Review

Long-term complications of systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is still a disease with significant mortality. Although 5 yr after diagnosis 92% of patients are alive, the prognosis falls to 82% survival at 10 yr, 76% at 15 yr and only 68% at 20 yr in Toronto [1]. There has been improvement in survival, with the standardized mortality ratio in patients recruited to the Toronto cohort in 1970–1977 being 10.1 (95% CI 6.5–15.0), compared with 3.3 (95% CI 1.8–5.7) for those recruited between 1986 and 1994 [2]. Data from other centres in the USA and Europe has been similar. Studies published around 1980 found that about 80% of patients survived 5 yr and about 60% of patients survived 10 yr. More recent studies have shown that 5-yr survival is now nearer 90–95% and that 70–85% of patients survive 10 yr [3]. In most studies, patients with renal involvement have had a poorer prognosis than those without renal disease. Nevertheless, survival has shown improvement in those with renal disease presenting to a UK centre between 1976 and 1986 (81% 10-yr survival), compared with those presenting between 1963 and 1975 (56% 10-yr survival) [4].

The commonest cause of death has been infection, both in early and late deaths [1, 3]. Active SLE contributes to about a third of early deaths but less commonly to late deaths. However, deaths related to acute and chronic vascular disease including sudden death are more common in those dying more than 5 yr after diagnosis. However, there is more to prognosis than just death. There is considerable morbidity associated with more prolonged survival after the diagnosis of SLE. Most physicians caring for lupus patients will be familiar with patients in whom active disease has resolved but the patients have suffered from symptoms related to the accumulation of chronic damage [5].

Both active disease and damage can be associated with impaired quality of life and reduced functional ability, although other factors such as the psycho-social background of the patient will affect a patient’s perception of their disease as well [6]. Having improved therapy for active lupus disease, the challenge is now to understand and prevent the long-term complications of this disease, whether they are due to effects of the disease itself, the therapies used, or co-morbid disease (perhaps with associated underlying disease mechanisms or linked genetic predisposition).

Chronic damage

Chronic damage in lupus patients is defined as non-reversible change, present clinically, that has developed since the onset of lupus. The assessment of damage has been facilitated by the development of the Systemic Lupus International Co-operating Clinics and American College of Rheumatology (SLICC/ACR) damage index (DI) [7, 8]. This SLICC/ACR DI covers 39 items that are divided between 12 systems. It has been shown to have construct validity and reliability, and is distinct from disease activity. However, the DI score increases more in patients with active disease at two time points 5 yr apart, than it does in those with less active disease [7, 8]. Renal or pulmonary damage within 1 yr of diagnosis has been shown to predict patients at risk of dialysis or death within 10 yr of diagnosis [9]. The increased risk of death in those with early damage (within 2 yr of diagnosis) was also demonstrated in further studies from the SLICC group and the Toronto group [10, 11].

About 40% of the Birmingham lupus cohort patients have developed at least one item of damage. The most often involved systems are musculoskeletal (15% patients), neuropsychiatric (11% patients) and cardiovascular (9% patients). The least commonly affected systems are malignancy (3% patients), diabetes mellitus (3% patients) and premature gonadal failure (2% patients) (unpublished observations). The remainder of this review will address just three of these long-term complications of lupus: vascular disease (the major cause of neuropsychiatric and cardiovascular damage), osteoporosis (potentially the most avoidable item of musculoskeletal damage) and malignancy (an item of damage of debatable association with lupus disease and its treatment).

Coronary artery disease in SLE patients

The commonest form of cardiovascular damage is coronary artery disease. Urowitz et al. [12] first drew attention to this when he reported a bimodal pattern of...
mortality in SLE, with early deaths due to lupus and late deaths due to myocardial infarction in the Toronto cohort. Subsequently, Petri et al. [13] reported that 30% of the deaths in the Hopkins lupus cohort were due to coronary artery disease. In 1997, Manzi et al. [14] showed that the relative risk for a myocardial infarction in women with lupus aged 35–44 yr was 52.3 times the risk for women without lupus. Most surprisingly, two thirds of all coronary events in this cohort were in women under the age of 55 yr [14]. Recently, Bruce et al. [15] confirmed a low age of onset of coronary artery disease in the Toronto cohort. They found that the mean age for myocardial infarction in the lupus patients was 49 yr whereas the peak incidence in the local general population was in the group aged 65–74 yr [15]. However, there is some variation between cohorts. In a recent review, Petri [16] discussed 13 studies showing that the prevalence of coronary artery disease in lupus patients varied from 6 to 54% and the mortality from this condition varied 3–45%. This is likely to reflect the different patient populations reported in these studies. In California, the risk of hospitalization of lupus patients aged 18–44 yr due to acute myocardial infarction, congestive cardiac failure and stroke is over seven times that of women without lupus in California [17, 18]. Unfortunately, this risk of premature vascular disease is still not widely appreciated. I am aware of casualty staff in the UK who have sent home women with lupus and chest pain without full assessment, on the grounds that they are too young to have ischaemic heart disease, when they were actually suffering from acute myocardial infarction in their late 30s. This problem is not restricted to lupus patients in the UK however, as women with ischaemic heart disease without lupus have been turned away from emergency rooms in the USA as well [19].

The above studies have shown that risk factors for coronary artery disease in SLE include older age at diagnosis, longer disease duration, longer steroid use (especially higher cumulative dose), hypercholesterolaemia, hypertension, post-menopausal status, obesity, diabetes mellitus. In some studies additional risk factors include pericarditis, myocarditis, raised homocysteine levels, anti-phospholipid antibodies (lupus anticoagulant), male sex and renal insufficiency. However, there is still something about lupus disease itself which seems to confer the greatest risk for coronary artery disease and the underlying cause for this remains uncertain. It is quite possible that the additional risk conferred by lupus is related to specific effects of this inflammatory and immune complex mediated disease on blood vessels. But it is hard to disentangle effects of severe disease from the effects of high dose steroids as the same patients are affected by both.

We have demonstrated significantly increased levels of total cholesterol and triglycerides, and increased small, more atherogenic, LDL subfractions in SLE patients compared with controls. There is also a higher level of lipid hydroperoxides consistent with oxidative stress in the SLE patients [20]. Bruce et al. [15] have shown that SLE patients with sustained increase in cholesterol are most likely to develop coronary artery disease. Sustained hypercholesterolaemia is associated with cumulative steroid dose, absence of anti-malarial therapy and onset of lupus at greater than 35 yr old in the Toronto cohort [21]. In an attempt to identify subclinical disease, Manzi et al. [22] has studied the prevalence of carotid plaque in SLE patients. Out of 175 women of whom 15% had had a previous arterial event, 40% were found to have focal plaque on B mode ultrasound. Even in those under 35 yr, 19% had carotid plaque. Logistic regression analysis showed that the presence of plaque was independently associated with a previous coronary event, prolonged steroid use, older age, higher systolic blood pressure readings and higher LDL levels. A previous coronary event, older age and high systolic blood pressure were associated with more severe plaque formation. Other methods of identifying subclinical disease include myocardial SPECT scans, thallium myocardial scans and endothelial function by brachial artery ultrasound. Studies using these modalities have suggested that 20–40% of SLE patients have subclinical ischaemic heart disease. Methods more related to clinical disease such as exercise-induced ischaemia and segmental wall movement by echocardiography showed only 4–12% of patients were abnormal [16, 18, 23, 24].

At the present time the focus of therapy should be to get optimal lupus disease control with the minimum of steroids, through the judicious use of anti-malarial agents and other immunosuppressive agents. Advice about not smoking, appropriate exercise, low cholesterol diets, lipid lowering therapy, control of blood pressure and screening for diabetes mellitus should be reviewed regularly. The role of folate, B group vitamins and anti-oxidants such as vitamins E and C remain uncertain but worthy of further study.

Osteoporosis in SLE patients

Osteoporotic fractures are probably the most preventable form of musculoskeletal damage. The most comprehensive study was published by Ramsey-Goldman et al. [25] in 1999. They found that 86 (12%) of 702 women with lupus had suffered at least one self-reported fracture since the onset of SLE. The standardized morbidity ratio was 4.7 (3.8–5.8). Associations with time from lupus diagnosis to fracture are very reminiscent of the risk factors for cardiovascular disease: older age at diagnosis, longer disease duration, longer duration of steroid use, post-menopausal status and, in this case, less use of oral contraceptives [26]. Furthermore, Ramsey-Goldman and Manzi [27] have recently shown an association between decreased bone mineral density (BMD) and both an increased carotid plaque index and the presence of coronary artery calcification in a pilot study of 65 women with lupus. This supports the concept that inflammatory and immune-mediated mechanisms involved in lupus may also contribute to the development of atheroma and osteoporosis.
Kipen et al. [28] studied 97 female lupus patients with a mean age of 44.2 yr and found that there was low bone mass (> 1 s.d. below young adult mean) in the spine and femoral neck in over 40% of the patients. There was osteoporotic level BMD (> 2.5 s.d. below the young adult mean) in the spine of 13% of the patients and in the femoral neck of 6% of the patients [28]. There was a much clearer inverse relation between steroid use ever and the spine BMD result than the femoral neck BMD.

Even pre-menopausal lupus women have been found to have reduced BMD. Sinigaglia et al. [29] studied 84 pre-menopausal women (mean age 30.5 yr) and found that 22% were in the osteoporotic range in at least one site. Again there was a strong association with longer disease duration and higher steroid use, as well as an association with higher SLICC/ACR DI score and low body mass index. Jardinet et al. [30] also found reduced BMD in the spine of pre-menopausal women given daily doses of prednisolone of 7.5 mg or more in a longitudinal study.

In Birmingham we have studied 242 patients, median age 39.9 yr (range 18–80 yr) [31]. We found that 10% of our patients were osteoporotic and 41% were osteopenic by BMD scanning. Fractures had occurred in 9% of patients since the onset of lupus in the absence of significant trauma; one in five of those who were osteoporotic, one in seven of those who were osteopenic and one in 22 of those with normal BMD at spine and femoral neck. As with Ramsey-Goldman et al.’s study [25], we found that age was the strongest independent predictor of fracture [31]. Ethnic group, steroid use and disordered menstrual history were associated with reduced BMD but not with fractures. Impaired mobility was strongly associated with low BMD and fractures on univariate analysis. Multiple logistic regression showed that age was the best predictor of fractures with a modified DI score (which excluded fractures as a damage item) and osteoporotic BMD exerting less influence. Impaired mobility and menopausal status were not independent predictors of fractures in our cohort [31].

Genetic and environmental factors contribute to the determination of bone mass and the risk of fracture. The most relevant risk factors include oestrogen metabolism/status, sun exposure, vitamin D polymorphisms/levels, disease activity, levels of bone resorbing cytokines, development of renal failure, steroid exposure, physical activity and smoking history. To reduce the risk of fracture, keep steroid doses as low as possible while controlling disease activity with the use of other immunosuppressive agents if necessary, encourage a good diet with appropriate physical activity and strongly advise against smoking, as for the prevention of cardiovascular disease. Pre-menopausal women should usually be given high doses of vitamin D3 and calcium, as bisphosphonates are contraindicated in those planning pregnancy. They are retained in the body for long periods even after therapy has ceased and, in animal studies, have caused fetal abnormalities [32]. Thus, bisphosphonates should only be used in pre-menopausal women if they are likely to require high-dose steroids for a prolonged period despite the use of steroid sparing agents. They should have completed their families or be considered too unwell to be likely to become pregnant in the future (at least for several years) and they should be regularly counselled against becoming pregnant on bisphosphonates.

In post-menopausal women without renal impairment, bisphosphonates are often used as not all women can tolerate or wish to try HRT. For many years it has been said that lupus improves after the menopause and that HRT may exacerbate the disease or prevent this improvement. Studies have shown that HRT can be used in post-menopausal women with lupus without increasing disease activity significantly [33]. Nevertheless, many physicians (including myself) remain cautious about HRT in patients who have had severe disease in the past, particularly if they deteriorated on oestrogen-containing contraceptive pills or in pregnancy, or have anti-phospholipid antibodies [34]. Oestrogen receptor modulators (for example raloxifene) may be a useful alternative for patients without pro-thrombotic tendencies. At present, unless patients with anti-phospholipid antibodies are on warfarin they should not be given HRT or oestrogen receptor modulators due to the risk of thrombosis. Calcitonin provides a useful therapy for patients with recent fractures as it has some pain-killing properties. Unfortunately, the intranasal preparation, which is the most convenient for patients, may be hard to obtain compared with the subcutaneous form.

Malignancy in SLE patients

The final topic for discussion, the risk of malignancy in SLE patients, is a less common problem than the issues discussed above. But it is of considerable concern to lupus patients and is a subject often raised by them or by other physicians. If lupus patients develop a cancer or lymphoma, oncologists often blame immunosuppressive therapy, even if the patient has only been exposed to the therapy for a few months. However, there is no data to support the concept that steroids or cytotoxic agents are predisposing factors for malignancy in SLE patients, although there is in rheumatoid arthritis [35]. In lupus it is possible that disturbances in immune surveillance are associated with the risk of developing malignancy, as it is a disease characterized by immune system dysfunction. Certainly, in Sjögren’s syndrome, which is rarely treated with cytotoxic therapy, non-Hodgkin’s lymphoma is a well recognized complication [36].

There have been a number of studies attempting to establish whether or not there is an increased risk of malignancy in SLE [37]. Eight cohort studies in which the standardized incidence rate (SIR) or standardized mortality rate (SMR) could be calculated are shown in Table 1 [37–44]. The SIR for malignancy in lupus patients is greater than 1.0 in all of these studies, but in only three studies are the SIRs >2.0 with 95%
Table 1. Standardized incidence rates for malignancies in SLE patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Report type</th>
<th>No. of patients</th>
<th>No. (%) of malignancies</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pettersson et al. (1992) [38]</td>
<td>Cohort</td>
<td>205</td>
<td>15 (7.3)</td>
<td>2.6 (1.5, 4.4)</td>
</tr>
<tr>
<td>Sweeney et al. (1995) [39]</td>
<td>Cohort</td>
<td>412</td>
<td>20 (4.8)</td>
<td>1.4 (0.9, 2.2)</td>
</tr>
<tr>
<td>Abu-Shakra et al. (1996) [40]</td>
<td>Cohort</td>
<td>724</td>
<td>24 (3.2)</td>
<td>1.1 (1.1, 1.6)</td>
</tr>
<tr>
<td>Mellemkjaer et al. (1997) [41]</td>
<td>Cohort</td>
<td>1585</td>
<td>102 (6.4)</td>
<td>1.3 (1.1, 1.6)</td>
</tr>
<tr>
<td>Ramsey-Goldman et al. (1998) [42]</td>
<td>Cohort</td>
<td>616</td>
<td>30 (4.9)</td>
<td>2.0 (1.4, 2.9)</td>
</tr>
<tr>
<td>Sultan et al. (2000) [43]</td>
<td>Cohort</td>
<td>276</td>
<td>16 (5.8)</td>
<td>1.16 (0.55, 2.13)</td>
</tr>
<tr>
<td>Stahl-Hallengren et al. (2000) [44]</td>
<td>Cohort</td>
<td>116</td>
<td>16 (13.8)</td>
<td>SMR 1.52M, SMR 1.12F</td>
</tr>
<tr>
<td>Nashi (2000)</td>
<td>Cohort</td>
<td>312</td>
<td>22 (7.0)</td>
<td>2.4 (1.5, 3.7)</td>
</tr>
</tbody>
</table>

SIR, standardized incidence rate; SMR, standardized mortality rate.

Confidence intervals > 1.0 suggesting an increased risk of malignancy in SLE patients compared with controls. Interestingly, these three studies used cancer registry data, not just a review of medical notes and questionnaires. Overall, six studies have shown an increase in non-Hodgkin’s lymphoma, three have shown an increase in Hodgkin’s lymphoma, and one each have shown an increase in ovarian, male genital tract, and hepatocellular cancer. Five studies have looked for a relationship to cytotoxic therapy and not found any association. Not addressed in these studies, but demonstrated separately, has been an increase in cervical dysplasia, usually associated with viral infection and not necessarily related to previous cytotoxic therapy [45, 46]. It is important that women with lupus receive regular cervical screening to ensure that they do not develop cervical cancer.

In Isenberg’s cohort in London [43], there was no increase in malignancy compared with the local population overall, but there was an increase in Hodgkin’s lymphoma. Six patients out of 276 followed between 1978 and 1999 had died from malignancy (2.2% of the cohort). However, malignancy accounted for 23% of all deaths in this cohort. Our experience in Birmingham is very similar (unpublished observations). We have followed an inception cohort of 333 patients since 1991 for a median of 4 yr with a range up to 10 yr. There have been 25 deaths within the study period. Active lupus was the primary cause in 8% and a contributing cause in 13% of deaths. Most patients died of respiratory (25%) and cardiovascular (21%) causes. Malignancy was the third most common cause of death and occurred in 17% of lupus patients. Thirteen malignancies were identified in the cohort, giving an overall standardized incidence ratio of 3.6, and that of non-Hodgkin’s lymphoma was 29.0. However, in the Toronto cohort, malignancy accounted for only 7% of early deaths and 6% of late deaths [1, 40]. The SLICC group is currently organizing a multi-centre, international collaborative study to assess the risk of malignancy in lupus patients more reliably, and with enough patients to look at individual tumours separately and to address the issue of the role of therapy [37, 47].

Conclusions

The morbidity and mortality associated with SLE is still considerable despite improvements in initial immunosuppressive therapy for active disease. There is still much to learn about the long-term complications of this disease and how best to manage lupus, without putting patients at risk of additional disease such as atherosclerosis, osteoporosis and possibly malignancy. Patients require life-long follow-up by physicians aware of the broad range of conditions that may ensue. The lupus patients themselves need to understand why this is important and their own role in modifying lifestyle factors that increase the risks of cardiovascular disease and osteoporosis in particular.

References

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44. Stahl-Hallengren C, Jonsen A, Nived O, Sturfelt G. Late complications of SLE 1099.

