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Treatment of proliferative lupus nephritis: a changing landscape

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Grootscholten *et al.* report a randomized controlled trial comparing azathioprine plus intravenous methylprednisolone and oral prednisolone (AZA group) with intermittent intravenous cyclophosphamide and oral prednisolone (CY group) in patients with proliferative lupus nephritis. AZA-treated patients were more likely to develop non-sustained doubling of their serum creatinine, although not significantly so, and significantly more likely to have a relapse of their nephritis than CY-treated patients.

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The overall survival of patients with systemic lupus erythematosus and a proliferative glomerulonephritis (World Health Organization classes III and IV) has improved considerably over the last few decades.[1] Nevertheless, after 10 years of treatment, 5%–10% of patients have died and a further 5%–15% have developed end-stage renal failure.[2,3] For reasons that are not clear, survival to death and end-stage renal failure is much poorer in African Americans than in American or European whites. Improvement in outcome can be achieved only by careful randomized controlled trials such as the study of Grootscholten *et al.*[4] (this issue). This and other recently reported randomized controlled trials of therapy in lupus nephritis increase our options for management but at the same time challenge our long-held beliefs.

Depending on how it is defined, a significant proportion of patients with lupus nephritis do not achieve complete remission despite treatment with cyclophosphamide. This proportion ranges from 30% to 50%[5,6] or even higher.[7] Failure to achieve a remission of the renal disease is associated with a significantly increased risk of end-stage renal failure, relapses, and death. In the study by Illei *et al.*,[6] 36% of patients did not achieve a complete or partial remission, and of these 9% died and 49% developed end-stage renal failure. Between 20% and 40% of patients who achieve a complete remission of their renal disease relapse over a mean follow-up of about 10 years.[3,6] These relapses are associated with an increased risk of developing end-stage renal failure. In studies at the United States National Institutes of Health (NIH), a longer duration of cyclophosphamide treatment (up to 2 years) reduced the cumulative probability of relapse as compared with 6 months of cyclophosphamide ($P = 0.006$)[8] but was associated with increased gonadal toxicity.

Any doctor who looks after patients with lupus nephritis knows that the management of these patients remains a challenge. It is also a source of real disagreement. The clinical presentation, histology, clinical course, and responsiveness to treatment of lupus nephritis are heterogeneous. Disagreements on the optimal management of lupus nephritis result in part from this heterogeneity and also from the paucity of adequately powered randomized controlled trials. Several questions remain unanswered, such as (1) the optimal therapy for inducing remission and the duration of treatment required, (2) the optimal therapy for maintaining remission, and (3) the best ways of treating relapses.

The careful randomized controlled studies from the NIH made intermittent intravenous cyclophosphamide and oral prednisolone the accepted method for the management of severe lupus nephritis (World Health Organization classes III and IV).[9] Pulse intravenous cyclophosphamide has been preferred in most centers to continuous oral cyclophosphamide, because it appeared to be associated with less toxicity. Some argue that continuous oral cyclophosphamide is as effective as pulse cyclophosphamide, but there have been few randomized controlled studies to address this issue. The major toxicities of cyclophosphamide are dose dependent, and the intermittent regime typically leads to a lower dose. A recent study[10] showed that a shorter 12-week course of intravenous cyclophosphamide given every 2 weeks at a dose of 500 mg followed by azathioprine was as effective as an abbreviated NIH regime (six monthly pulses of 0.5 g/m^2 with the dose increased on the basis of the white blood cell count) followed by two quarterly pulses in inducing remission and preventing end-stage renal failure after a median follow-up of 72 months.

In a recent meta–analysis of randomized controlled studies,[11] when compared with prednisolone on its own, cyclophosphamide and prednisolone reduced the risk of doubling of the serum creatinine (relative risk (RR) 0.59; 95% confidence interval (CI) 0.4–0.88), whereas azathioprine did not (RR 0.98; 95% CI 0.36–2.68). Neither drug reduced the risk of developing end-stage renal failure, although our unpublished meta-analysis shows that cyclophosphamide does so. Azathioprine reduced the risk of death (RR 0.60; 95% CI 0.36–0.99), whereas cyclophosphamide did not (RR 0.98; 95% CI 0.53–1.82). Lupus affects predominantly women of childbearing age, and the gonadotoxicity of cyclophosphamide (RR 2.18; 95% CI 1.10–4.34) makes it an inherently unattractive agent for therapy and one that is justified by its effectiveness in reducing the risk of renal impairment and relapses.

Azathioprine is a safe drug, and many argued that it was safer than and prob-

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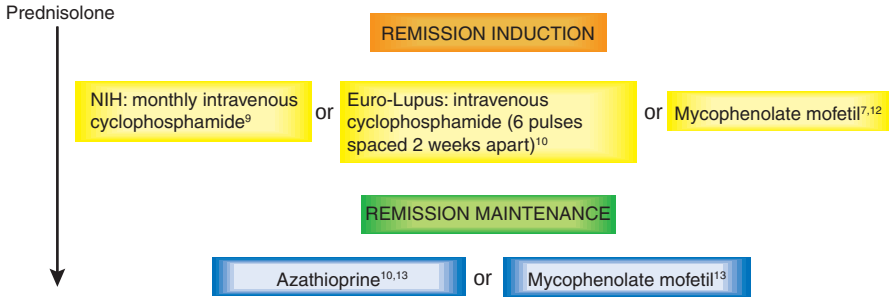

Figure 1 | Treatment of proliferative lupus nephritis (World Health Organization class III or IV). Evidence-based treatment of proliferative lupus nephritis.

ably as effective as cyclophosphamide in the management of lupus nephritis. Grootscholten *et al.*[4] report a randomized controlled trial comparing methylprednisolone, prednisolone, and azathioprine with prednisolone and intravenous cyclophosphamide in patients with mostly proliferative lupus nephritis. After a mean follow-up of 5.7 years, they found that azathioprine was less effective, although not significantly so, than cyclophosphamide in reducing the risk of non-sustained doubling of serum creatinine and was significantly less effective in reducing relapses. This is important in a disease where relapses increase the risk of progressive renal damage. An important observation is that cyclophosphamide treatment is more effective in maintaining remission than azathioprine. That is an issue that needs to be addressed when the studies of mycophenolate mofetil are considered.

Mycophenolate mofetil (MMF) is a powerful immunosuppressant that is licensed for renal transplantation. Pilot studies suggested that it might be effective together with steroids in induction treatment of lupus nephritis, and this has now been tested by two randomized controlled trials. Chan *et al.*[12] compared MMF and prednisolone with prednisolone and oral cyclophosphamide followed by azathioprine in 64 patients with lupus nephritis. In this study the dose and duration of treatment with MMF were increased in patients who were recruited later. Mean follow-up was 57.8 ± 18.7 months. There was no significant difference in the rates of doubling of serum creatinine, end-stage renal failure, and relapses. The risk of amenorrhea was, however, significantly lower with MMF than with cyclophosphamide/azathioprine. Ginzler *et al.*[7] randomized 140 patients with lupus nephritis to treatment with MMF (3 g/d) and prednisolone or with monthly intravenous cyclophosphamide (0.5–1.0 g/m^2) and prednisolone in a 24-week study. Complete remission (defined as a return to within 10% of normal values of serum creatinine, proteinuria, and urinary sediment) was achieved in 16 of 71 patients treated with MMF (22.5%) and in 4 of 69 patients treated with cyclophosphamide (5.8%) ($P = 0.005$). On follow-up, there was no difference in the rates of renal relapse, end-stage renal failure, or death. Both of these studies excluded patients with severe renal failure. One can conclude from these studies that MMF is probably as effective as and less toxic than cyclophosphamide in patients with new-onset mild to moderate lupus nephritis. Further large, adequately powered randomized controlled trials and longer-term follow-up are necessary to establish the role of MMF in induction treatment of lupus nephritis.

Contreras *et al.*[13] compared three monthly intravenous cyclophosphamide pulses (0.5–1.0 g/m^2) with azathioprine (1–3 mg/kg) or MMF (0.5–3.0 g/d) in 59 patients in whom remission had been induced with intravenous cyclophosphamide. All were also treated with prednisolone. Survival was higher in patients treated with azathioprine than in those on intravenous cyclophosphamide ($P = 0.02$). Although there were no significant differences in progression to renal failure, the composite end point of death or chronic renal failure was less common in MMF-treated and azathioprine-treated patients than in patients treated with cyclophosphamide ($P = 0.05$ and $P = 0.009$, respectively). Relapse-free survival was also higher in patients treated with MMF as compared with cyclophosphamide ($P = 0.02$). A criticism of this study is that the number of patients studied was relatively small. Thus MMF may have a role as remission-maintenance therapy in lupus nephritis, but larger randomized controlled studies are needed to confirm this.

Recent randomized controlled trials in lupus nephritis are beginning to allow us to define the role of old drugs (azathioprine and cyclophosphamide) and new drugs (MMF) in the management of lupus nephritis (Figure 1). Important end points in trials should include the risk of developing renal failure or of dying. This requires long-term follow-up and standardization of post-remission therapy. Other end points include the rates of remission induction and relapses, as these may be surrogates for the development of renal failure. Progress will only come from such studies. The place of newer therapies for lupus nephritis such as anti-CD20 antibodies remains to be established.

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Increased cyclooxygenase-2, hyperfiltration, glomerulosclerosis, and diabetic nephropathy: put the blame on the (pro)renin receptor?

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Interaction between the renin–angiotensin system and cyclooxygenases in the kidney regulates renal microcirculation. Activation of the (pro)renin receptor has profibrotic effects, and now Kaneshiro *et al.* show that it also increases COX-2 synthesis. These results may have therapeutic implications, as blocking (pro)renin–receptor interaction would prevent the increase of angiotensin generation and prostaglandin synthesis, two phenomena underlying the pathogenesis of diabetic nephropathy.

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Diabetes mellitus is a fascinating pathological situation associated with high prorenin and low renin concentrations in plasma, resulting in low plasma renin activity and a tissue activation of the renin–angiotensin system especially in the kidney. Renin exists in two forms, mature active renin and the inactive proenzyme prorenin (hereafter the term (pro)renin will refer to prorenin and renin collectively). Although many tissues can synthesize and secrete prorenin, the cleavage of 43 amino acids of the prosegment of prorenin, yielding mature renin, takes place only in the juxtaglomerular apparatus, precisely in the myo-epithelioid cells of the afferent glomerular artery, and there is no known physiological processing of prorenin into renin in plasma or tissue (reviewed by Danser[1]). How can we reconcile the fact that the occurrence of microvascular complications in diabetes, such as microalbuminuria, is correlated with inactive prorenin and not active renin levels, and the paradoxical activation of the renal renin–angiotensin system and increased angiotensin II (Ang II) generation? Because renin controls the rate-limiting step of angiotensinogen cleavage in angiotensin I, one would expect a lower degree of activation of the renin–angiotensin system and not the contrary.

The (pro)renin receptor may provide one explanation. The receptor binds specifically renin and prorenin and, upon binding renin, increases its catalytic activity, and prorenin displays full enzymatic activity similar to that of mature renin;[2] thus the receptor can be regarded as a means to amplify angiotensin generation at the cell surface. In addition, binding of renin and prorenin triggers extracellular signal-regulated kinase-1/2 activation that may have profibrotic consequences.[3] Ichihara *et al.* hypothesized that inhibition of prorenin binding to the receptor would have beneficial effects in diabetes. As no antagonist to the (pro)renin receptor is available, they tested a peptide against the prorenin 'handle region,' a region described by Suzuki *et al.* to be involved in prorenin conformational change and non-proteolytic activation.[4] Indeed, these authors showed that infusion of the 'handle region' decoy peptide (HRP) was able to reduce local Ang II generation and fibrosis in an impressive set of experimental rat models including streptozotocin-induced diabetes,[5] cardiac fibrosis in stroke-prone spontaneously hypertensive (SHR) rats,[6] and ocular inflammation in endotoxin-induced uveitis.[7] Furthermore, these authors also reported the prevention of glomerulosclerosis by HRP infusion in streptozotocin diabetic Ang II receptor type $1a^{-/-}$ mice, indicating that the profibrotic effect of prorenin–receptor interaction was essentially mediated by phosphorylation of the mitogen-activated protein kinases due to (pro)renin receptor activation and not to Ang II generation.[8] These results raise two questions: (1) Renin also binds to the receptor with affinity even higher than that of prorenin,[2] indicating that (pro)renin binding is not dependent on the prosegment that was cleaved during the maturation process, and HRP inhibits only prorenin binding. Therefore, why should inhibition of prorenin binding be sufficient to prevent all receptor activation and pathogenic

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