21.10.3 The kidney in rheumatological disorders 50

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21.10.3 The kidney in rheumatological disorders 5001 Yates M, et al. (2016). EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis, 75, 1583–94. Zonozi R, Niles JL, Cortazar FB. (2018). Renal involvement in antineutrophil cytoplasmic antibody-associated vasculitis. Rheum Dis Clin North Am, 44, 525–43. 21.10.3 The kidney in rheumatological disorders Liz Lightstone and Hannah Beckwith ESSENTIALS Many rheumatological conditions have systemic effects. Antibody production, complement activation, and protein deposition can all result in damage to the kidney, sometimes with devastating sequelae. Systemic lupus erythematosus Lupus nephritis is clinically evident in up to 75% of patients with systemic lupus erythematosus (SLE) and end stage renal disease (ESRD) occurs in 5 to 10% of patients at 10 years. Proteinuria is the most common clinical presentation, closely followed by nonvisible haematuria and tubular abnormalities. Patients with active lupus nephritis often have features of active SLE. The gold standard for lupus nephritis diagnosis is a renal biopsy, with treatment related to histopathological features observed. Class I (minimal mesangial) and II (mesangial proliferative) lesions are generally associated with a good prognosis; treatment is usually determined by extrarenal manifestations. First-line renal treatment would be renin–angiotensin system blockade to reduce proteinuria. Class III (focal proliferative) and IV (diffuse proliferative) lesions are the most common renal manifestations of SLE. Prior to modern immunotherapy, patient and kidney survival

was poor. Treatment for these classes of lupus nephritis has induction and mainten- ance phases: initially a rapid reduction in kidney inflammation is sought with intensive immunotherapy (often cyclophosphamide or mycophenolate mofetil (MMF) based). Once this has been attained, maintenance therapy is commenced (MMF/azathioprine) with the aim of maintaining disease remission and minimizing treatment side effects. Class V (membranous) lupus nephritis is associated with the
development of chronic kidney disease and ESRD, particularly if there is marked proteinuria. Treatment is generally as for class III and IV, although there is a less secure evidence base for this. Adjunctive immunosuppressive agents such as rituximab and tacrolimus are emerging as increasingly important lupus nephritis therapies. Systemic sclerosis Systemic sclerosis is a multiorgan connective tissue disease. Most renal manifestations are clinically silent. By contrast, the scleroderma renal crisis is characterized by accelerated-phase hypertension and impaired renal function. It carries a high mortality risk. Rheumatoid arthritis Rheumatoid arthritis can affect the kidneys in many ways, most commonly by causing amyloid A amyloidosis. This presents with proteinuria, often severe enough to cause nephrotic syndrome, with 50% progressing to ESRD after 5 years (90% at 10 years). Renal vasculitis, mesangiocapillary glomerulonephritis, and mesangial IgA proliferative glomerulonephritis are also described. Gold and penicillamine (now rarely used) can cause proteinuria, sometimes with nephrotic syndrome. Sjögren's syndrome Renal involvement in Sjögren's syndrome is generally mild, but up to a quarter of patients develop acute or chronic kidney disease, typically with evidence of tubular dysfunction. Glomerular abnor- malities are rare and the most common histological abnormality is tubulointerstitial nephritis. Drug nephrotoxicity Conventional anti-rheumatics and over-the-counter nonsteroidal anti-inflammatory drugs are used exceptionally widely in the com- munity and are nephrotoxic. Their almost ubiquitous use, especially during intercurrent illnesses, means they are frequent contributors to acute and chronic kidney damage. Systemic lupus erythematosus/lupus nephritis Lupus nephritis is clinically evident in up to 75% of patients with systemic lupus erythematosus, a multisystem disease characterized by the presence of antinuclear autoantibodies (ANA) (see Chapter 19.11.2). Lupus nephritis ranges from mild, asymptomatic subclinical disease, to rapidly progressive nephritic and or/nephrotic syndromes, with end stage renal disease (ESRD) seen in 5 to 10% of patients with systemic lupus erythematosus (SLE) at 10 years. The prognosis of lupus nephritis has improved considerably with the advent of effective antihypertensive medication, immunosuppression, antibiotics, dia- lysis and transplantation, but renal failure and cardiovascular dis- ease remain important determinants of morbidity and mortality. Pathophysiology Renal damage seen in lupus nephritis is multifactorial and involves both immune-mediated and nonimmune-mediated pathways. Defective clearance of apoptotic cells and autoreactive T cells results in persistent exposure of self-antigens with subsequent development of autoimmunity. This loss of immunological tolerance then leads to increased production of autoreactive cells driving inflammation, either through direct infiltration (T cells, macrophages) and/or through production of autoantibodies or cytokines, antibody depos- ition, cellular infiltration, and proliferation. Further stimulation of inflammatory, fibrogenic processes perpetuates disease progression, along with the presence of hypertension and proteinuria. Structural maladaptations that result from lupus nephritis can also cause glomerular hypertension, activation of the renin–angiotensin– aldosterone system, and hyperlipidaemia. Subsequent upregulation

 of proinflammatory cytokines, progressive glomerulosclerosis, and interstitial fibrosis leads to a further reduction in functioning

nephron mass, increasing the risk of further renal damage. Thus a vicious cycle of inflammation, destruction, and the development of disease is formed. Clinical presentations Most patients with SLE have evidence of renal involvement at pres- entation, usually in the form of asymptomatic proteinuria with or without nonvisible haematuria. Over time, the proportion with overt renal disease increases to approximately 60%, with higher rates in children. This is more common and generally more severe in nonwhite patients. Nearly 100% of patients with lupus nephritis have proteinuria, closely followed by nonvisible haematuria (80%) and tubular abnormalities (60–80%). Other clinical findings in- clude nephrotic syndrome (45–60%), hypertension (15–50%), and granular casts (30%): rapidly declining renal function is much less common. Lupus nephritis may, however, be 'clinically silent', with no biochemical or urinary abnormalities. Patients with active lupus nephritis often have features of active extrarenal SLE, including serositis, a vasculitic rash, ulcers, fevers, or alopecia. However, although relatively rare, lupus nephritis can occur in isolation, and as a presenting feature of SLE. Investigations/assessment All patients with SLE should have regular urinalysis (including urinary albumin-to-creatinine ratio or urinary protein-to-creatinine ratio quantification) and monitoring of their serum creatinine. Anti double-stranded DNA and anti-C1q antibodies are often abnormal in patients with lupus nephritis, their titres frequently correlating with disease activity. Decreasing serum third compo- nent of complement system (C3), particularly in conjunction with rising levels of anti double-stranded DNA, correlates well with ac- tive lupus nephritis. Anti-Sm antibody is also positive in up to 30% of black patients, but is not necessarily indicative of active disease. Rising antinucleosome antibodies may predict a renal flare. The gold standard for diagnosis of lupus nephritis remains a renal biopsy, enabling determination of lupus involvement and degree of activity or damage, and providing important prognostic indica- tors. This is justified when there is evidence of glomerular disease with renal impairment and/or urinary sediment indicative of active nephritis: • Proteinuria (>100 mg/24 h or protein:creatinine ratio >100 mg/ mmol) • Haematuria (>10 dysmorphic red blood cells per high power field) • Casts of red and white blood cells Histopathology Various glomerular patterns of immune complex-mediated injury are seen on biopsy and classification of lupus nephritis is based primarily on the location (mesangial, endothelial, and epithelial) and nature of lesions seen (active, chronic, focal, or diffuse) (Figs. 21.10.3.1–21.10.3.3 and Table 21.10.3.1). Immunofluorescence microscopy of biopsies with lupus nephritis can show florid de- position (the classical 'full-house' picture) of immunoglobu- lins, IgG, IgA, and IgM, as well as complement proteins, C3, C4, and C1q (Fig. 21.10.3.4). The 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of

Fig. 21.10.3.1 Lupus nephritis. The glomerulus has mild mesangial increase (ISN/RPS class II) (periodic acid–methenamine silver staining, magnification ×50). Courtesy of Professor A.J. Howie.

Fig. 21.10.3.2 Lupus nephritis. The glomerulus has marked mesangial increase with wire loops, a few doubled basement membranes, and segmental lesions (ISN/RPS class IV) (periodic acid–methenamine silver staining, magnification ×40). By courtesy of Professor A.J. Howie.

Fig. 21.10.3.3 Lupus nephritis. The glomerulus has marked swelling of the glomerular basement membrane (membranous lesions; ISN/RPS class V). Reproduced with permission from Condon M, Dodd P, Lightstone L. The patient with systemic lupus erythematosus: clinical features, investigations, and diagnosis. In: Turner N, Lameire N, Goldsmith DJ, Winearls CG, et al. Oxford Textbook of Clinical Nephrology. 4th ed. Oxford: Oxford University Press (2015).

 lupus nephritis (Table 21.10.3.2 and Fig. 21.10.3.5) was developed to enable a more uniform description of histopathological lesions,

promoting standardization of patient care and enabling improved comparison of outcomes between multinational centres. Inclusion of renal vascular lesions in the 2003 ISN/RPS classification system improves the prediction of renal outcomes. Treatment of lupus nephritis Decisions regarding treatment of patients with lupus nephritis are primarily dependent on histological lesions seen, but also reflect Table 21.10.3.1 Active and chronic glomerular lesions Active Chronic Endocapillary hypercellularity Glomerular sclerosis (segmental or global) Crescents—cellular or fibrocellular Fibrous crescents Karyorrhexis Fibrous adhesions Fibrinoid necrosis Rupture of glomerular basement membrane Wire loops Hyaline thrombi Table 21.10.3.2 The 2003 International Society of Nephrology/Renal Pathology Society classification of lupus nephritis (which is a modification of the 1995 WHO classification) 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 microscopy with mesangial immune deposits May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy (Fig. 21.10.3.1) 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 Class III (A) Active lesions: focal proliferative lupus nephritis Class III (A/C) Active and chronic lesions: focal proliferative and sclerosing lupus nephritis Class 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. The 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 (Fig. 21.10.3.2) 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 Class IV-S (A) Active lesions: diffuse segmental proliferative lupus nephritis Class IV-G (A) Active lesions: diffuse global proliferative lupus nephritis Class IV-S (A/C) Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis Class IV-G (A/C) Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis Class IV-S (C) Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis Class 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 morphological sequelae by light microscopy by immunofluorescence or electron microscopy with or without mesangial alterations (Fig. 21.10.3.3) Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed Class VI Advanced sclerotic lupus nephritis ≥90% of glomeruli globally sclerosed without residual activity A, active; C, chronic. Fig. 21.10.3.4 Lupus nephritis. IgG deposition within the glomerulus. Reproduced with permission from Condon M, Dodd P, Lightstone L. The patient with systemic lupus erythematosus: clinical features, investigations, and diagnosis. In: Turner N, Lameire N, Goldsmith DJ, Winearls CG, et al. Oxford Textbook of Clinical Nephrology. 4th ed. Oxford: Oxford University Press (2015).

 the severity of clinical presentation (the degree of associated pro- teinuria, hypertension, and/or extrarenal manifestations of SLE). Proliferative disease (class III and class IV lupus nephritis) is more aggressive than nonproliferative

lupus nephritis and requires inten- sive immunosuppressive treatment to induce remission and prevent lasting kidney damage. Management of nonproliferative lupus nephritis Class I and class II ISN/RPS class I and class II lesions are associated with a better prognosis and consequently renal-specific therapy is not indi- cated. Patients with class I lupus nephritis and class II with pro- teinuria less than 1 g/day should have treatment dictated by the extrarenal manifestations of SLE. For those patients with class II lupus nephritis and proteinuria greater than 3 g/day, treatment with corticosteroids or calcineurin inhibitors can be useful if proteinuria cannot be controlled by renin–angiotensin system blockade alone. Class VI From a renal perspective, immunosuppression is not indicated in class VI lupus nephritis, which reflects chronic insult without ac- tive immune-mediated injury. However, many patients with class VI lupus nephritis exhibit extrarenal manifestations of SLE necessitating immunosuppressive treatment. Class V (membranous nephropathy) Class V lupus nephritis, while generally regarded as a less aggres- sive form of lupus nephritis compared to types III and IV, is still associated with the development of chronic kidney disease and ESRD, particularly if there is marked proteinuria (even with normal baseline renal function). Given the adverse effects of subnephrotic proteinuria on kidneys, most nephrologists would treat these pa- tients with antiproteinuric and antihypertensive medications. Sustained heavy proteinuria (and associated hypercoagulable state) is associated with adverse cardiovascular effects, but there is only a limited evidence base looking at treatment of class V lupus neph- ritis. Steroids, ciclosporin, and cyclophosphamide treatment have been used, along with other immunosuppressive agents including mycophenolate mofetil (MMF), azathioprine, and tacrolimus. Appropriately sized randomized controlled trials would need to be undertaken before these immunosuppressive therapies can be un- equivocally recommended, and such trials are unlikely to be done. In a post hoc review of the outcomes of patients with ‘pure’ class V lupus nephritis in two trials, the combination of MMF and steroids was as effective as high-dose cyclophosphamide and steroids. Management of proliferative lupus nephritis (class III and class IV) Proliferative lupus nephritis is the most common renal manifest- ation of SLE. Prior to the advent of immunotherapy regimens, kidney survival and overall patient survival in diffuse prolifera- tive lupus nephritis was only 20 to 25%. While patient and kidney survival in class III and class IV lupus nephritis has markedly im- proved through intensive immunosuppression (current reviews suggest c.90% survival over 10 years, in those who achieve remis- sion), the response to treatment is often slow, and the risk of relapse remains high. Active or sclerotic lesions? YES YES YES YES YES YES NO NO NO NO NO NO Membranous change? Mesangial hypercellularity? Immune deposits on immunofluorescence? No lupus nephritis Class I Class II Class V 50% or more of glomeruli involved? Class III (A or A/C or C) Class IV (A or A/C or C) 50% or more of involved glomeruli have segmental lesions? Class IV-G Class IV-S Class VI if >90% global sclerosis without activity Fig. 21.10.3.5 Algorithm showing how the class of lupus nephritis is determined. In Class III or IV, A = active lesions only, A/C = active and chronic lesions, C = chronic lesions only, and if >50% glomeruli have >50% capillary walls with membranous change = Class III + V, or Class IV + V. See Table 21.10.3.1 for further explanation.

 The goal of treatment for active proliferative lupus nephritis is to induce a remission with intensive immunotherapy aimed at switching off the renal inflammation. Once this has been attained, maintenance therapy is commenced with the aim of continuing dis- ease remission, with minimal treatment side effects and ideally pre- vention of relapse. Induction regimens Traditionally, the mainstay of induction therapy in lupus nephritis has been corticosteroids plus cytotoxic agents. If disease is more severe, pulses of intravenous

methylprednisolone are used prior to commencing oral corticosteroids. Since the early 1980s, cyclophos- phamide has dominated as the cytotoxic of choice, but concerns about the side effect profile, specifically risks of bladder toxicity, ovarian failure, leucopenia, and alopecia, have led to trials exam- ining reduced doses of cyclophosphamide and the introduction of MMF as an alternative immunosuppressant. The 'Euro-Lupus' regimen compared a lower-dose of cyclophos- phamide (500 mg intravenously every 2 weeks for 3 months) to the original 'National Institutes of Health (NIH) regimen' (0.5–1 g/m2 given monthly for 6 months). The trial demonstrated that the lower- dose regimen was as effective at inducing remission as the higher dose, but patients suffered fewer severe infections. The original study was in an exclusively northern European Caucasian popula- tion, but a more recent trial (the Abatacept and Cyclophosphamide Combination Therapy for Lupus Nephritis (ACCESS) study) used Euro-Lupus as the standard of care to which abatacept or placebo was added. There was no significant improvement gained by the addition of abatacept, but the trial demonstrated well that the Euro- Lupus regimen was effective in African American and Hispanic patients. The Aspreva Lupus Management Study (ALMS) was an inter- national trial designed to compare MMF to intravenous cyclophos- phamide (NIH regimen, plus standard glucocorticoid tapering) as induction therapy. The study was designed as a superiority study, with the aim of demonstrating that MMF would be superior at inducing complete remission at 6 months. It was not, but the rates were very similar for cyclophosphamide and MMF, with a similar incidence of adverse effects, serious infections, and deaths in both the MMF and cyclophosphamide arms. Post hoc analysis of the study suggested MMF was as efficacious as cyclophosphamide in the small group of patients with an estimated glomerular filtration rate of less than 30 ml/min per 1.73 m2 at the outset and in those with class V lupus nephritis. All the recent guidelines on therapy suggest that induction for class III or IV lupus nephritis can be with cyclophosphamide- or MMF-based regimens. They have suggested that in severe class III/ IV lupus nephritis 'a cyclophosphamide-containing protocol for initial therapy may be preferred', but it is worth noting that MMF may be more effective than cyclophosphamide in patients of African descent and Hispanic patients. A Cochrane review in 2012 system- atically analysed nine studies, concluding that MMF is as effective as cyclophosphamide, but with reduced side effects. A key factor in deciding which induction regimen to use is the importance of preserving fertility. Cyclophosphamide causes infertility in a dose- and age-related manner that may be offset to a degree by the con- comitant use of ovarian protection regimens. By contrast, MMF does not cause infertility so may be preferable as a first-line agent, although patients must be warned to avoid pregnancy while taking it as it is teratogenic. Regardless of initial therapy used, response needs to be assessed at 6 months to guide further management. There have been several analyses of very long-term outcomes of the Euro-Lupus trial and ALMS trial patients. These have clearly demonstrated that early re- duction in proteinuria predicts long-term renal survival and that proteinuria of less than between 500 and 800 mg/day at 1 year is associated with good long-term outcomes. Maintenance therapy Following initial therapy to induce remission, the goal of treatment of lupus nephritis is to prevent systemic and lupus nephritis flares, and to preserve renal function while minimizing potential side ef- fects of long-term therapy. Prolonged maintenance therapy after initial treatment is usually required as patients who receive only a short-term (6 month) course of therapy have been shown to have an increased frequency of lupus nephritis relapse. Current options for maintenance therapy include azathioprine, MMF, cyclophospha- mide, and ciclosporin. When determining long-term maintenance therapy options, patient-specific factors, for example, tolerability of side effects, and desire for pregnancy should be considered. Initial studies in maintenance therapy for lupus nephritis com- pared cyclophosphamide pulses with maintenance

azathioprine or MMF and demonstrated that patients treated with MMF or azathioprine were significantly less likely to develop chronic kidney disease. Mortality was similarly reduced compared to the cyclo- phosphamide group at 72 months. This has led to preferential use of MMF and azathioprine over cyclophosphamide. Trials to determine MMF or azathioprine superiority have yielded mixed results. Two key studies to date have been the ALMS trial ex- tension phase and the Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy of Lupus Nephritis Trial (MAINTAIN Nephritis Trial). In a Caucasian population, azathioprine appears to be equivalent to MMF, whereas MMF is the treatment of choice in a multiethnic population. Differences between the two drugs as maintenance therapy are small, and so if one drug is not tolerated, then the other should be tried. Similarly, patient circumstances may dictate the use of one drug over another: MMF is contraindicated in pregnancy, and azathioprine will be the preferred option in re- gions where cost or drug availability is an issue. The optimal time to remain on maintenance therapy has not been determined but in general is at least 2 to 3 years after remission induction. Novel therapies Some patients fail to respond to available treatment, and for others treatment-associated side effects, particularly from corticosteroid therapy, limit patient adherence and subsequent treatment efficacy. Consequently, there is an urgent need to identify and develop new immunotherapies, enabling steroid-sparing treatment regimens and to better manage refractory cases. Current lupus nephritis immunosuppressive therapies are anti- inflammatory, anti-complement and anti-cytokine in a relatively nonspecific manner. In recent years there has been an increased focus on targeting critical pathways in SLE pathogenesis with the aim of disrupting autoimmune mechanisms leading to kidney in- flammation and acute and chronic kidney injury (B- and T-cell ac- tivity, costimulatory molecules, and antibody production). Sadly, all

 trials of new agents to date, all of which have been evaluated as ‘add- on’ therapies to standard of care, have not shown significant super- iority. The list of negative studies in lupus nephritis includes the use of rituximab, CTLA4-Ig, and ocrelizumab. In each case, the trial has failed not necessarily due to lack of efficacy of the drug, but because the study was too small, or because of a finding of increased rates of infection (often attributable to higher doses of steroids). However, there remains optimism that better designed trials may translate into improvements in outcomes. Anti CD20 (rituximab) therapy Rituximab is a chimeric anti-CD20 human/mouse monoclonal antibody that has been used extensively in the treatment of non- Hodgkin’s lymphoma and has an excellent safety profile. Binding of rituximab to CD20+ cells results in both complement and FcγR- mediated cell killing, and clinically rituximab is an effective B-cell depleter. B-cell depletion ultimately might not only lead to reduction in autoantibodies (though note rituximab does not deplete plasma cells) but may also disrupt antigen presentation to T cells, critical for maintaining the autoimmune response, and markedly reduce cyto- kine production. A small subgroup of patients appear not to respond to rituximab, failing to deplete their B cells. The degree and duration of B-cell depletion usually correlates with improvements in disease activity and scores. Prospective open-label studies have reported widely on the efficacy of rituximab in both renal and non renal lupus, and rituximab has been found to be generally safe and well tolerated. However, the LUNAR study (Lupus Nephritis Assessment with Rituximab) and EXPLORER trial (Exploratory Phase II/III SLE Evaluation of Rituximab)—two large, prospective, placebo- controlled trials—both failed to find a benefit of rituximab in renal or non renal lupus when added to standard-of-care treatment. Trial design has been implicated in the failure of these studies to meet their primary endpoints. In both studies participants were given high-dose corticosteroids in addition to immunosuppressives such as MMF, which may have

obscured the ability to discrim- inate between the rituximab and placebo arms. Efforts continue to try to find regimens using rituximab and MMF (and other agents) that would allow omission of oral steroids without compromising efficacy. Other targets in lupus nephritis As B cells are depleted in response to rituximab, levels of the B- lymphocyte-stimulating factor (BlyS, also known as BAFF) increase, which may increase the generation of new autoreactive B cells. To counteract this potentially detrimental rise in BAFF, an anti-BlyS monoclonal antibody, belimumab, has been trialled. A post hoc ana- lysis of phase III belimumab studies in non renal SLE patients exam- ined renal outcomes and demonstrated a reduction in the number of renal flares in belimumab-treated patients. This is now being evalu- ated in an ongoing trial in lupus nephritis comparing belimumab and placebo in addition to the standard of care (ClinicalTrials.gov identifier: NCT01639339). Tacrolimus (FK506), a calcineurin inhibitor, has demonstrated similar efficacy to mycophenolate mofetil as induction therapy, and other studies include trials of an interferon-α receptor blocker, an anti-CD40, another anti-CD20 (obinutuzumab, a humanised monoclonal), a novel calcineurin inhibitor (voclosporin), as well as studies of small-molecule inhibitors. It is a crowded area and the trials need to be smart to overcome the limitations of previous negative studies. Refractory lupus nephritis Up to 22% of patients with proliferative lupus nephritis are re- fractory to therapy with cyclophosphamide or MMF. If induction therapy fails, the general consensus is to switch and use the alterna- tive (MMF or intravenous cyclophosphamide). Rituximab is often added at this stage: although trial evidence is generally lacking, there have been reports of some promising results, for example, Jonsdottir and colleagues demonstrated that the addition of rituximab results in clinical and histological improvements in patients with refrac- tory lupus nephritis. The RING trial (ClinicalTrials.gov identi- fier: NCT01673295) was formally assessing whether the addition of rituximab in refractory lupus nephritis improved responses. Relapse of lupus nephritis Some patients have persistent relapses of lupus nephritis despite repeated treatment. It is important to recognize and treat relapses quickly, as with each relapse further renal damage is sustained. This is associated with both the development of chronic kidney disease and ESRD. Relapse is diagnosed clinically: increasing proteinuria, rising serum creatinine level, and changes in urinary sediment should all alert clinicians. A reduction in serum complement levels and in- crease in anti-double stranded DNA antibody titres may be seen prior to clinical relapse, and while these do not justify treatment per se, it is wise to see the patient more frequently in order to de- tect relapse early. If a renal relapse is suspected, then a renal biopsy may well be indicated to confirm the diagnosis and identify the class of lupus nephritis, which may transform spontaneously from one histological class to another and such changes cannot be predicted clinically with certainty. The most common transformations seen are from class III to class IV, or from a proliferative to nonproliferative class. Importantly, the development of increased proteinuria may represent chronic damage rather than acute inflammation, or a podocytopathy rather than proliferative or class V lupus nephritis.
A definitive diagnosis requires a renal biopsy. Prognosis While the overall prognosis of patients with SLE and a proliferative glomerulonephritis has improved significantly with the judicious use of immunosuppressants, 5 to 10% of patients will have died after 10 years of treatment, and a further 5 to 15% will have devel- oped ESRD. The prognosis is poorer in African and Hispanic people (the reasons are unclear), and this needs to be remembered when interpreting results of randomized control trials. Proliferative glomerulonephritis (class III and IV) is associated with a worse outcome, along with the presence of chronic histo- logical changes on renal biopsy. Many patients with lupus nephritis (30–50%) do not achieve complete remission and this is associated with a significantly increased risk of having further renal relapses, of developing ESRD and of dying. In patients who do achieve com- plete remission, relapses develop in 20–40% over a follow-up of about 10 years, and

these are also associated with an increased risk

21.10.3 The kidney in rheumatological disorders 5007 of developing ESRD. Significant reduction in proteinuria at 3 and 6 months, and persistent reduction in proteinuria at 1 year, predicts better long-term renal outcomes. Antiphospholipid antibody nephropathy in SLE Antiphospholipid antibodies are associated with a syndrome (antiphospholipid syndrome) characterized by arterial and venous thromboses and repeated miscarriages. These antibodies have reactivity against cardiolipin and the lupus anticoagulant and are found in 15 to 30% of patients with SLE. Antiphospholipid syndrome can be primary or associated with SLE. Renal mani- festations of antiphospholipid syndrome include thrombotic microangiopathy and chronic vascular lesions, superimposed on those of lupus nephritis. If there is evidence of extrarenal throm- bosis, oral anticoagulants should be commenced. Patients with lupus nephritis and antiphospholipid antibodies have a worse renal prognosis, presumably because of the superimposed renal vasculopathy. See Chapter 14.14 for further discussion. Long-term outcome The main causes of death in lupus nephritis are treatment-related sepsis (early) and cardiovascular causes (late). Renal failure can be treated with transplantation and dialysis; generally the activity of lupus nephritis reduces once dialysis is initiated. Overall survival on dialysis is approximately 75% at 10 years. Graft survival in pa- tients with SLE after kidney transplantation is similar to patients with other diseases, and recurrence of lupus nephritis is rare. Systemic sclerosis/scleroderma Systemic sclerosis (SSc) is a multiorgan connective tissue disease of uncertain aetiology that is characterized by progressive inter- stitial and vascular fibrosis in the skin and other organs. There are three subtypes of SSc: limited cutaneous SSc (lcSSc) where cutaneous involvement is limited to the hands, forearms, face, and feet; diffuse cutaneous SSc (dcSSc) with proximal extension above the elbows or knees; and scleroderma sine scleroderma where skin involvement is absent and patients present only when end-organ damage has occurred (see Chapter 19.11.3). Renal involvement in SSc can be acute or chronic and most renal manifestations are clinically silent, with autopsy studies detecting occult renal pathology in 60 to 80% of patients. By con- trast, scleroderma renal crisis demonstrates the acute effects of microvasculopathy in SSc. Scleroderma renal crisis Scleroderma renal crisis predominantly affects patients with dcSSC, occurring in 10 to 15% of patients with this disease. Mortality in scleroderma renal crisis remains high, particularly in patients who develop ESRD. Patients with early dcSSc are at greatest risk, and rapidly progressive skin disease or tendon fric- tion rubs are independent risk factors. Other studies have sug- gested that recent high-dose corticosteroid use, the presence of anti-RNA polymerase III antibodies, anaemia, and new-onset cardiac failure are also risk factors for the development of sclero- derma renal crisis. Pathogenesis The pathogenesis of renal involvement in SSc is not fully under- stood. Acute vascular injury activates the coagulation and other inflammatory pathways, culminating in proliferative fibrovasculo pathy and thrombotic microangiopathy. Decreased renal perfusion from arterial constriction leads to hyperplasia of the juxtaglo- merular apparatus and hyperreninaemia, resulting in a hyperten- sive crisis and rapidly progressive renal injury. Pathology The smaller arcuate and interlobular arteries are predominantly involved in scleroderma renal crisis, showing intimal hyper- plasia with concentric mucoid intimal degeneration, but the in- ternal and external elastic laminae remain intact. The adventitia of interlobular arteries shows an abnormal degree of fibrosis. There is fibrinoid necrosis of afferent arterioles and glomeruli, and also glomerular thrombosis. Ischaemia of the glomerular tuft leads to wrinkling and thickening of the glomerular base- ment membrane and glomerular sclerosis (Fig. 21.10.3.6). These lesions resemble those seen in accelerated hypertension or the haemolytic uraemic syndrome, although the vessels involved tend to be larger

and adventitial fibrosis is not seen in accelerated hypertension. Clinical presentation Mild proteinuria without loss of renal function is the most common presentation of SSc renal disease. An isolated reduction in glom- erular filtration rate is also in seen in patients with SSc and often follows a benign, non progressive course. By contrast, scleroderma renal crisis is characterized by new-onset accelerated-phase hyper- tension and a decrease in renal function of at least 30%. It is often associated with systemic symptoms including headache, visual dis- turbances, seizures, or encephalopathy. Flash pulmonary oedema can occur, and arrhythmias, myocarditis, and pericarditis are all associated with poorer prognosis. Fig. 21.10.3.6 Scleroderma kidney. A small artery has concentric mucoid intimal thickening, an arteriole has thrombosis and fibrinoid necrosis, and tubules and a glomerulus have ischaemic damage (periodic acid–methenamine silver staining, magnification ×25). By courtesy of Professor A.J. Howie.

 Scleroderma renal crisis can (rarely) develop in individuals with a normal blood pressure. They are more likely to have a micro angiopathic haemolytic anaemia (90 vs 30%), thrombocytopenia (83 vs 21%), and pulmonary haemorrhage than patients with a hypertensive scleroderma renal crisis. Investigations/assessment Autoantibodies (antinuclear antibodies (ANA)) are detectable in virtually all patients with SSc. A speckled ANA pattern is also seen in approximately 60% of patients with scleroderma renal crisis. Other autoantibodies associated with renal disease in SSc include anti-RNA polymerase III antibodies (ARA) and anti-fibrillarin antibodies (AFA, also known as anti-U3 RNP antibodies). In con- trast, SSc patients with anti-centromere or anti-topoisomerase 1 antibodies are less likely to develop renal disease. Renal function should be monitored and blood pressure checked at least monthly, with daily self-monitoring introduced if hyper- tension develops. Urinalysis may reveal the presence of proteinuria (non-nephrotic range) and nonvisible haematuria, with casts vis- ible on direct microscopy. Anaemia can be an early feature of scleroderma renal crisis. Thrombocytopenia and anaemia occur in up to 50 and 60% of cases respectively. Elevated levels of lactate dehydrogenase, low hapto- globin, and schistocytes in the peripheral blood smear may also be seen. Occasionally, disseminated intravascular coagulation can develop. Many clinical features of a scleroderma renal crisis are similar to those seen in thrombotic thrombocytopenic purpura. It is im- portant to differentiate the two because management varies mark- edly. Assays for plasma ADAMTS13 enzyme can be useful to exclude thrombotic thrombocytopenic purpura. Treatment Control of hypertension is fundamental in preventing irreversible vascular injury. A gradual decrease in blood pressure should be targeted because a rapid reduction can reduce renal perfusion and increase the risk of acute tubular necrosis. Angiotensin-converting enzyme inhibitors are first-line therapy and lead to regression of skin manifestations in some patients: they should be titrated up to maximum doses. In an acute crisis, continuous intravenous iloprost infusion can help reverse microvascular changes and con- trol blood pressure; if substantial thrombotic microangiopathy is present, plasma exchange can be used. Prognosis Approximately 25% of patients with scleroderma renal crisis re- quire dialysis at presentation, and 40 to 66% of these may not re- cover. Assessment of prognosis may be guided by renal biopsy, but clinical predictors of poor outcome include dcSSc, high skin scores (>20), older age, and evidence of cardiac involvement. Long-term survival following scleroderma renal crisis is poor, especially for patients who do not recover renal function. Increased mortality is seen in males, those with normal blood pressure at presentation, and older patients. Scleroderma renal crisis is one of the few con- ditions where late recovery of renal function is sometimes seen as the inflammatory process resolves and blood pressure is tightly controlled. Rheumatoid arthritis Historically, the main causes of renal

disease in rheumatoid arth- ritis have been secondary (amyloid A) amyloidosis and nephro- toxicity from drugs used in treatment (Box 21.10.3.1) (see Chapter 19.5). Renal vasculitis and glomerulonephritis are also described. However, the pattern of renal disease in rheumatoid arthritis is changing. Gold and penicillamine are now infrequently used, hence nephrotoxicity from these causes has become rare, and the incidences of amyloid A amyloidosis and rheumatoid vas- culitis have declined, probably as a result of early use of disease- modifying agents.

Secondary amyloidosis Secondary amyloidosis results from deposition of fibrils containing amyloid A protein that is antigenically related to the acute-phase reactant serum amyloid A (see Chapter 12.12.3). Rheumatoid arth- ritis is the commonest disease producing secondary amyloidosis in developed countries. Prevalence rates of 8 to 17% are reported in autopsy series and 5 to 10% in biopsy series, but the incidence has dropped dramatically due to much more aggressive therapy of rheumatoid disease, with fewer patients being left with a persistently active acute-phase response. Cases of crescentic glomerulonephritis superimposed on renal amyloidosis in patients with rheumatoid arthritis have been described. Clinical features and diagnosis The presentation of renal amyloid is with proteinuria that is often severe enough to cause a nephrotic syndrome. Renal vein throm- bosis is particularly common. Diagnosis is established by renal bi- opsy (Fig. 21.10.3.7), where histological Congo red staining, which is birefringent in polarized light, is characteristic of amyloid. This staining is abolished by potassium permanganate in reactive amyl- oidosis but not in primary amyloidosis. Monoclonal and polyclonal antibodies that specifically bind amyloid A are available and of use for histological diagnosis. The diagnosis of amyloid is also aided by the availability of scans using radiolabelled serum amyloid P (SAP) Box 21.10.3.1 Renal disease in rheumatoid arthritis Consequences of rheumatoid arthritis • Amyloid A amyloidosis • Vasculitic glomerulonephritis • Mesangiocapillary glomerulonephritis • Mesangial IgA proliferative glomerulonephritis Drug nephrotoxicity Nonsteroidal anti-inflammatory drugs • Reversible haemodynamically mediated renal impairment • Acute tubular necrosis • Acute interstitial nephritis with or without a nephrotic syndrome Gold and penicillamine • Proteinuria • Nephrotic syndrome • Membranous nephropathy • Rare reports of a crescentic glomerulonephritis

 protein, utilizing the strong calcium-dependent affinity of SAP for amyloid fibrils of any protein type. Treatment and prognosis There is no specific therapy for amyloid A amyloidosis, the general principle being suppression of the underlying chronic inflamma- tion. Uncontrolled evidence suggests that aggressive treatment of rheumatoid arthritis may be effective in delaying the deterioration of renal function in patients with renal amyloid, and treatment with prednisolone and cyclophosphamide or methotrexate can induce remission of the nephrotic syndrome due to amyloid in patients with this condition. Treatment with antitumour necrosis factor-α anti- bodies is also reported to lead to remission of renal disease due to amyloidosis. Renal amyloid leads to progressive renal failure; 50% of patients develop ESRD after 5 years, rising to 90% at 10 years, treatment of which is by dialysis and renal transplantation. Gold and penicillamine nephropathy Clinical features and diagnosis The most frequent presenting feature is proteinuria, which occurs in approximately 10% of patients receiving gold and up to 30% of those taking penicillamine. This progresses to the nephrotic syn- drome in 30 and 16%, respectively. Haematuria is uncommon, although it is seen more frequently with penicillamine, and still re- quires the exclusion of other causes when occurring in the context of therapy with these drugs. Renal function is usually normal. Gold and penicillamine are no longer widely used to treat patients with rheumatoid arthritis and nephrotoxicity from these agents is cor- respondingly uncommon. About 55 to 80% of patients who present with penicillamine- or gold-induced

proteinuria will have a membranous glomer- ulonephritis. Minimal-change nephropathy is the next most frequently encountered histological lesion. Other less common renal lesions include mesangiocapillary glomerulonephritis and tubulointerstitial inflammation. Penicillamine may lead to the de- velopment of a rapidly progressive glomerulonephritis with cres- cents and pulmonary haemorrhage, resembling Goodpasture's syndrome but without anti-glomerular basement membrane antibodies. Treatment and prognosis In general, gold and penicillamine should be discontinued when significant proteinuria develops (>0.5 g/24 h). After cessation of the drug, proteinuria peaks at around 1 month then gradually disap- pears, and most patients will have clear urine by 1 year and almost all will achieve this by 2 years. Renal function does not deteriorate in uncomplicated cases. Glomerulonephritis The most commonly described glomerulonephritis in rheuma- toid arthritis that is not related to drug use is a mesangiocapillary glomerulonephritis, which in many cases is accompanied by IgA deposits (IgA nephropathy). Membranous nephropathy is also described. Renal vasculitis The clinical spectrum of rheumatoid arthritis includes a systemic necrotizing vasculitis with involvement of blood vessels ran- ging in size from capillaries to small and medium-sized arteries. With more aggressive treatment of rheumatoid arthritis, vascu- litis from this cause is now uncommon. The clinical presentation includes nail-fold infarcts, a leucocytoclastic vasculitis, a periph- eral neuropathy, pericarditis, gastrointestinal infarcts, and renal vasculitis. Renal abnormalities are found in about 25% of patients with rheumatoid vasculitis, usually nonvisible haematuria, proteinuria, and renal impairment. Renal histology shows a large-vessel renal arteritis and a segmental necrotizing glomerulonephritis with crescent formation (vasculitic glomerulonephritis) (Fig. 21.10.3.8). Fig. 21.10.3.7 Amyloidosis in rheumatoid arthritis. Arterioles and glomeruli contain acellular masses of amyloid (periodic acid– methenamine silver staining, magnification ×40). By courtesy of Professor A.J. Howie. Fig. 21.10.3.8 Vasculitic glomerulonephritis in rheumatoid arthritis. Two glomeruli have sharply defined segmental lesions where there has been disruption of the tuft and partial obliteration of Bowman's space (periodic acid–methenamine silver staining, magnification ×32). By courtesy of Professor A.J. Howie.

 Treatment is with prednisolone and cyclophosphamide, usually leading to improvement of renal function. Renal disease in juvenile chronic arthritis Renal involvement in juvenile chronic arthritis is infrequent, but its presence is associated with a poor outcome. Proteinuria is found in 3 to 12% of patients and nonvisible haematuria in 3 to 8%. The renal lesions reported are usually complications of the underlying rheumatic disease, such as amyloidosis, or those arising as side effects of the drugs used. Cases of necrotizing crescentic glomer- ulonephritis, focal segmental glomerulosclerosis, and mesangial glomerulonephritis have all been described in children with the condition. Renal amyloid is found in 1.2 to 6.7% of patients with juvenile chronic arthritis, and affects patients with chronic and active dis- ease, with a predilection for systemic-onset disease. It typically pre- sents with nephrotic-range proteinuria. Aggressive treatment with chlorambucil has been shown to improve survival in patients with juvenile chronic arthritis and amyloid A amyloidosis. Sjögren's syndrome Sjögren's syndrome is an autoimmune condition in which there is inflammatory cellular infiltration of the exocrine glands (particu- larly the salivary and lacrimal glands) (see Chapter 19.11.4). The condition can occur in isolation (primary Sjögren's syndrome) or in conjunction with other autoimmune diseases, usually lupus or mixed connective tissue disease (secondary Sjögren's syndrome). Clinical features Dry mouth (xerostomia) and dry eyes (keratoconjunctivitis) are characteristic of Sjögren's syndrome. Renal involvement is usually mild and often subclinical. Some patients present with distal tubular acidosis, impairment of urinary concentration, hypokalaemia, or

rarely with Fanconi’s syndrome. Clinical manifestations of these renal tubular disorders include sterile pyuria, the development of renal calculi, polyuria, and (very rarely) the development of hypo- kalaemic periodic paralysis. Up to a quarter of patients can develop acute or chronic kidney disease. Investigation/assessment Urine dip might reveal occasional leucocytes and moderate protein- uria. The most common histological abnormality is tubulointerstitial nephritis with predominantly T-lymphocyte infiltrate, but various types of glomerulonephritis are also described. Glomerular abnor- malities are rare. Mixed connective tissue disease Mixed connective tissue disease is a rheumatological overlap syn- drome associated with anti-U1-RNP antibodies and clinical signs including synovitis, myositis, Raynaud’s phenomenon, acrocyan- osis, and hand oedema. Renal involvement occurs in up to one-third of cases. Treatment has generally been with steroid therapy along with steroid-sparing agents. Glomerular involvement will generally be treated in a similar manner to lupus nephritis, depending on the histology. Drug nephrotoxicity following treatment for rheumatic disorders Nonsteroidal anti-inflammatory drugs The widespread use of nonsteroidal anti-inflammatory drugs (NSAIDs) for the relief of pain and inflammation has meant that, although in any individual patient the risk of renal adverse events is small, renal complications are frequently seen. Non se- lective NSAIDs inhibit both constitutive cyclooxygenase (COX)-1 and inducible COX-2 enzymes involved in the prostaglandin and thromboxane A2 pathways responsible for the regulation of pain, renin release, and vascular tone. Since both COX-1 and COX-2 are expressed in the kidney, adverse effects are associated with both non selective and COX-2 selective NSAIDs. Clinical syndromes as- sociated with NSAID use reflect either predictable abnormalities arising from their mode of action, especially in volume-depleted individuals, or those with vascular impairment or idiosyncratic allergic responses. The clinical syndromes seen include acute tubular necrosis, acute tubulointerstitial nephritis, nephrotic syn- drome (minimal-change disease or membranous nephropathy), and renal papillary necrosis. In addition, NSAID therapy may in- duce salt and water retention, hypertension, hyperkalaemia, and chronic kidney disease. In patients with chronic kidney disease or a functioning renal transplant, NSAIDs should not be used without careful consider- ation of the balance of benefit versus risk. Great care must be taken when prescribing NSAIDs to patients with volume depletion, and when using concomitant nephrotoxins. Chronic analgesic nephropathy Chronic analgesic nephropathy is characterized by renal pap- illary necrosis and chronic interstitial nephritis caused by prolonged and excessive consumption of analgesic mixtures. Compound analgesic mixtures are associated with the develop- ment of analgesic nephropathy, and classic radiographic find- ings (bilateral small kidneys, irregular contour, and renal papillar calcifications) are easily seen on CT. The course of the disease is dependent on severity of chronic damage at presentation, and unless analgesic consumption ceases, renal dysfunction will pro- gress. If analgesics are discontinued, renal function stabilizes or improves slightly in most patients, but there is an association with the later development of urinary tract malignancies in these patients. Renal toxicity of anti-rheumatic drugs Many conventional antirheumatic drugs are nephrotoxic, even in the absence of chronic kidney disease. Calcineurin inhibitors (ciclosporin and tacrolimus) are associated with significant renal toxicity. Acute renal impairment and hypertension are usually dose dependent and improve with dose reduction. Chronic renal dys- function is associated with characteristic histological changes (vas- cular hyalinosis, interstitial fibrosis, tubular atrophy, and glomerular

 sclerosis), is often progressive, and irreversible unless calcineurin inhibitors are stopped. The commonest manifestation of drug toxicity in the kidney is tubulointerstitial nephritis, often with an eosinophilic infiltrate. The presentation may be acute with systemic symptoms such as a drug rash and fever, and may be associated with

systemic eosino- philia and hypocomplementaemia as well as acute kidney injury that can be severe. Patients usually have sterile pyuria, may have haematuria and can have nephrotic range proteinuria, though more commonly much lower levels of urinary protein loss. Some patients have a slower more insidious renal limited progression and the major finding will be unexplained chronic kidney dis- ease and sterile pyuria. Unless biopsied, the inflammation will be missed and these patients will present with irreversible advanced tubulointerstitial scarring. Nowadays the commonest drugs as- sociated with tubulointerstitial nephritis are penicillins, NSAIDs, proton pump inhibitors, furosemide, and sulphasalazine (which can also cause crystalluria and urinary stone formation)—all used frequently in patients with rheumatic diseases. Treatment involves stopping the causative drug, if known, plus a course of oral steroids. Although there are no trials, a large retrospective study strongly suggested that those treated with steroids had better preservation of renal function than those who were not. In patients with pre-existing chronic kidney disease, leflunomide is contraindicated (the active ingredient is renally excreted) and other medications including methotrexate, azathioprine, chlorambucil, and cyclophosphamide require reduced doses. Hydroxychloroquine is not reported to cause renal toxicity, but increased retinal monitoring should be undertaken in the pres- ence of renal impairment. At present, there has been no reported incidence of renal tox- icity in clinical trials of new biological therapies, but their use in patients with severe renal impairment has not been fully evaluated. Also of interest is the pharmacokinetics of these drugs in the face of severe nephrotic syndrome: are larger and/or more frequent doses needed? FURTHER READING Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group (2012). KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Int Suppl, 2, 139–274. Rovin BH, et al. (2019). Management and treatment of glomerular diseases (part 2): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int, 95, 281–95. Lupus nephritis Almaani S, Meara A, Rovin BH (2017). Update on lupus nephritis. CJASN, 12, 825–35. Appel GB, et al. (2009). Mycophenolate mofetil versus cyclophospha- mide for induction treatment of lupus nephritis. J Am Soc Nephrol, 20, 1103–12. Austin HA, et al. (1986). Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Eng J Med, 314, 614–19. Austin HA, et al. (2009). Randomised controlled trial of prednisone, cyclophosphamide and cyclosporine in lupus membranous neph- ropathy. J Am Soc Nephrol, 20, 901–11. Boumpas DT, et al. (1992). Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. Lancet, 340, 741–5. Condon M, et al. (2013). Prospective observational single-centre co- hort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. Ann Rheum Dis, 72, 1280–6. Dooley MA, et al. (2011). Mycophenolate versus azathioprine as main- tenance therapy for lupus nephritis. N Engl J Med, 365, 1886–95. Dooley M, et al. (2013). Effect of belimumab treatment on renal out- comes: results from the phase 3 belimumab clinical trials in patients with SLE. Lupus, 22, 63–72. Gordon C, et al. (2018). The British Society for Rheumatology guide- line for the management of systemic lupus erythematosus in adults. Rheumatology, 57, e1–e45. Henderson L, et al. (2012). Treatment for lupus nephritis. Cochrane Database Syst Rev, 12, CD002922. Houssiau FA, et al. (2002). Immunosuppressive therapy in lupus neph- ritis: the Euro-Lupus Trial, a randomised trial of low-dose versus high dose intravenous cyclophosphamide. Arthritis Rheum, 46, 2121–31. Houssiau FA, et al. (2010). Azathioprine versus mycophenolate mofetil for long term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. Ann Rheum Dis, 69, 2083–9. Houssiau FA, et al. (2010). The 10-year follow-up data of the Euro- Lupus Nephritis Trial comparing low-dose and high-dose intra- venous cyclophosphamide. Ann Rheum Dis, 69, 61–4. Jónsdóttir T, et al. (2013). Long-term follow-up in lupus nephritis patients treated with rituximab—clinical and histopathological re- sponse.

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