patients, respectively (Mok, 2005a). Another multi-ethnic US cohort of SLE patients reported that renal disease occurred in 51% of Africans and 43% of Hispanics but only in 14% of Caucasians (Bastian, 2002). In a prospective study of 216 Chinese patients with new onset SLE, 31% patients had active renal disease at the time of initial presentation (Mok, 2004). Of 148 patients without overt renal disease at SLE onset, 33% developed active renal disease after a median of 14 months. The overall cumulative incidence of renal disease as defined according to the ACR renal criteria in this cohort of patients was 60% at 5 years post-SLE diagnosis (Mok, 2004). The actual incidence of renal disease might have been underestimated as the renal definition does not include subtle renal involvement such as proteinuria of less than 500mg/day or microscopic hematuria, or both. These studies illustrate that lupus renal involvement is more common in the Africans, Hispanics and Chinese than the Caucasians.

3. Clinical presentation of lupus renal disease

The presentation of renal disease in SLE is variable, ranging from no symptoms (detected by routine renal biopsy or "silent" lupus nephritis), trace proteinuria or active urinary

sediments (microscopic hematuria, pyuria or cellular casts), to more serious proteinuria (nephrotic syndrome), and acute nephritic syndrome with rapid progression to acute renal failure. Occasionally, patients may present with chronic renal failure, isolated renal insufficiency and hypertension as the initial manifestation.

The wide range of presentations of lupus nephritis does not necessarily correlate with the histological findings from renal biopsy. "Silent" lupus nephritis has long been recognized in the literature. A retrospective study of 21 SLE patients with low level of proteinuria (<1gm/day) who underwent renal biopsy showed that proliferative lupus nephritis was present in 57% patients (Christopher-Stine, 2007). This emphasizes the frequent discordance of the histological severity with clinical presentation, and the need for renal biopsy, especially for new onset renal disease as evidenced by abnormal urinalysis and/or renal function impairment.

4. Renal biopsy

Renal biopsy is the gold standard of confirming the diagnosis of lupus glomerulonephritis. The finding of positive staining for immunoglobulin G, A and M, together with C1q, C3 and C4, constitutes the "full house" staining pattern for lupus nephritis. In addition to establishment of the diagnosis of lupus renal disease and confirming renal flares, renal biopsy also provides information on the histological classes of lupus nephritis, and the degree of inflammation and damage in the kidneys so as to guide therapeutic decision. Renal biopsy should be considered in SLE patients with new onset of proteinuria of more than 1g/day with and without active urinary sediments, especially in the presence of active lupus serology or impaired renal function. Some experts recommend renal biopsy at a lower threshold of proteinuria (eg. ≥500mg/day).

Patients with lupus nephritis that is refractory to treatment should be evaluated for other possible causes for the persistence of proteinuria or deterioration in renal function such as the nephrotoxic side effects of medications (eg. the calcineurin inhibitors and non-steroidal anti-inflammatory drugs), renal vein thrombosis, infections, overdiuresis and poorly controlled hypertension. Treatment compliance should be checked. A repeat renal biopsy should be considered in patients with persistently active serological markers because it provides information on the following: (1) histological transformation of the classes of lupus nephritis; (2) the degree of residual activity in the kidneys; and (3) the extent of chronic irreversible changes and its progression since the initiation of immunosuppressive treatment. These data may help to guide further treatment decisions.

5. Histological classification of lupus glomerulonephritis

The histological classification of lupus nephritis has undergone several modifications. The first WHO classification was formulated in 1974 and was last revised in 1995. According to this system, lupus glomerulonephritis was classified according to the extent and pattern of immune deposits and inflammation, which were detected by immunohistochemistry on light microscopy. There were 5 histological subtypes of lupus nephritis (class I to V) in the 1974 WHO classification (McCluskey, 1975). The differentiation of class III and class IV disease was based on the percentage of glomeruli affected by proliferative lesions (>50% was classified as Class IV). No qualitative differences between class III and class IV lesions

were described. Tubulointerstitial and vascular lesions were not included in the classification.

The WHO classification was revised in 1982 (Churg, 1982). Class I disease was subdivided into 2 subclasses based on the presence and absence of immune deposits on immunofluorescence or electron microscopy. Class III was denoted focal segemental glomerulonephritis and Class IV was referred to diffuse proliferative glomerulonephritis. There were no description on the percentage of involvement of glomeruli for the differentiation between class III and class IV disease. Class III and IV disease was subdivided into active, chronic, or mixed types of glomerular injury. Class V was denoted membranous glomerulonephritis, which was subdivided into 4 subclasses: pure membranous nephropathy without or with mesangial hypercellularity (Va and Vb, respectively), membranous nephropathy with segmental endocapillary proliferation and/or necrosis (Vc) and membranous nephropathy with diffuse endocapillary proliferation and/or necrosis (Vd). Class VI was introduced to denote advanced sclerosing glomerulonephritis.

The WHO system was further revised in 1995 (Churg, 1995), with the emphasis of segmental glomerular capillary wall necrosis to be the defining feature of class III lesions, regardless of the percentage of glomeruli affected. For membranous lupus nephropathy, as the long-term prognosis is dependent on the proliferative than membranous component, the 1995 WHO classification removed Vc and Vd to be included into class III and class IV lupus nephritis, respectively. Class V retained only the subclasses Va and Vb, under the category "diffuse membranous glomerulonephritis".

The histological classification system was modified once again in 2003 by the International Society of Nephrology and the Renal Pathology Society (Weening, 2004) (Table 1). One of the reasons was the demonstration of the poor outcome of diffuse segmental necrotizing glomerulonephritis involving over 50% of glomeruli, (a "severe" form of class III disease), as compared to class IV lupus nephritis. Class III disease referred to focal lupus nephritis, which was defined as involvement of less than 50% of glomeruli by segmental endocapillary proliferative lesions, with or without capillary wall necrosis and crescents, and subendothelial deposits. Class IV disease was denoted diffuse lupus nephritis which involved more than 50% of the glomeruli. This class is subdivided into diffuse segmental lupus nephritis (class IVS) when >50% of the involved glomeruli showed segmental lesions, and diffuse global lupus nephritis (class IVG) when >50% of the glomeruli having global lesions. The proportion of glomeruli with active and chronic lesions, fibrinoid necrosis or crescents, tubulointerstitial and vascular pathology should be separated reported.

Class V, or membranous lupus nephritis, was defined as global or segmental continuous granular subepithelial immune deposits, often in the presence of concomitant mesangial immune deposits and hypercellularity. The distinction between pure membranous nephropathy and membranous nephropathy superimposed on mesangial changes was eliminated. When a diffusely distributed membranous lesion is associated with an active lesion of class III or IV, both diagnoses are reported ('V+III' or 'V+IV'). Finally, minimal change nephropathy (class I) was renamed minimal mesangial lupus nephritis, which was characterized by normal light microscopy of the glomeruli with accumulation of mesangial immune complexes identified by immunofluorescence and/or electron microscopy. A complete lack of renal abnormalities by light microscopy, immunofluorescence, and electron microscopy no longer qualified Class I lupus nephritis.

Class I	Minimal mesangial lupus nephritis Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	Mesangial proliferative lupus nephritis Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microsocpy, with mesangial immune deposits. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	Focal lupus nephritis Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
III (A)	Active lesions: focal proliferative lupus nephritis
III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	Diffuse lupus nephritis Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.
IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
IV-G (A/C)	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V	Membranous lupus nephritis Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations. Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed Class V lupus nephritis may show advanced sclerosis
Class VI	Advanced sclerotic lupus nephritis ≥90% of glomeruli globally sclerosed without residual activity

Table 1. ISN/RPS 2003 classification of lupus nephritis

6. Prognosis of lupus renal disease

Renal involvement of SLE carries significant morbidity and mortality. The renal survival (survival without dialysis) rates of lupus nephritis in the 1990's range from 83-92% in 5 years and 74-84% in 10 years (Mok, 1999; Donadio, 1995; Bono, 1999; Neumann, 1995). The risks of end stage renal failure were particularly high in patients with diffuse proliferative glomerulonephritis, with figures ranging from 11-33% in 5 years (Mok, 1999; Dooley, 1997, Donadio, 1995; Neumann, 1995; Bakir, 1994; Nossent, 2000; Korbet, 2000). The prognosis of lupus nephritis depends on a large number of demographic, racial, genetic, histopathological, immunological and time-dependent factors (Mok, 2005b). Renal disease that fails to remit with conventional immunosuppressive therapies is a major risk factor for subsequent deterioration of renal function and poor outcome (Mok, 1999; Korbet, 2000; Mok, 2006b). Other unfavorable prognostic factors for lupus neprhitis include younger age, male sex, histological cellular crescents, fibrinoid necrosis, subendothelial deposits, glomerular scarring, tubular atrophy and interstitial fibrosis, impaired renal function at presentation, persistent hypertension, hypocomplementemia, low hematocrit, as well as delay in treatment due to problems of access to health care and poor compliance (Mok, 2005b).

A recent hospital registry study of 5686 patients with SLE showed that there was a loss in life expectancy of 20 years in female and 27 years in male patients, respectively (Mok, 2011). Among 514 lupus deaths, direct complications of renal disease accounted for 9% of all cases (Mok, 2011). This reiterates that the prognosis of renal disease in SLE has yet to be improved by novel therapies in the future.

7. Current treatment of lupus glomerulonephritis

The immunosuppressive therapy of lupus nephritis is divided into an induction phase which targets at reducing inflammation and glomerular injury and a maintenance phase that aims to reduce the long-term risk of renal flares and renal function decline. Adjunctive therapies such as vigorous control of blood pressure to less than 120/80mmHg may retard the deterioration of renal function. The early use of renal protection agents such as the angiotensin converting enzyme inhibitors (ACEIs) and the angiotensin II receptor antagonists is mandatory. Hyperlipidemia should also be aggressively controlled to offer protection against accelerated vascular disease, especially in the membranous type of lupus nephritis. Calcium and vitamin D should be adequately supplemented to reduce the risk of aggravation of disease activity related to vitamin D deficiency, and to protect against loss in bone mineral density. Low-dose aspirin should be considered in patients with histological evidence of antiphospholipid syndrome nephropathy, although there is still no published evidence that this will protect against renal function decline. Anticoagulation may be considered in patients with persistent nephrotic range of proteinuria and the presence of the antiphospholipid antibodies.

8. Induction therapy for lupus nephritis

Milder form of lupus nephritis (ISN/RPS Class I, II) is usually manageable with corticosteroids (Mok, 2010b). Azathioprine (AZA) can be added as a corticosteroid sparing agent and for the treatment of concomitant extra-renal manifestations. Mild class V disease can be treated with ACEIs. Proliferative lupus nephritis (class III and IV or mixed III/V and IV/V) and more serious class V (nephrotic range of proteinuria or deteriorating renal

function) disease requires more aggressive induction regimens consisting of corticosteroids and a non-corticosteroid immunosuppressive agent.

The standard therapy for severe proliferative lupus nephritis has been a combination of high-dose glucocorticoid and cyclophosphamide (CYC). From the series of randomized controlled trial conducted by the National Institute of Health (NIH), it was demonstrated that prednisone combined with intravenous (IV) pulse CYC offered better long-term protection against renal function decline than prednisone alone (Austin, 1986; Gourley, 1996; Illei, 2001). However, the use of CYC is associated with a number of untoward side effects, which include infection, ovarian and bladder toxicities, leukopenia, increased risk of cervical intraepithelial neoplasia and malignancy. Some of these toxicities are dose dependent, with a higher risk related to a higher cumulative dose (Mok, 1998). IV pulse CYC has gained popularity over continuous daily oral CYC because it is associated with less toxicity on the bladder and the gonads. Whether oral CYC is more efficacious than IV pulse CYC in lupus nephritis remains controversial because of the lack of large controlled trials (Austin, 1986; Mok, 2001). A recent analysis of a large cohort of patients with diffuse proliferative lupus nephritis showed a trend of better efficacy of oral CYC than IV pulse CYC in preserving renal function after a mean follow-up of 8.8 years (Mok, 2006b). In a multivariate model, the cumulative dose of CYC delivered instead of the route of CYC was an independent factor for a complete renal response. This suggests that the higher potency of the oral CYC regimen is probably related to the higher cumulative dose delivered instead of the route of administration per se. However, ovarian toxicity leading to premature menopause was more frequent in users of oral CYC.

Although the optimal route of CYC and duration of therapy in lupus nephritis remains to be defined, recent evidence supports the use of a shorter course and lower dose of CYC to minimize toxicities (Mok, 2001; Mok, 2002; Houssiau, 2010a). Houssiau et al. (2010a) compared the efficacy and toxicity of two less intensive intravenous pulse CYC regimens for the initial treatment of lupus nephritis. Eighty-four patients (predominantly Caucasians) were randomized to receive either 8 intravenous pulses of CYC (0.5g/m² to a maximum of 1.5gm) or 6 biweekly low dose pulses of CYC (500mg each). In both regimens, CYC was later substituted with AZA for long-term maintenance. Patients who participated in the study had milder renal disease compared to other lupus nephritis trials, as reflected by a lower proportion of patients having class IV disease, nephrotic syndrome and renal function impairment. After 10 years, rates of mortality, sustained doubling of serum creatinine and end stage renal disease did not differ between the two groups (36). The incidence of cardiovascular events and was also similar. Cancers, however, were numerically more common in patients who had received the low-dose regimen. Thus, for less serious lupus nephritis, a low-dose CYC regimen, followed by AZA is a viable strategy if there are no alternatives to CYC for initial treatment.

Nevertheless, CYC remains the treatment of choice for high-risk patients with proliferative lupus nephritis such as those with impaired or rapidly deteriorating renal function, histological cellular crescents or a combination of high activity and chronicity scores (Tang, 2009). The course of CYC should be limited to less than 6 months, with subsequent replacement by another immunosuppressive agent, to reduce the incidence of toxicities (Mok, 2002).

9. Recent controlled trials for induction therapy of severe lupus nephritis

Six randomized controlled trials comparing the efficacy and adverse effects of different treatment protocols for the induction therapy of severe lupus nephritis have recently been

presented (Appel, 2009; Grootscholten, 2006, Bao, 2008; Chen, 2011; Mok, 2008; Furie, 2009). These are briefly summarized in Table 2.

In the largest lupus nephritis controlled trial to-date, called the Aspreva Lupus Management Study (ALMS), 370 patients with histologically ISN/RPS class III, IV or V lupus nephritis were randomized to receive either monthly IV pulse CYC (0.5-1.0g/m^2) or MMF (target 3g/day) on top of high-dose prednisone (60mg/day initially and then tapered) (Appel, 2009). Two-third of the participants had class IV disease. Asians and Hispanics comprised 33% and 35% of the participants, respectively. Three hundred and six (83%) patients completed the 24-week protocol. Clinical response, defined by a decrease in urine protein/creatinine ratio (P/Cr) to <3 in patients with baseline nephrotic range P/Cr ≥3, or by ≥50% in patients with subnephrotic baseline P/Cr (<3), and stabilization (±25%) or improvement in serum creatinine at 24 wk as adjudicated by a blinded clinical endpoints committee, was not significantly different between the CYC (53%) and MMF (56%) group. Subgroup analyses revealed that MMF was associated with a significantly higher response rate than CYC (60% vs 39%; p=0.03) in the non-Caucaisan non-Asians, which were mainly Hispanics. The rates of adverse events and serious adverse events were not significantly different between the two groups. Specifically, nausea, vomiting and alopecia were numerically more frequent in the CYC group, whereas diarrhea was more commonly reported in the MMF group. The induction phase of the ALMS study did not allow comparison of long-term side effects such as sustained amenorrhea and malignancies. There were 9 and 5 deaths in the MMF and CYC group, respectively. Of the 9 deaths in the MMF group, 7 were Asians (mainly Chinese), suggesting that Asian patients tolerated high-dose prednisone and MMF (3g/day) less well.

A controlled trial comparing the efficacy of CYC and azathioprine (AZA) in lupus nephritis was reported by Grootscholten et al. (2006). In this study, 87 patients with proliferative lupus nephritis (class III and IV) were randomized to receive either oral prednisone combined with intravenous pulse CYC (750mg/m^2 monthly for 6 months and then quarterly for another 7 doses) or intravenous pulse methylprednisolone (1 gram daily for 3 days for 9 pulses) together with AZA (2mg/kg/day). At the end of the third year, both groups of patients received AZA for long-term maintenance (2mg/kg/day). The dosage of AZA was reduced to 1mg/kg/day after 4 years of treatment. This cohort of patients consisted mainly of Caucasian patients (76%) who had serious renal disease as evidenced by a high proportion of patients having hypertension (57%), nephrotic syndrome (53%) and impaired creatinine clearance (56%) at presentation. In the first 2 years, no significant difference in the rates of complete and partial renal remission could be demonstrated between the two regimens. After a median follow-up of more than 5 years, significantly more patients in the AZA arm relapsed and there was a trend of higher incidence of doubling of serum creatinine in the AZA-treated patients. Interestingly, the incidence of herpes zoster infection was lower in the CYC than AZA arm during the first two years of treatment.

Although this was a randomized controlled trial, the number of patients assigned to the two treatment arms was unequal (50 patients in the CYC arm vs 37 patients in the AZA group). The corticosteroid regimens of the two treatment arms were also different, which confounded a proper interpretation of whether CYC was more effective than AZA by its own. However, taking the observation that relapse of nephritis and renal function decline was more common in AZA-treated patients despite the use of a more intensive corticosteroid regimen, it was not unreasonable to conclude for the superiority of CYC over AZA in the treatment of severe lupus nephritis.

Author, year	N	Study duration	Histological classes of lupus nephritis	Steroid regimen	Comparators	Primary end points	Adverse events
Houssiau, 2010a	84	10 yrs	WHO III, IV, Vc,Vd	Prednisolone (0.5mg/kg/d) for 4wks, then taper to 5-7.5mg/d for at least 30mths	IV CYC (0.5g/m² to a max of 1.5g) monthly for 8 doses vs 6 biweekly low dose pulses of 500mg, followed by AZA in both	Rates of mortality, sustained doubling of serum creatinine and end stage renal disease similar between the two groups	Cardiovascular events similar; but cancers were numerically more common in the low dose CYC group
Appel, 2009	370	24 wks	ISN/RPS III,IV,V	Prednisolone 60mg/day then taper	IV CYC (0.5-1.0g/m²) monthly for 6 doses vs MMF (3g/d)	Clinical response similar at 6 months; MMF higher reponse rate than CYC in non-Caucasians non-Asians	Nausea, vomiting and alopecia more common in CYC group; diarrhea more common with MMF; numerically more deaths in MMF group
Grootscholten, 2006	87	5.7 yrs	WHO III, IV, Vc, Vd	Prednisone 1mg/kg/day, tapered to 10mg/d after 6 mths vs IV MP for 9 doses + prednisone 20mg/d and taper	IV CYC (750mg/m²) monthly for 6 then 3-monthly for another 7 doses followed by AZA vs AZA (2mg/kg/d) following pulse MP	Complete and partial response rate similar at 2 years; at 5 years, significantly more relapses in AZA group with a higher incidence of doubling of serum creatinine	More herpes zoster in the AZA group than CYC; major infection rate similar; more ovarian toxicities in the CYC-treated patients
Bao, 2008	40	9 mths	Mixed IV+V	Pulse MP (0.5g/day x 3d) + prednisolone (0.6-0.8mg/kg/day) then taper	IV CYC (0.5-1g/m²/ monthly for 9 months) vs MMF (1g/d) + Tac (4mg/d)	Complete response rate significantly higher in MMF + Tac than CYC group at 6 and 9 mths	Gastrointestinal upset, leucopenia, alopecia, menstrual irregularities and upper respiratory tract infection more common in CYC group
Chen, 2011	81	6 mths	ISN/RPS III,IV,V	Prednisolone (1mg/kg/d) then taper	IV CYC (0.5-1g/m²/ monthly for 6 months) vs Tac (0.05mg/kg/d) titrating to a level of 5-10ng/ml	Clinical response at 6 months similar between the two groups	Infection rate similar; more leucopenia and gastrointestinal upset with CYC
Mok, 2008	130	6 mths	ISN/RPS III,IV,V	Prednisolone (0.6mg/kg/d) then taper	MMF (2-3g/d) vs Tac (0.1-0.06mg/kg/d)	Clinical response similar at 6 months	Herpes zoster more common with MMF; alopecia, tremor and reversible increase in serum creatinine more common with Tac
Furie, 2009	144	52 wks	ISN/RPS III,IV	High-dose prednisone	MMF (2-3g/d) in both; rituximab x 2 courses (1g x2 each course) vs placebo	Clinical efficacy similar at 52 wks	Infection rate and major infection rate similar between the two groups

Yrs = years; mths = months; CYC = cyclophosphamide; MMF = mycophenolate mofetil; AZA = azathioprine; Tac = tacrolimus

Table 2. Recent randomized controlled trials of induction therapy for lupus nephritis

Bao et al. (2008) studied 40 patients with mixed proliferative and membranous lupus nephritis (ISN/RPS IV+V) by randomizing them to receive either IV pulse CYC (0.5-1g.m^2 monthly) (N=20) or low-dose combination of MMF (500mg BD) and tacrolimus (Tac) (2mg BD) (N=20), on top of high-dose prednisolone (0.6-0.8mg/kg/day) after 3 daily pulses of methylprednisolone (0.5g). The mean creatinine clearance at recruitment was 97.6ml/min and 85% patients had normal serum creatinine level. At 6 months, the rate of complete response, defined as daily proteinuria <0.4g/day with normal urinary sediments and stabilization of serum creatinine (<15% increase), was significantly higher in the MMF / Tac group (50%) than the CYC group (5%). The corresponding rates at 9 months of treatment were 65% and 15%, respectively. Leukopenia, gastrointestinal upset, upper respiratory tract infection, alopecia and irregular menses were more common in the CYC than MMF/Tac group of patients.

A randomized controlled trial comparing the short-term efficacy of IV pulse CYC with tacrolimus (Tac) in lupus nephritis were recently presented (Chen, 2011). In this study, 81 patients with class III, IV or V lupus nephritis were randomized to receive IV pulse CYC (0.5-1g.m^2 monthly) (N=39) or Tac (0.05mg/kg/day titrating to a level of >5ng/mL) (N=42) in combination with high-dose prednisolone (1mg/kg/day). The study population consisted of moderate to high-risk patients as shown by a high proportion of class IV disease (77%) and impaired renal function (11%) at presentation. At 6 months, the rate of complete remission, which was defined as proteinuria <0.3g/day, stabilization of serum creatinine and normalization of urinary sediments, was not significantly different between the CYC and Tac group of patients (38% vs 52%, p=0.2). Regarding adverse events, gastrointestinal upset and leucopenia were significantly more frequent in the CYC group but the rate of infection was similar between the CYC- and Tac-treated patients. Transient increase in serum creatinine was reported in 8% of patients receiving Tac.

Our group has conducted a controlled trial comparing the efficacy of MMF (2g/day, titrating to 3g/day if response suboptimal at 3 months) with Tac (0.1mg/kg/day in first 2 months with tapering to 0.06mg/kg/day) in combination of high-dose prednisolone (0.6mg/kg/day for 6 weeks and taper) for lupus nephritis (Mok, 2008). Up to March 2011, 130 patients with ISN/RPS class III, IV or V lupus nephritis were recruited. Our preliminary analysis showed that the clinical complete and partial response rates were not significantly different between the two treatment arms at month 6. The rate of infection, in particular herpes zoster reactivation, was higher in MMF than Tac-treated patients, whereas alopecia, tremor and reversible increase in serum creatinine was more frequent in the Tac group of patients. Dose-related neurological and metabolic adverse effects of Tac, and the possibility of early renal relapse upon completion of the induction phase and substitution of Tac have to be carefully monitored.

The LUNAR study is a phase III randomized, double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of rituximab in patients with active proliferative lupus nephritis (Furie, 2009). Patients with ISN/RPS Class III or IV lupus nephritis and urine protein to creatinine (UP/Cr) ratio >1 were randomized to receive rituximab (1000mg) or placebo infusion on days 1, 15, 168 (week 24) and 182 (week 26), on top of corticosteroid and MMF (>2g/day). Seventy-two patients were recruited in each treatment arm. Two-third of the patients had class IV nephritis and the mean UP/Cr at entry was 4.0±2.8. At week 52, no statistically significant differences in the primary and secondary endpoints were observed between the rituximab and placebo groups of patients, although there were numerically more responders in the rituximab group (57% vs 46% in the placebo group). Africans and Hispanics treated with rituximab tended to have better response compared to

placebo than the Whites. Rituximab had a greater effect than placebo on anti-dsDNA and complement levels at week 52. Serious adverse events and infection rates were similar between the two groups but two deaths occurred in the rituximab-treated patients.

Taken the evidence from these recent studies together, it appears that MMF should be used as the first line treatment in combination with corticosteroids for severe lupus nephritis because of its stronger evidence (largest sample size) compared to other agents and lower incidence of toxicities compared to conventional CYC. Although Tac has similar efficacy with either CYC or MMF, it has been tried in a smaller population of patients and disadvantages such as transient and long-term nephrotoxicity, as well as higher relapse rate upon substitution with another immunosuppressive agent are of concern. However, Tac is a definite option when patients are contraindicated for or intolerant to MMF. Moreover, Tac is indicated as salvage therapy for refractory lupus nephritis. Tac is preferred to cyclosporin A for the lower incidence of cosmetic side effects. The initial results of the B cell depleting agents such as rituximab are disappointing. Although evidence does not support an additional benefit of rituximab on top of MMF treatment for lupus nephritis, rituximab is an option to be considered in recalcitrant lupus nephritis, as evidenced by a number of uncontrolled case series (Jonsdottir, 2010; Melander, 2009; Vigna-Perez, 2006).

10. Maintenance therapy for lupus nephritis

There are no randomized controlled trials with the main objective of delineating whether maintenance therapy of lupus nephritis is effective or not. However, some indirect evidence suggests that maintenance therapy is probably necessary in severe lupus nephritis. In a long-term follow-up of 145 patients who participated in the NIH lupus nephritis studies, renal flares occurred in 45% of the patients when immunosuppression was completely stopped (Illei, 2002). A recent retrospective review of 32 patients with predominantly diffuse proliferative lupus nephritis described a relapse of lupus activity in 53% of patients after immunosuppression was discontinued (Moroni, 2006). In our experience with 212 patients with diffuse proliferative lupus nephritis (Mok, 2006b), despite maintenance treatment was given to 73% of patients, more than one-third of patients still had renal flares which might be serious. The use of maintenance therapy for more than 3 years was independently associated with an increased likelihood of having the composite outcome of doubling of serum creatinine, end stage renal failure or death (hazard ratio 4.62 [1.35-15.8]; p=0.02).

In a 2006 retrospective review of 32 patients with proliferative lupus nephritis in whom immunosuppressive therapy was stopped for a median of 203 months, clinical remission persisted in 47% of patients (Moroni, 2006). Patients who experienced sustained remission had received a longer total median duration of immunosuppressive treatment since renal biopsy than those who did not experience remission (median 57 months vs 30 months; $p<0.01$). This finding, coupled with the observation that maintenance treatment for less than 3 years after successful cyclophosphamide induction was a predictor of poor renal outcome in proliferative lupus nephritis (Mok, 2006b), suggests that maintenance immunosuppressive therapy should be continued for at least 3 years after a complete clinical response is achieved.

Four recent randomized controlled trials compare the efficacy of different immunosuppressive agents in maintaining remission in lupus nephritis (summarized in Table 3). Contreras et al. (2004) randomized 59 patients with lupus nephritis (mainly African and Hispanic Americans; 78% had class IV disease) to receive one of the three treatment arms after induction with 4-7 pulses of intravenous CYC: (1) MMF (0.5-3g/day); (2) quarterly pulse CYC; (3) AZA (1-

3mg/kg/day). Long-term observation showed that either MMF or AZA was superior to CYC in the prevention of the composite outcome of renal failure and death. MMF was more efficacious than pulse CYC in the prevention of renal flares. Moreover, maintenance treatment with CYC was associated with more side effects such as nausea, vomiting and infection. Although the sample size is small, this study shows that maintenance treatment of lupus nephritis with either AZA or MMF is safe and effective. However, whether MMF is more cost-effective than AZA is not clear because significant difference in all outcomes is not apparent between MMF- and AZA-treated patients. Moroni et al. (2006) studied 69 patients (mainly Caucasians) with lupus nephritis and compared the efficacy of cyclosporin A (CSA) with AZA for maintenance therapy. After initial induction treatment with pulse methylprednisolone, prednisone and oral CYC (91.5±23.8 mg/day for a median of 3 months), patients were randomized to receive either cyclosporin A (Neoral; 4.0 to 2.5-3.0mg/kg/day) (N=36) or AZA (2mg/kg/day) (N=33) for maintenance. At 4 years of follow-up, flare occurred in 24% of AZA-treated and 19% of CSA-treated patients, respectively (no significant difference). Minor infections and leucopenia were more commonly reported with AZA treatment whilst arthralgia and gastrointestinal symptoms were more common in CSA-treated patients.

Author, year	N	Follow-up duration	Histological classes of lupus nephritis	Induction regimen	Comparators	Primary end points	Adverse events
Contreras, 2004	59	Beyond 5 yrs	WHO III, IV, Vb	IV CYC (0.5-1g/m²) for 4-7 pulses	IV CYC (0.5-1g/m²) every 3 months vs MMF (0.5-3g/d) vs AZA (1-3mg/kg/d)	Renal flare and renal function deterioration was significantly more common with CYC than MMF; MMF no better than AZA in the above outcomes	Nausea, vomiting, major infection rate and sustained amenorrhea more common with CYC than the other 2 groups
Moroni, 2006	69	4 yrs	Class IV nephritis	Pulse MP + high dose prednisone + oral CYC for 3 mths	CSA (4mg/kg/d) and taper to 2.5-3mg/kg/d vs AZA 2mg/kg/d	7 flares in CSA (19%) vs 8 flares in AZA (24%) group; reduction in proteinuria, blood pressure and creatinine clearance similar in both groups	Gum hypertrophy, hypertrichosis, hypertension, arthralgia, gastrointestinal symptoms more common with CSA; Infections and leucopenia more common with AZA
Houssiau, 2011	105	53 mths	WHO class III, IV, Vc, Vd	Pulse MP + high dose prednisone + IV CYC (500mg) x 6 doses	AZA (2mg/kg/d) vs MMF (2g/d)	Frequency of renal and extra-renal flares, doubling of serum creatinine similar in both groups	Infection rate similar; but drug-related cytopenias more common with AZA; withdrawal due to pregnancy wish more common with MMF
Wofsy, 2010	227	2.1 yrs	ISN/RPS III,IV,V	High dose prednisone + either IV CYC (6 pulses) or MMF (3g/d) x 6 mths	AZA (2mg/kg/d) vs MMF (2g/d)	Treatment failure, defined as the composite outcome of renal flares, doubling of serum creatinine or end stage renal failure, death or need for rescue therapy significantly less common in MMF than AZA group	No information yet

Yrs = years; mths = months; CYC = cyclophosphamide; MMF = mycophenolate mofetil; AZA = azathioprine; CSA = cyclosporin A

Table 3. Recent randomized controlled trials of maintenance therapy for lupus nephritis

In the MAINTAIN study conducted by Houssiau et al. (2010b), 105 patients with class III, IV, Vc and Vd lupus nephritis were randomized to receive either MMF (2g/day) (N=53) or AZA (2mg/kg/day) (N=52) after an initial induction regimen that consisted of IV pulse methylprednisolone, high-dose prednisone and IV pulse CYC (500mg 2-weekly for 6 doses). Participants were mainly Caucasians and 10% of patients had impaired renal function at study entry. After a mean follow-up of 53 (15-65) months, 24 (23%) patients withdrew from the study mainly because of pregnancy wish (in the MMF group) and adverse effects. Frequency of renal and extra-renal flares, doubling of serum creatinine and incidence of infections occurred at similar frequency in the two arms. However, drug-related cytopenias were more common with AZA.

Results of the maintenance phase of the ALMS study was released in the 9th International Lupus Congress at Vancouver in 2010 (Wofsy 2010). Two hundred and twenty-seven patients who had completed the induction phase of the ALMS (IV pulse CYC or MMF 3g/day) were randomized to receive either MMF (2g/day) (N=116) or AZA (2mg/kg/day) (N=111) for maintenance treatment. The mean daily doses received by the patients were 1.87±0.43g and 120±48mg, respectively, for MMF and AZA. After a mean follow-up of 2.1 years, the rate of treatment failure, defined as renal flare, doubling of serum creatinine or end stage renal disease, need for rescue therapy or death, was significantly less common in MMF than AZA-treated patients. The results were similar in patients induced by CYC or MMF at recruitment.

Taken these studies together, it appears that MMF is the preferred agent for long-term maintenance therapy for lupus nephritis. However, the cost-effectiveness of this approach has to be evaluated in future analysis. AZA and CSA are alternative options for patients who are intolerant to MMF or plan for pregnancy. The long-term use of the calcineurin inhibitors such as Tac and CSA is not encouraged because of the increased risk of nephrotoxicity, hyperlipidemia and atherosclerosis.

11. Membranous lupus nephropathy

Membranous lupus nephropathy (MLN), defined as global or segmental continuous granular subepithelial immune deposits, often in the presence of mesangial immune deposits and mesangial hypercellularity, comprises only one-fifth of all cases of histologically confirmed lupus nephritis (Mok, 2009). Reported rates of patient survival and end-stage renal disease in MLN vary considerably, because of substantial heterogeneity among the published studies. The risk of progression of MLN to renal failure is generally reduced in the absence of proliferative lesions, but patients are nevertheless at risk of thromboembolic complications.

The optimal therapy for MLN remains elusive because of the paucity of clinical trials. Mixed membranous and proliferative lupus nephritis should be treated in the same way as pure proliferative lupus nephritis. If MLN is not accompanied by proliferative lesions but is associated with clinically relevant proteinuria, renal insufficiency or failure to respond to supportive therapies, immunosuppressive treatment is indicated. In addition, cardiovascular protection and blockade of the renin-angiotensin system should be instituted early in all patients.

Austin et al. (2009) randomized 42 patients (71% Blacks or Hispanics) with MLN to receive one of the following regimens: (1) alternate day prednisone (1mg/kg/day for 8 weeks and taper to 0.25mg/kg/day throughout); (2) similar prednisone regimen plus IV pulse CYC (0.5-1.0g/m^2

every two months); or (3) similar prednisone regimen plus CSA (5mg/kg/day). At 12 months, the cumulative probability of complete (<0.3g/day proteinuria) or partial (<2.0g/day proteinuria or improvement by 50% from baseline) remission was highest with CSA (83%), followed by IV pulse CYC (60%) and prednisone alone (27%). The response rates of either CSA or CYC were significantly better than prednisone alone. However, relapse of nephrotic syndrome was significantly more common after discontinuation of treatment with CSA than IV pulse CYC. Adverse effects during the 12-month period included insulin-requiring diabetes (one with prednisone and two with CsA), pneumonia (one with prednisone and two with CsA), and localized herpes zoster (two with IVCY).

A recent pooled analysis of 65 patients with pure membranous lupus nephritis recruited for two randomized controlled trials and completed 24 weeks of treatment (Ginzler, 2005; Appel, 2009) showed that there were no differences in the measured end points, response rate, mortality and withdrawal rate between MMF and IV pulse CYC (Radhakrishnan, 2010). There was also no difference in the change in proteinuria or partial response rate between MMF and CYC in those patients presenting with nephritic syndrome.

Therefore, similar to the proliferative types of lupus nephritis, more serious MLN should be treated with a combination of glucocorticoids and non-glucocorticoid immunosuppressive agent. A number of uncontrolled series have reported efficacy of various regimens for MLN such as AZA, tacrolimus and MMF in combination with glucocorticoids (Mok, 2009). Taken these together, possible options for MLN include MMF, IV pulse CYC, CSA, AZA and tacrolimus. Many specialists will start with MMF or AZA for their lower incidence of adverse effects, reserving other agents for salvage therapy when the clinical response is not optimal. Controlled trials comparing existing immunosuppressive agents and experimental modalities such as rituximab, infliximab and sirolimus should be undertaken in the future (Jonsdottir, 2011).

12. Refractory lupus nephritis

There is no international consensus on the definitions of remission and treatment refractoriness in lupus nephritis. In the absence of reliable and readily available biomarkers for ongoing activity / inflammation in the kidneys and histological / immunological data from routine post-therapy renal biopsy, true remission of lupus nephritis is difficult to define. Despite the discrepancies in the clinical criteria used, up to 20% of patients with lupus nephritis are reported to be resistant to initial immunosuppressive therapy (Mok, 2006a). They are more likely to be patients with multiple unfavorable prognostic factors such as the African ethnicity, delayed institution of CYC, poor treatment compliance, impaired serum creatinine, severe nephrotic syndrome, arterial hypertension at presentation, and the presence of active crescents and a higher degree of chronicity in renal histology (Mok, 2005b).

Using the similar renal response criteria as suggested by the NIH investigators (Boumpas, 1998), we reported that 14% of a cohort of 212 patients with diffuse proliferative lupus nephritis did not respond to either continuous oral or intermittent pulse CYC therapy at the end of the induction courses (Mok, 2006b). The failure to respond to immunosuppressive treatment in the first year is associated with increased risk of renal function decline and the development of end stage renal disease (Mok, 1999).

Controlled trials in refractory lupus nephritis are unavailable. Open-labeled studies have reported success of newer immunosuppressive drugs, immunomodulatory therapies and

the biological agents such as MMF, calcineurin inhibitors (CSA and tacrolimus), leflunomide, intravenous immunoglobulin, immunoadsorption and rituximab in the treatment of CYC-refractory lupus nephritis. More aggressive CYC regimens such as daily oral CYC and the immunoablative CYC protocol have been used in lupus nephritis, but at the expense of more toxicities (Petri, 2010). Novel biological agents that are undergoing clinical trials in renal and non-renal lupus include epratuzumab, ocrelizumab, belimumab, abatacept and atacicept (summarized in Table 4) (Mok, 2010c).

B cell depletion
Fludarabine, rituximab, epratuzumab, ocrelizumab, belimumab, atacicept
B cell tolerization
Abetimus sodium
Blockade of the co-stimulatory pathways
Abatacept (CTLA4-Ig)
Neutralization of cytokines
IL-10, TNF, IL-6, type I interferons
Anti-complement
anti-C5b (eculizumab)

Table 4. Biological therapies for renal and non-renal lupus

13. Biomarkers for lupus nephritis

Current laboratory markers for lupus nephritis such as proteinuria, urine protein-to-creatinine ratio, creatinine clearance, anti-dsDNA and complement levels are unsatisfactory. They lack sensitivity and specificity for differentiating renal activity and damage in lupus nephritis. Significant kidney damage can occur before renal function is impaired and first detection by laboratory parameters. Persistent proteinuria may not necessarily indicate ongoing inflammation in the kidneys; and may be contributed by pre-existing chronic lesions or recent damage in the kidneys during the course of the disease. Flares of nephritis can occur without any observable and recent increase in the degree of proteinuria. Renal biopsy is the gold standard for providing information on the histological classes of lupus nephritis and the relative degree of activity and chronicity in the glomeruli. However, it is invasive and serial biopsies are impractical in the monitoring of lupus nephritis. Thus, novel biomarkers that are able to discriminate lupus renal activity and its severity, predict renal flares, monitor treatment response and disease progress, and stratify prognosis are necessary.

A biomarker refers to a biologic, biochemical or molecular event that can be assayed qualitatively and quantitatively by laboratory techniques. An ideal biomarker for lupus nephritis should possess the following properties: (1) Good correlation with renal activity as reflected by the degree of proteinuria and urine sediments; (2) Sensitive to change so that it can be used for serial monitoring of disease activity in the kidneys and defining treatment response and clinical remission; (3) Ability to predict renal activity / flares before an obvious change in conventional clinical parameters occurs so that early treatment / preventive strategies can be considered; (4) Specific to nephritis among patients with SLE; and (5) Specific to SLE for aiding early diagnosis of lupus nephritis. In addition, a useful biomarker should be easy to assay, simple to interpret and readily available in most laboratories with a reasonable cost.

Hitherto, quite a number of serum and urine biomarkers have been studied in lupus nephritis (summarized in Table 5). Many of these markers have only been tested in cross-sectional studies with small sample size, and none has been rigorously validated in large-scale longitudinal cohorts of patients with different ethnic background. It is unlikely at this juncture that a candidate biomarker stand-alone can replace conventional clinical parameters to monitor disease progress and detect early renal flares. Urine biomarkers appear to be more encouraging than serum biomarkers possibly because they are the direct products or consequences of kidney inflammation or injury. Future directions in SLE biomarker research should focus on a combination of novel markers with conventional clinical parameters to enhance the sensitivity and specificity for the prediction of renal flares and prognosis in lupus nephritis (Mok, 2010a).

Urinary monocyte chemoattractant protein-1 (uMCP-1)
Plasma and urine neutrophil gelatinase–associated lipocalin (NGAL)
Urinary tumor necrosis factor (TNF)-like inducer of apoptosis (uTWEAK)
Urine proteomics
Hepcidin
Anti-C1q antibodies
Anti-nucleosome antibodies
Anti-α-actinin antibodies
MAGE-B2 antibodies
Anti-CRP antibody
Serum and urine IL-12
Peripheral blood leukocyte chemokine transcriptional levels
Serum apoCIII
Serum ICAM-1
Anti-endothelial cell antibody
Urine osteoprotegerin (OPG)
FOXP3 mRNA expression in urinary sediments
Urine endothelin-1
Urine CXCR3+CD4+T cells
Urine VCAM-1, P-selectin, TNFR-1 and CXCL16
Urine TGFβ-1
TGFβ and MCP-1 mRNA expression in urine sediments
Chemokine and growth factor mRNA level in urinary sediments
Serum nitrate and nitrite level
Anti-ribosomal P antibody
Urine glycoprotein panel

Table 5. Novel biomarkers for lupus nephritis

14. Conclusions

Renal involvement is a major determinant of the prognosis of SLE. Lupus renal disease is more frequent in certain ethnic groups such as the Africans, Hispanics and Asians. Of the various histological types of lupus nephritis, diffuse proliferative lupus nephritis carries the worst prognosis. Treatment of lupus nephritis should target at disease remission, prevention of relapse and complications, and long-term preservation of renal function. The main stay of

treatment of lupus nephritis is immunosuppression using a combination of high-dose glucocorticoid and a non-glucocorticoid immunosuppressive agent. Mycophenolate mofetil combined with prednisone has emerged to be the standard regimen. Intravenous pulse or daily oral cyclophosphamide is reserved for more serious or refractory cases of lupus nephritis. The evidence for calcineurin inhibitors in lupus nephritis is less strong and these agents are reserved for patients intolerant or recalcitrant to standard therapies. B cell modulation is emerging as novel therapeutic modalities for lupus nephritis. While further evidence from controlled trials is eagerly awaited, the current use of B cell modulating agents is confined to recalcitrant lupus renal disease. Conventional markers for activity of lupus nephritis are neither sensitive nor specific. Novel biomarkers are being studied for earlier detection of renal flares and better prognostic stratification so that intervention can be instituted early to minimize damage to renal function.

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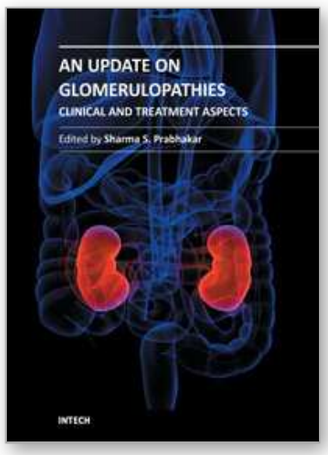

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An Update on Glomerulopathies - Clinical and Treatment Aspects is a systemic overview of recent advances in clinical aspects and therapeutic options in major syndromes of glomerular pathology. The book contains twenty four chapters divided conveniently into five sections. The first section deals with primary glomerulopathies, and the second section is devoted to glomerulopathies complicating infectious conditions. The third section deals with systemic autoimmune disorders and vasculitides which constitute major causes of glomerular disease and often renal failure. The fourth section includes chapters discussing the glomerular involvement in some major metabolic and systemic conditions. The final section has chapters which relate to some general aspects of glomerular diseases. This book will form an excellent reference tool for practicing and academic nephrology community.

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