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Leaders

Curing lupus—views from the foothills

The contemporary therapy of systemic lupus is framed by two very distinct, but quite separate, realities. The simple truth is that most lupus patients respond well to current treatments and many develop lasting remissions. The credit is equally shared between the availability of a number of drugs that effectively control manifestations of the disease and the apparent propensity of the natural disease course towards remission. In contrast, we continue to be confronted with occasional patients who present with severe, progressive illness, fail to respond to all available therapies, and either succumb to the disease or develop substantial morbidity. The practising clinician caring for lupus patients and investigators charged with developing better ways to treat the disease need to distinguish these groups as work towards curing the disease progresses.

Of the drugs commonly used in the treatment of lupus, corticosteroids continue to be the mainstay of therapy. However, corticosteroids have been implicated in most of the serious residual complications that plague the lupus patient in remission including osteonecrosis, osteoporosis, and coronary artery disease. In an effort to minimise these adverse effects, the standards for practice of corticosteroid usage in lupus have changed substantially over the past decade. Prolonged courses of high dose oral corticosteroids have been largely replaced by alternative strategies and aggressive attempts to reduce the dose of oral corticosteroids once the disease is under control. In many patients, however, oral corticosteroids are never completely discontinued, either because of the reappearance of lupus symptoms during the decrease towards discontinuation, or because of the belief on the part of the physician that low dose corticosteroids serve a preventative role and are not by themselves harmful. There are surprisingly few data bearing on these latter tenets. If we ever hope to reduce the large population of lupus patients who become chronically steroid dependent, better clinical studies of the benefits and toxicities of chronic ‘maintenance’ corticosteroids must be conducted.

For severe manifestations of lupus, bolus cyclophosphamide has clearly emerged as a drug of major therapeutic importance. Although it is most widely used in the setting of active nephritis, its therapeutic role extends to most other serious clinical features of the disease. The clinical improvements after bolus cyclophosphamide can often be surprisingly rapid, suggesting that mechanisms other than direct effects on the immune system must be operative. The potential for toxic effects from cyclophosphamide is substantial and has appropriately limited the use of the drug. The risks for most short term toxic effects including infection, bone marrow suppression, and amenorrhoea, have been reasonably well defined. Toxic effects on the bladder, a substantial concern with chronic oral therapy, are substantially reduced with intermittent bolus therapy. Moreover, use of mesna to bind the metabolite acrolein that is responsible for urototoxic effects has become an increasingly common practice that, in conjunction with bolus cyclophosphamide, should ease worries about the late bladder toxicity of carcinosa. Lupus patients, however, seem particularly prone to the development of mesna induced drug eruptions which can easily be mistaken for rashes caused by the lupus itself. The single very important complication for which there are insufficient data to judge risk is late malignancy; data from available studies seem to indicate that the risk is likely to be low.

Questions related to many of the important practical issues of bolus cyclophosphamide abound, with few clear answers. Therapy is generally initiated with monthly infusions of cyclophosphamide in a dose of about 1.0 g/m²—an empirical schedule used in randomised trials of lupus nephritis. How different drug doses or other intervals between infusions compare with regards to efficacy and toxicity is unknown and, moreover, unlikely ever to be rigorously studied. The high rate of disease relapse after discontinuation of cyclophosphamide after a six month course suggests that some form of maintenance drug therapy other than corticosteroids is required, at least in most patients with lupus nephritis. Most experts recommend lengthening the interval between infusions to every several months, although when one can feel safe in ultimately stopping the therapy altogether has never been satisfactorily defined. There is a general feeling that the risks of serious complications of cyclophosphamide, including malignancy and bone marrow aplasia, escalate with the duration of the drug therapy. This would seem to indicate a role for other strategies after an intensive induction course of cyclophosphamide—substitution of a ‘safer’ immunosuppressive drug (perhaps low dose azathioprine), or giving patients who relapse a repeat, brief, induction therapy are attractive options, but have not been carefully studied. Finally, what to do with the patient who fails to respond to cyclophosphamide presents a major problem, with no clear reason to believe that any modality is truly effective in these circumstances.

Several other chemotherapies thought to function via suppressive effects on the immune system are used in the
management of lupus. Although none of these drugs has been as thoroughly studied as cyclophosphamide, there is no evidence to suggest that any of them approaches the efficacy observed with cyclophosphamide. The anti-malarial hydroxychloroquine has come to assume a prominent role in the therapy of most lupus patients, albeit with some concern as to whether it can ever be safely discontinued.9 There is a large clinical experience with low dose, daily azathioprine and, because of its more reassuring record of safety, many physicians continue to use this drug instead of cyclophosphamide. There is much less clinical experience with drugs such as low dose, weekly methotrexate10 or cyclosporin,11 but available evidence would seem to suggest a role for these drugs in moderately active disease.

Improvements in the therapy of lupus will require continued investments in clinical trials of the disease. Among the more promising interventions in immediate prospect are new nucleoside analogues that have a prolonged effect on immune function,12 androgens,13 and biological products.14 It seems reasonable to assume these may have a clinical impact in lupus therapy in the very near future. However, perhaps of far greater importance, are possible therapeutic approaches that would correct the fundamental immune abnormalities responsible for lupus. In particular, the induction of immune tolerance to autoantigens, as has been attempted in studies of patients with rheumatoid arthritis15 or multiple sclerosis,16 would seem to be a highly worthy subject for future clinical investigation. Moreover, it is not too premature to begin consideration of reconstitution of the immune system by bone marrow transplantation17 or, ultimately, selective gene therapy. Basic and clinical studies have begun the search for candidate genes associated with autoimmunity,18-20 but considerably more work will be required before clinical protocols for gene therapy of the disease can be developed.

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