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The Treatment of Lupus Nephritis in 2008, 60 Years on

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ABSTRACT

Surprisingly, given its very high incidence and prevalence in all populations outside Africa with a West African genetic component, lupus nephritis seems not to be common in West Africa, although its presence is probably under-reported. Nevertheless it is an important disease for which successful – but toxic - treatments are available. For forty years no new therapies were introduced after the major advances of the 1950s and 1960s, but now in the 1990s and 2000s major advances are again being made, with the introduction of exciting agents capable of modifying the course of the disease, some based directly on new knowledge of immunology at a cellular and molecular level. Unfortunately some of these new agents are poorly available, and all are expensive. Treatment of lupus and its nephritis falls into an induction phase followed by a maintenance phase, in which treatment goals and problems encountered are different. This article reviews briefly the options available now and suggests courses of treatment based on a database increasingly made up of information derived from randomised, prospective controlled trials. Much of this information however relates to Caucasian or Chinese populations, and its applicability to Africans is unknown.

INTRODUCTION

Lupus is a common disease in Afro-Americans and in Afro-Caribbean populations in the Caribbean itself as well as in the United Kingdom and in France, but its incidence and prevalence in Africa has been disputed. Few reports of lupus from rural populations anywhere in Africa have appeared, and it does seem to be relatively rare - although no good epidemiological studies have been conducted in any part of the continent. It may be commoner in urban populations with a more Westernised lifestyle, and it is likely that there is under–reporting of lupus in West Africa – for example a recent study identified 11 children with lupus nephritis in only one centre in Nigeria during a period as short as 4 years [1]. Genetic influences in lupus are strong, however, and it has been suggested that admixture of genes leads in part to its undoubted very high incidence in mixed but predominantly West African populations in North America, the Caribbean and in Europe [2], rather than differences in lifestyle.

Lupus presents a challenge to physicians whenever it occurs, and one must never forget that it is a truly systemic disease. But since the kidneys are commonly involved and renal involvement is a major prognostic factor, and it is treatable at least in part, lupus is of importance in Nephrology beyond its rather low incidence [3, 4].

Sixty years ago, before any effective treatment was available, if lupus was found to affect the kidneys the outcome was that two thirds of patients were dead within a year or two. Now, at least three quarters of patients can be expected to survive a decade or more [3-5]. Despite these dramatically improved results, the blunt fact must be admitted that as this is a disease of young adults and thus many life-years are still lost, and also that the cost (in terms of side-effects) in cohorts treated with success (in terms of survival) can only be described as horrendous [5].

The current therapeutic strategies used in lupus were introduced and developed in a mostly empirical fashion during the [illegible]. The first time an immunosuppressant agent (nitrogen mustard) was used in lupus was probably [illegible] Dave Baldwin's unit in New York. The agents used for almost half a century [illegible] azathioprine (1964) and cyclophosphamide (1974), but nitrogen mustard [illegible] These, in various [illegible] of administration and dosages, [illegible] norm for the next 40

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years [3]. Most effort was put into optimising treatment using these drugs, and especially in minimising their inevitable toxicity, which later longer-term studies showed to have been even more devastating than seemed initially to be the case.

Now after this long period of stasis, within little more than a decade there has been the rapid introduction of a number of new agents, some based on more and more precise knowledge of the immune system at a cellular and molecular level, some of them developed primarily for other clinical situations e.g. organ transplantation, rheumatoid arthritis or immune-based disorders in general [7-9]. These agents are still in the process of evaluation, both in terms of absolute efficacy and how they compare with the established treatments, and also in relation to both levels of success and to frequency and severity of side-effects. This complex process is still in full flood, which makes it difficult to summarise the situation today, or to provide durable evidence-based guidance as to the best courses to take. Unfortunately also, most of these new agents have a common feature which goes against their wider application: high cost.

General Treatment Strategy

Two main data sets should determine the type, dose and duration of treatment [3,4] for an individual patient. The first is the *severity of the disease,* judged by clinical and renal histological findings: immunological and other laboratory tests (other than those of renal function and the urine sediment) are of little value here. The second is *the phase of the disease* - has it just begun, or has it already run its course in part? For many years I have advocated the useful division (derived from oncology) of dividing treatment of patients with lupus nephritis (with other than minor disease) into an *induction phase* and a *maintenance phase*. The induction phase of treatment typically deals with severe, acute life-threatening disease, often affecting many systems and usually near the onset of the condition; here the threat of the disease is paramount. There follows, after a period of several weeks or a few months, the maintenance treatment and long-term management of chronic, one hopes more or less indolent disease. Here protection from the side-effects of treatment while preventing relapses ("flares") becomes more and more important.

Use of the clinical picture and the older WHO and current ISN/RPS biopsy classification can serve as a guide to therapy [3, 4]. In general, patients with ISN/RPS histological Class I and II need no therapy directed at the kidney, although a few will have an important nephrotic syndrome despite normal or near normal renal function. Whether treatment with corticosteroids or other immunosuppressive agents at this point might prevent subsequent evolution to severe disease in the future is unknown. The majority of patients will have a benign long-term outcome, and the potential toxicity of any immunosuppressive regimen will negatively alter the risk-benefit ratio of treatment. An exception is the group of recently-described lupus patients with minimal change syndrome or lupus podocytopathy. These patients respond to a short course of high dose corticosteroids in a fashion similar to patients with minimal change disease [8].

It is in the groups of patients with reduced or falling renal function, profuse proteinuria and often an "active" urinary sediment, who show in addition on renal biopsy active focal proliferative lupus nephritis (ISN class IIIA and IIIA/C), active diffuse proliferative lupus nephritis (ISN class IV A and IV A/C), and membranous lupus (ISN class V), that immunosuppression is most widely and appropriately used. Only recently have any really long-term data on outcomes emerged [9,10], and demonstrate that whilst treatment is effective, it is also toxic, increasingly so in those who continue to require active treatment.

There is now good evidence that clinical exacerbations of lupus ("flares") are associated with a poorer prognosis [11], and should in general be treated with further courses of induction therapy. Conversely there is also evidence that diminution and absence of proteinuria generally signals a more benign prognosis, and should permit a lighter treatment regime. The very long-term outcome of patients suffering lupus nephritis under treatment is poorly established [5,11], but overall some 15% of patients will enter renal failure over about 15 years, while around one half will go into complete clinical remission within 10-15 years. Within a similar period, about one third will be able to discontinue treatment altogether. With the treatment tailored to the severity of the disease as outlined above these figures are little different for those who have initially less or more severe renal disease.

The Treatment of Proliferative Lupus Nephritis – Induction Phase

Corticosteroids

Many clinicians treat all patients with active proliferative lupus nephritis with high doses of corticosteroids. These have typically been used alone in the past, and more commonly with other immunosuppressives in recent studies. High dose oral regimens (e.g. starting dose prednis(ol)one 60 mg/day) as well as "pulse" intravenous methylprednisolone infusions (0.5 – 1.0 g daily for one to three days) followed by lower doses of oral corticosteroids have been utilised since early non-randomized data did suggest a benefit from higher treatment doses. Both oral and intravenous regimens carry a significant risk of side effects. Cosmetic effects, risk of gastrointestinal ulceration, hypertension, psychoses, and an enhanced risk of infectious complications have all led to attempts to minimise prolonged courses of corticosteroid therapy in lupus patients. Some small trials suggested that intravenous pulse therapy is either more effective or less toxic than high dose oral therapy.

Cytotoxic Agents

Cytotoxic agents in conjunction with corticosteroids have played – and still play - a major role in most induction therapies for lupus nephritis [12, +-28]. The most recent of three consecutive meta-analyses of randomised controlled trials, performed during a 20-year period [13] confirmed that in lupus nephritis, the addition of a(ny) cytotoxic agent certainly confers benefit in terms of survival compared with corticosteroids alone. For 40 years the two main agents available were azathioprine and cyclophosphamide. Anecdotal results using either agent were always similar [3], but only one direct randomized comparison of cyclophosphamide (by the intravenous route, 13 pulses over 2 years) and oral azathioprine (backed by 3 pulses i.v. methylprednisolone 1 g. in the acute phase) has been performed [14]. This involved 87 patients followed for 5.7 years, of whom 50 received i.v. cyclophosphamide and only 37 an azathioprine regime. During the first 24 weeks, there was no differences in the decline in plasma creatinine or diminution of proteinuria, or in return of anti dsDNA antibody or C3 complement concentrations to normal. Nevertheless, this study reported only in 2006, and in the meantime the controlled studies at the NIH in the United States (which however included only a tiny number treated with azathioprine alone), plus inferences from the pharmacology of the two drugs, led to cyclophosphamide becoming the usual mode of treatment.

Cyclophosphamide is a powerful inhibitor of B cells, as well as other phases of the immune response. Whether oral therapy or intravenous pulses of cyclophosphamide may be more effective in treating the nephritis remains inconclusive [15, 45], but the latter is presumed (but never yet proven) to produce less toxicity.

Trials at the National Institute of Health (NIH) in the United States initially established a role for every third month intravenous pulses of cyclophosphamide in preventing renal failure in patients with diffuse proliferative lupus nephritis. Subsequent randomized, controlled trials in patients with severe proliferative lupus nephritis [16, 29] established that a regime consisting of six pulses of intravenous cyclophosphamide (0.5-1g/m^2) on consecutive months, followed by every third month follow-up pulses along with low dose corticosteroids, was effective and prevented relapses better than a shorter regimen limited to six doses. A subsequent controlled trial established than pulse cyclophosphamide when given with monthly pulses of methylprednisolone led to a better preservation of GFR than either regimen alone [17, 30]. Long-term follow-up of these patients showed that the regimen of intravenous pulse cyclophosphamide plus methylprednisolone had no more side effects than the regimen using pulses of cyclophosphamide alone. This in part may have been due to fewer relapses and greater initial efficacy of the prior regimen leading to less need for retreatment in the follow-up period. Nevertheless, side effects were significant (see below) in both therapeutic arms of this study [17, 30].

A recent study used intravenous cyclophosphamide to induce remissions in 59 patients with severe lupus nephritis, almost one-half African American, with a mean serum creatinine of 1.6 mg/dl and average urinary protein to creatinine ratio of over 5 [18, 31]. With six to eight monthly intravenous doses 83% had a remission, with mean creatinine reduction from 1.5% to 0.97 mg dl, mean urinary protein/creatinine ratio declining from 5.1 to 1.7, and correction of hypertension and serologic abnormalities. Thus it is clear that cyclophosphamide is effective in induction therapy, and studies using newer agents therefore have focused on achieving similar high induction response rate, but with fewer side effects.

A recent trial by the Euro-Lupus Group tried to decrease the risk of side effects from cyclophosphamide therapy without sacrificing efficacy [19, 32]. This study randomized 90 patients with diffuse or focal proliferative, or membranous plus proliferative disease to receive either standard six monthly pulse of cyclophosphamide, followed by every third monthly infusions; or to a shorter treatment course consisting of 500 mg intravenous every two weeks for six total doses, followed by a switch to azathioprine maintenance therapy. Both regimens were equally effective with regard to both renal and extra-renal outcomes . The shorter regimen had less toxicity, with significantly less severe and total numbers of infections as a complication of treatment. This trial was largely performed, however, in Caucasians and may not be applicable to all populations at high risk for poor renal outcomes such as Afro-Americans and Afro-Caribbeans. In all areas there is a paucity of good data – and especially trial data – in those from the major areas of Africa, including West Africa.

Mycophenolate Mofetil (MMF)

MMF is the pro-drug of mycophenolic acid, an inhibitor of IMP dehydrogenase which inhibits DNA synthesis amongst other actions. Several recent controlled trials have examined the role of MMF in the induction of remission of severe lupus nephritis [20, 21-23, 33-35]. In one performed in an exclusively Chinese population, 42 patients randomized to receive either twelve months of oral MMF (2g/d for six months followed by 1 g daily for six months) or six months of oral cyclophosphamide (2.5 mg/kg/day) followed by oral azathioprine (1.5 mg/kg/day) for six months [21, 33] were evaluated. Both groups received concomitant tapering doses of corticosteroids. At twelve months, the number of complete or partial remissions and relapses was not different between the regimens. Infections were less in the MMF arm, and mortality was all in the cyclophosphamide group (0 vs 10%). Longer follow-up confirmed the long-term benefits of the MMF group [24, 36]. A second trial, also in a Chinese population, evaluated 46 patients treated with either pulse intravenous cyclophosphamide or MMF for six months [22, 34]. Patients treated with MMF had greater reductions in proteinuria, haematuria, anti-DNA antibody titre, and greater improvement on renal biopsy.

Another trial examined 140 patients with proliferative lupus nephritis [23, 35]. One half was randomised to intravenous cyclophosphamide monthly pulses and one half to MMF in conjunction with a fixed tapering dose of corticosteroids as induction therapy over six months. The study included over 50% African Americans and allowed cross-over at three months for treatment failures. Complete remissions at six months were significantly more common in the MMF arm as were complete plus partial remissions. Side effect profile was better in the MMF group. At three years there were no significant differences in numbers of patients with renal failure, ESRD, or mortality. A large international multicentre trial of induction therapy with either MMF or monthly intravenous cyclophosphamide is underway, and should help to resolve present uncertainties. A meta-analysis of the principal trials [20] concluded that MMF both increased remission with lower incidence of infection, and thus at present we would recommend MMF as the first choice for a cytotoxic agent during the induction phase. However in many area of West Africa it is not readily available, and its cost is high compared with cyclophosphamide. Our treatment preferences for both induction and maintenance therapy are summarised in Figure 1.

Other Agents

A number of other therapeutic interventions have been directed at blockade of specific areas of the immune response in attempts to induce remissions in patients with lupus nephritis.

Plasma exchange has been added to other induction therapies, e.g. cyclophosphamide, in several controlled randomized trials in patients with proliferative glomerulonephritis. There was no benefit in terms of renal or patient survival or in reduction of proteinuria or improvement of GFR. However there remains the possibility that exchange may be of benefit in certain special situations, e.g. alveolar haemorrhage, thrombotic thrombocytopenic purpura, major anti-phospholipid antibody syndromes, symptomatic cryoglobulinaemia and lupus with severe vasculitis [25].

Intravenous gamma globulin has given encouraging results as adjunct therapy for patients with severe lupus and nephritis although it has not been studied in adequately powered controlled trials [4]. A major problem is that there is no standard preparation of i.v. IgG, even from a single manufacturer, and hence no dosage can be recommended generally. Moreover a fall in GFR may be seen during administration, not always reversible.

For patients with life-threatening resistant disease small pilot studies have utilized *total lymphoid irradiation or marrow ablation* with or without reconstitution with allogenic stem cells [3, 4]. These approaches are experimental at this time and have potentially high toxicity.

Monoclonal antibodies

Early studies using monoclonal antibodies directed against B and T cell co-stimulation (anti-CD 40 ligand) proved unsuccessful, in part due to lack of efficacy and in part due to thrombotic complications. New trials using CTLA4Ig to block T and B cell co-stimulation are underway . Anti B-cell antibodies represent an attractive approach, and in uncontrolled, non-randomized trials of small numbers of patients (ca 100 so far) *rituximab*, a mouse/human chimaeric monoclonal antibody (and hence itself immunogenic) directed against CD19 and CD20 B cells, has been used. It has proven useful in inducing remissions in some patients with severe lupus nephritis including some who have failed cyclophosphamide or MMF therapy either alone [26,37] or with concomitant cyclophosphamide [27]. It is currently being studied in multicentre, controlled and randomised trials in the United States and the Americas, both for acute disease (LUNAR) and longer term (EXPLORER). Other new medications to block other areas of the immune response [6-8] such as anti-BLyS are being examined as well.

The Treatment of Proliferative Lupus Nephritis – Maintenance Therapy

In most patients the acute renal disease will come under control by 3 months of therapy. By six months almost all responders will have improving serologic markers (anti-DNA antibody titer, serum complement), improvement of GFR and decline in proteinuria. Persistent, but declining, levels of proteinuria or some urinary sediment abnormalities at six months are not rare and do not indicate disease activity. The challenges once remission has been induced is to avoid relapse and flares of disease activity, to avoid "smouldering" activity leading to chronic irreversible renal scarring, and to prevent long-term side effects of therapy. A number of agents have been studied in maintenance regimens for lupus nephritis patients once induction has been induced.

Corticosteroids are a major component of treatment in the maintenance phase of lupus nephritis therapy. There are no studies which exclude the use of steroids in maintenance therapy. To minimise the side effects of long-term corticosteroids, the dosage should be limited (e.g. predniso(lo)ne 5-15 mg/day) and osteoporosis prophylaxis should be given concomitantly (Figure 1). Both daily and alternate-day corticosteroid regimens have been used.

A number of meta-analyses unequivocally favour the additional benefit of using a *cytotoxic agent* during the maintenance phase of lupus nephritis therapy [13]. Also in the long-term trials at the NIH, over 10-15 years follow-up regimens of either intravenous cyclophosphamide, oral cyclophosphamide, or oral cyclophos-phamide plus oral azathioprine showed less progression of renal scarring than either prednisone or azathioprine alone regimens .

While oral *cyclophosphamide* has been used for induction therapy in a number of trials, its use for longer than 3-6 months should be avoided due to toxicity. Alopecia is especially unpleasant for the young female lupus population. Bladder toxicity which can include haemorrhagic cystitis, bladder scarring, and bladder cancer occurs rarely with intravenous cyclophosphamide administered with adequate hydration. However, intravenous cyclophosphamide, like prolonged daily oral treatment carries a considerable dose and age dependent risk of gonadal damage and early menopause. Timing of the intravenous cyclophosphamide pulse in co-ordination with the menstrual cycle and the use of leuprolide acetate have been attempted, but infertility remains a major complication of all women over the age of thirty, and especially those receiving longer than a six month induction course. The oncogenic risk of regimens including alkylating agents may not be evident for many years. Clearly the risk of infection and marrow suppression increases with extended use of more aggressive immunosuppression. Chlorambucil is rarely used in lupus patients since its gonadal and oncogenic properties are if anything greater than cyclophosphamide.

Azathioprine in doses of 1-2.5 mg/kg/24 h has proven remarkably safe in the very long term. Macrocytosis, leukopaenia at high doses, and interaction with allopurinol making it difficult to use in patients with gout, are all potential side effects, along with the ever-present risk of infection from immunosuppression. Pancreatitis and hepatotoxicity are rare side effects of treatment. Azathioprine has only a small oncogenic potential, and pregnancy during maintenance azathioprine is relatively safe. Two recent studies used azathioprine successfully as maintenance therapy after induction with short or long

Supportive treatment throughout:

- ACE inhibitor/ ARB, other antihypertensives as needed, statin if nephrotic syndrome
- Osteoporosis prophylaxis
- Measures for primary or secondary prevention of cardiovascular disease (statin etc.)

Specific treatment

Induction phase (3 – 6 months)

Methyl prednisolone IV 1g. for 3 days
or
Oral prednisolone 1 mg/kg/24h
PLUS
Mycophenolate mofetil 1- 1.5 g. b.d.

- OR replace MMF with i.v. cyclophosphamide
0.5 – 1.0 g. IV monthly for 6 months

- OR replace MMF with oral cyclophosphamide
1-3 g. /24h for 3 – 6 months

Maintenance phase (indefinite)

Low dose prednisolone (5-10 mg/ 24h. OR alt days
PLUS
Mycophenolate mofetil 0.5 – 1.0 g. b.d.

-OR replace MMF with oral azathioprine 1-2 mg/kg/24h. *(Based on [4])*

Fig. 1: Treatment of the induction and maintenance phases of active focal, and diffuse lupus nephritis (class IIIA and IV ISN/RPS)

Change to an alternative agent – if on MMF, change to cyclophosphamide and *vice versa*
Use 3 i.v. injections of 1 g. methylprednisolone either again or *de novo*, and repeat monthly for 3 months.
Add rituximab (1g. i.v. over 4 hours, repeat after 2 weeks)
Add i.v. gamma globulin in whatever dose the manufacturer recommends
(Based on [4])

Fig. 2: Continued induction management of resistant severe forms of lupus nephritis

course of cyclophosphamide or MMF [18, 31, 19, 32]. This treatment also is much more popular with patients than i.v. intermittent cyclophosphamide, and much cheaper to administer.

Mycophenolate mofetil has been used to maintain remission after induction therapy with the drug in a number of lupus trials [18, 31, 24, 36]. Moreover, in one study azathioprine and MMF both proved superior at maintaining remissions and preventing mortality or ESRD than did continued every third month intravenous cyclophosphamide [18, 31]. Major side effects (including number of hospital in-patient days, amenorrhoea and severe infections) were all significantly lower in the group receiving the oral agents. Finally the major worldwide ASPREVA/AMLS trial [28] currently underway compares mycophenolate with i.v cyclophosphamide for 6 months, followed by blinded allocation to oral azathioprine or mycophenolate, and had recruited 358 patients up to 2006 and should report soon. MMF therapy carries the risk of immunosuppression and infection, and gastrointestinal side effects, and in addition (unlike azathioprine) is teratogenic. This, and the much greater cost of MMF than azathioprine therapy, becomes an even more important factor in choosing a maintenance treatment.

Cyclosporine has been used with limited success as monotherapy for maintenance of remissions in patients with proliferative lupus nephritis, but is more commonly used with concomitant corticosteroid therapy. In a single controlled study reported [29] to date after induction with i.v. corticosteroids and oral cyclophosphamide, for maintenance therapy concomitant steroids were given to randomised groups treated with azathioprine or with cyclosporine. There were no differences in the following 4 years in outcomes, including number of flares, or in numbers stopping treatment because of treatment side-effects. Cyclosporine perhaps has a greater role in the treatment of both primary and later-emerging membranous nephropathy, with the aim of reducing the sometimes considerable proteinuria. Nephrotoxicity, hypertension, hyperuricaemia, and hyperkalaemia are all potential adverse side effects, however. *Tacrolimus* has similar toxicity and has been used only in limited non-controlled trials in lupus nephritis .

Several studies have been conducted with a designer molecule composed of a polyglycol platform and four DNA side chains, *LJP 394*, to try to prevent flares of lupus nephritis [30, 38]. Although anti-DNA antibody titres decreased, it still remains unclear if the drug can actually prevent flares of disease activity.

A summary of disease-specific maintenance treatment is given in Figure 1 for both induction and maintenance phases of treatment of severe proliferative lupus nephritis. General renoprotective measures such as the use of ACE inhibitors and/or ARBs, the use of statins for both their lipid lowering and pleiotropic effects, and optimal blood pressure control can all reduce morbidity in the lupus nephritis population. Other agents used to treat extra-renal findings in lupus patients, including non-steroidals, antimalarials, androgens, and fish oils, have not shown beneficial effects on nephritis.

The majority of patients will be maintained in remission by such treatment, but in a few cases the initial disease is so severe that it does not come under control, and/or frequent early relapses are seen. An approach to the management of such patients is summarized in Figure 2.

Membranous Lupus Nephropathy

In the past, investigators reported very different renal survival rates for different populations with "membranous lupus nephropathy". In part this was due to problems with the old pre-1995 WHO classification, since renal survival in WHO class Va and Vb (membranous without any or with only mesangial immune aggregates) was 75% after 5 years or longer, but in contrast was only 59% for class "Vc" and 18% for class "Vd" patients in whom more severe proliferation was evident as well as the membranous changes [31.39] whose outcome ws similar to diffuse proliferative disease. Moreover, patients with sub-nephrotic proteinuria and "pure" membranous lupus nephropathy do extremely well regardless of treatment options. Thus no consensus of management has emerged yet for this group of patients.

In a controlled trial, 42 patients with lupus WHO class Vc and Vd only were randomised to receive either monthly pulses of intravenous cyclophosphamide, oral cyclosporine, or oral prednisone alone for a year [32, 40]. The patients had preserved GFR, but mean proteinuria of almost 6g daily. At last follow-up, there were more complete and partial remissions in the cyclophosphamide and cyclosporine groups than in the prednisone alone group. Remissions occurred more quickly in the cyclosporine group, but there were fewer relapses in the cyclophosphamide group. Patients who relapsed

or failed to respond to cyclosporine could subsequently be brought into remission with intravenous cyclophosphamide. In the 140-patient induction trial in the United States, 27 patients had pure (Va or Vb) membranous lupus nephropathy [33, 41]. Remissions, relapses, and course were similar in the patients treated with oral MMF or intravenous cyclophosphamide induction therapy. Azathioprine along with corticosteroids has also been successful in some populations of membranous lupus.

Thus, for patients with membranous nephropathy who have sub-nephrotic levels of proteinuria and a preserved GFR one can recommend treatment as in Figure 3, based on opinion not adequate data. Either a short course of cyclosporine or corticosteroids may be given, of course along with an ACE inhibitor and/or ARBs, and statins. For fully nephrotic patients and those at higher risk for progressive disease there are multiple more or less unproven treatment options: a course of oral cyclosporine, or monthly intravenous pulses of cyclophosphamide, or MMF, or azathioprine plus corticosteroids. In all, the course will have to be at least six months, and avoiding side effects is paramount.

Remissions and Relapses

Achieving a remission of lupus nephritis predicts an improved long-term outcome. In one study the five year patient and renal survival was 95 % and 94% respectively for the group achieving remission and only 69% and 45 % respectively for the group not achieving a remission [34, 24].

Predictors of remission have avried from study to study but include lower baseline serum creatinine, lower baseline urinary protein excretion, better renal histologic class by the WHO/ISN system, lower chronicity index, stable GFR after 4 weeks of therapy, and Caucasian race. In American series, Afro-American patients consistently do worse than Caucasians [e.g. 35] but the reasons for this include socio-economic as well as biological factors, which influence survival in any complex chronic disorder. European Caucasian and Chinese patients seem to have similar outlooks, but where the prognosis for Africans with lupus nephritis might fit in is unknown.

Subnephrotic proteinuria without symptoms

Supportive treatment as in figure 1
PLUS
Oral prednisolone 5 –15 mg/24h. for 2-6 months
-OR
low-dose cyclosporine to maintain plasma drug levels <150 ng/ml

Nephrotic syndrome and/or symptomatic
Supportive treatment as in figure 1
PLUS
Low dose prednsiolone 5-10 mg/24h
PLUS
Mycophenolate mofetil 1-1.5g. b.d. for 6 months
OR
Cyclosporine 4-6 mg/kg/24h. for 4-6 months
OR
Azathioprine 1-2 mg/kg/24h

(Based on [4])

Fig. 3: Treatment of membranous lupus nephropathy (ISN RPS class V)

The relapse rate for lupus nephritis has ranged from 25 to almost 60% depending upon which population is studied, what criteria for relapse are used, and what maintenance therapy is used. Elevation of the anti-DNA antibody titre and decline in the serum

complement levels may presage relapse. However, a number of patients maintain elevated anti-DNA antibody titres for years without relapse, and most clinicians prefer not to treat "serologic" activity alone in the absence of clinical disease activity. A major value of a normal anti-DNA titre is to permit safe reduction of treatment during the chronic phase of maintenance therapy.

Relapses (flares) are common and are correlated with a poorer prognosis [10, 36, 37]. Thus they deserve treatment as for induction therapy in the majority of cases, although the stage of the disease at the time of the flare, the renal function and extra-renal manifestations of lupus will all influence duration and intensity of any escalation in treatment.

When can Treatment for Lupus Nephritis be Stopped?

The goal of long-term management in patients with lupus nephritis is suppression of disease with minimum side effects of treatment. While normal results from immunologic tests and urinary sediment examination may be helpful, a repeat renal biopsy will be useful in some patients to clarify whether a slow decline in GFR is the result of persistent active glomerular disease, or arise from secondary sclerosis .While some patients will relapse many years after remission and disease quiescence, it is often possible to stop treatment entirely in many patients after five or more years when the disease process has apparently "burnt out" [38] Stable GFR, lack of proteinuria, and normal immunologic tests predict successful discontinuation of immunosuppressives.

Pregnancy and Treatment of Lupus

As lupus is predominantly a disease of young women, issues of fertility and pregnancy are of particular importance, and have been much discussed [39]. In general, both corticosteroids and azathioprine appear not to affect either fertility or the outcome of pregnancy in lupus [40] and a very large additional data base exists in the field of organ transplantation to confirm this. In contrast, cyclophosphamide both induces early menopause in many patients and also is markedly teratogenic. Few data are yet available on mycophenolate, but fetal the drug should be avoided if pregnancy is contemplated..

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