Pathogenesis and treatment of lupus nephritis

J. STEWART CAMERON

Renal Unit, Guy's Campus UMDS, London, UK

Today I wish to spend a short period discussing briefly the pathogenesis of the lupus syndrome, then I will devote the bulk of my time to considerations of treatment in lupus nephritis. Finally, I would like to say a few words about pregnancy in women with lupus nephritis.

Pathogenesis of lupus

The genesis of autoimmunity is one of the key topics in Immunology today. A number of theories, none of them exclusive, have been proposed to explain the emergence of cells specifically committed against self antigens, and the consequent appearance of autoantibodies in the circulating plasma. The first of two main theories suggests that autoreactive cells are a part of the normal immunologic repertoire in normal individuals, but usually are not allowed expression. In disease, this inhibition breaks down and the autoreactive clones are in some way allowed to proliferate, either by polyclonal stimulation of all B cells or more specific loss of anti-idiotype control. The other theory suggests that autoantibodies are new specificities, requiring presentation of antigen and somatic alterations in the DNA of the V-line genes of the immunoglobulin molecule. The antigen might either be self antigen itself, or exogenous (e.g. viral) antigen which in some ways mimics the structure of self antigens (‘antigenic mimicry’).

Several factors modulate the appearance of autoimmune disease: these include particularly genetic and familial factors: familial lupus is common, and the disease is often associated with other rheumatologic conditions in the family. There is a 65% disease concordance in identical twins. Surprisingly, associations with MHC coded genes (tissue types) are poor, with the exception of C4 null genes. Second the presence of the female phenotype is important. Lupus is 10–12 times as common in women than men, and particularly occurs in their fertile years. In mice, castration and cross hormone injection experiments also suggests a facilitating role for the female phenotype and oestrogens. Finally it appears that a triggering factor is necessary, which is known in the case of drug induced lupus, but unknown in most cases of ordinary lupus.

All lupus is associated with the production of autoantibodies, particularly directed against nuclear components such as DNA, as well as RNA. Autoantibodies against a variety of other self antigens may be seen, and some are associated with tissue specific damage such as anti red cell antibodies (haemolytic anaemia) or anti white cell antibodies (leukopenia). Antibodies against exogenous, viral antigens are also present in large amounts in the circulation.

The role of the anti DNA antibodies in renal and other tissue damage still remains contentious 35 years after their discovery. Immune aggregates containing DNA and anti DNA antibodies are certainly present in damaged tissue, including the kidney, in both the glomeruli and the interstitium, but form only a tiny proportion of the total aggregate present. Direct binding of anti DNA antibodies to basement membranes including the glomerular basement membrane, and cells, has been proposed as a pathogenic mechanism. Other autoantibodies also bind in the kidney, and at the moment we do not know the details of how in-
flammation is triggered. The abundant immune complexes in the circulation, again formed of many other antigens besides DNA and nuclear antigens, appear now to be largely epiphenomena, and deposition of immune aggregates from the circulation into the kidney less likely. The possible role of defective uptake of circulating complexes by the reticulo endothelial system is not clear.

The modes of injury within the kidney in lupus nephritis appear to be similar to those found in other forms of nephritis: complement activation with the formation of both C5b-9 and attraction of inflammatory cells, of which monocytes seem to be the most important quantitatively, T cell activation, with a possible role in direct tissue injury, and activation of both fluid phase coagulation and platelets. It is worth noting that the interstitial cell-mediated damage may be more important in lupus than glomerular damage.

Finally the disposal or dissolution of the immune aggregates in the renal and other tissues may be defective. This is dependent upon solubilisation by complement, and perhaps explains why inherited complement deficiencies are strongly associated with lupus.

Treatment of lupus nephritis

This is one of the success stories of Internal Medicine. Despite all the problems of choice in the treatment of lupus which I wish to discuss, there is no doubt that the prognosis for patients with lupus nephritis, particularly its most severe forms, has improved greatly during the last few decades. A 10–20% survival at 5–10 years has been changed to a 10–15% death rate or less. Although there are many treatments that have been suggested for lupus, only a few have been adequately evaluated or appear really effective; I shall not discuss therefore some less often used treatments such as fish oil, anabolic steroids or danazol, etc.

It appears essential to me to discuss the treatment of lupus nephritis in two distinct sections: first, the induction treatment of the acute disease, in which the main danger is the lupus itself; a second the indefinite period of maintenance treatment, during which the main danger is often the side effects of the drugs used to control the disease, and not the disease itself.

Second, all clinicians know that lupus is above all variable disease, from patient to patient and with time even in a single patient. Thus treatments must be varied and individualised, and this makes the performance and interpretation of clinical trials particularly difficult.

It is my belief that a renal biopsy is an essential part of the initial evaluation of the patient with lupus and urinary abnormalities. It is also our belief that the initial, induction treatment of the patients should be the more aggressive the more severe the clinical and histological picture found. This belief has never been tested properly in any controlled trial, and of course adopting this strategy takes away from us the chance to test the idea. Nevertheless, it works, in that the prognosis of the most severe forms of nephritis, formerly much poorer than those with mild nephritis, now equals that of the mild forms.

In interpreting the renal biopsy, perhaps more important than the morphologic appearance as delineated by the WHO, is the degree of histological activity on the one hand, and the degree of irreversible scarring on the other, both to be assessed in the glomeruli and in the interstitium. Interstitial events predict prognosis in lupus, as in most glomerular diseases, better than glomerular appearances.

In patients with mild proteinuria and normal renal function, with the renal biopsy showing mesangial nephritis (WHO class 2) or membranous nephropathy (WHO class 5), we would use only oral corticosteroids in modest dose. If progression occurred despite this treatment, and especially if the histology evolved to more severe forms, we would add in a cytotoxic agent. We would also use a cytotoxic agent together with the corticosteroid from the outset in any patient with more severe forms of nephritis (WHO class 3 or 4, focal or diffuse proliferative nephritis), especially if a full nephrotic syndrome were present. In cases with reduced renal function, we would normally start the corticosteroid dosage off with intravenous pulses of methylprednisolone.

Three questions arise immediately from this policy:

First, what is the evidence that the addition of a cytotoxic agent improves prognosis in severe lupus nephritis? After some years of doubt, the meta analysis of several controlled trials, and the histological data from the National Institutes of
Health group in the USA have established clearly that there is advantage, in both clinical and histological terms, of a cytotoxic agent in addition.

Second, what cytotoxic agent should be used? For acute induction treatment, cyclophosphamide has advantages in that it brings the gross B cell overactivity and autoantibody formation under control very rapidly and powerfully, which neither azathioprine nor cyclosporine can do. I see no advantage of giving this orally absorbed drug, cyclophosphamide, by the intravenous route, and it should never be used for longer that 8–12 weeks because of gonadal and bladder toxicity, and its tumour inducing potential. For maintenance treatment, conversion to long term azathioprine at 8–12 weeks gives results as good as long term intermittent intravenous pulse cyclophosphamide, and I see no advantage in using this still toxic drug long term, as has been strongly advocated by the NIH group in the USA. The question of pregnancy arises also and I will discuss this aspect later in the talk.

Third, is there any evidence that intravenous methylprednisolone is any more effective than high dose oral prednisolone? The answer is no, but I still use the intravenous route because it allows low dose oral treatment from the start, is relatively safe, and rapid in effect with minimal side effects.

What should one do in the acute phase if all these measures, intravenous methylprednisolone, oral corticosteroids and cyclophosphamide, fail to arrest the disease and bring it under control? What role might plasma exchange have? In this area there are almost no data, but the recent controlled trial in the United States, whose results has not yet been published, did not show any advantage in WHO class 4 lupus of plasma exchange – although the regime used was not so intense or so prolonged as some advocates of exchange have used. Certainly there seems to be no justification for using plasma exchange as routine in all cases of severe lupus. Thus we use it on a daily basis for 7 consecutive days in patients who do not come under control, and in those with severe cerebral lupus or severe extra renal lupus vasculitis.

What of cyclosporine? So far the results in acute lupus have been rather disappointing. DNA antibodies are not reduced, and perhaps the main use of cyclosporine will be as maintenance treatment in order to reduce the dosage of prednisolone to more acceptable levels, perhaps as part of triple azathioprine-prednisolone-cyclosporine regimes, as used in renal transplantation.

Finally it is worth mentioning that total lymphoid irradiation may have a place in the occasional very severe resistant case which progresses despite all the treatments already mentioned. This has been applied with success in Stanford, USA, by Strober and his colleagues, in lupus as well as in transplantation, and there is no doubt that this has a powerful and asting immunosuppressive effect; but its long term side effects are not yet known.

Can treatment be stopped in lupus nephritis, and if so, when? This question can only be answered in very general terms. We have seen ‘flares' of severe lupus nephritis, with fresh crescents and glomerular necrosis, as long as 28 and 22 years from onset, so in some patients treatment must be maintained almost indefinitely. In others, however, the urine becomes normal, renal function is stable or normal, and the immunologic tests are all negative after only a few years. Under these circumstances we would do a repeat biopsy to ensure that the histological appearances were inactive, then stop treatment gradually, usually without replase. However, lupus can always surprise and such atients hould still be followed up and their immunological and urine tests checked to anticipate possible replace.

What of the future? So far as new immunosuppressive agents are concerned, naturally one would like to see trials of the new Japanese macrolide immunosuppressant, FK-506, in lupus, and it may be that someone in this hall today is already engaged on such a study. However the immunosuppressive approach is at best a clumsy one; much better would be to attach the dysregulation of the immune system at source. A beginning has been made on this more specific approach in murine lupus, using a variety of monoclonal antibodies. When ‘humanised' monoclonal reagents are more readily available with human Fc portion of the molecule, which do not evoke anti-mouse antibodies, the potential for blocking immune responses more specifically in humans will be present.
Pregnancy in lupus nephritis

Lupus is a disease of young women in their fertile years, and therefore successful pregnancies should be an aim in the treatment and rehabilitation of such patients. Until recently results were so bad that this could not be contemplated, but not with improved results the question is now an important one. Although there is a fair amount of data on lupus in general, recently have data been accumulated for women with clinical nephritis.

Most workers are agreed that pregnancy in lupus nephritis should only be contemplated if and when the disease is under control, and both treatment and renal function are stable. There are a number of factors which are adverse for the fetus, including the nephritis and its associated hypertension, possible reduced renal function, the transplacental passage of autoantibodies, and the effects of the treatments the mother may be taking.

There is now good evidence from transplant recipients that azathioprine and prednisolone are safe throughout human pregnancy, despite teratogenic effects in rodents. This is not so for cyclophosphamide, which even when given intermittently by the intravenous route accelerates the menopause and may also delay puberty. Therefore the wish for pregnancy seems to me another powerful argument for maintenance azathioprine rather than monthly or bimonthly intravenous cyclophosphamide pulses in the long term management of lupus nephritis.

Nevertheless, in our own and in other series of pregnancies in women with lupus nephritis there is a higher fetal loss rate than expected, which relates to immune attack on the placenta, but above all to the presence of anti-phospholipid antibodies. Fortunately, these are not often present in women with nephritis, especially after their disease has been stabilised on treatment, so that paradoxically lupus nephritis patients may have a better prognosis for pregnancy than lupus as a whole, since it is the ANF negative patients, those with lupus like disease, or without nephritis who most commonly have high titres of IgG anti phospholipid antibodies.

In our own series, 48 of 54 pregnancies were allowed to proceed, leading to the birth of 39 live babies (71%). Even better results have been recorded by Jungers and his colleagues in France.

Does pregnancy affect maternal disease or renal function adversely in lupus nephritis? The answer seems to be no in the great majority of cases although other workers have seen irreversible decline in renal function, which we have not.

Finally, the quite different situation of lupus nephritis arising during a pregnancy must be mentioned. The prognosis for the baby is very poor, and maternal deaths have been recorded, so such pregnancies should be interrupted in whatever fashion is appropriate for the stage of gestation whilst aggressive treatment of the lupus is begun.

Conclusions

The fact that we can discuss pregnancy and its successful outcome even in women presenting with the severest forms of lupus nephritis, once their disease is under control, is some measure of the success in treating lupus nephritis today. However it would be an illusion to suppose that nothing more needs to be done. We need to be looking at 20-30- or 40-year survival figures, and although the fact that after 10 years 80% of our patients are alive should encourage us, the fact that almost half of these survivors have clinical signs of continuing renal disease equally should worry us.