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Mangment of Systemic Lupus Erythematous

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Abstract

Neuropsychiatric events are common in patients with systemic lupus erythematosus (SLE), but less than one-third of these events can be directly attributed to SLE. Increased generalized SLE disease activity or damage, previous or concurrent major neuropsychiatric SLE (NPSLE) events, and persistently positive moderate-to-high antiphospholipid antibody titers are established risk factors, and their presence could facilitate proper attribution to the disease itself. Diagnostic evaluation is guided by the presenting manifestation; MRI is used to visualize brain or spinal pathologies. For neuropsychiatric events believed to reflect an immune or inflammatory process, or when these events occur in the context of active generalized disease, evidence (primarily from uncontrolled studies) supports the use of glucocorticoids alone or in combination with immunosuppressive therapy. Antiplatelet and/or anticoagulation therapy is recommended for NPSLE manifestations related to antiphospholipid antibodies, especially for thrombotic cerebrovascular disease. For the future, we anticipate that novel biomarkers and advanced neuroimaging tests will better define the underlying pathologic mechanisms of SLE-related neuropsychiatric disease, and help guide therapeutic decisions.

Introduction

Systemic lupus erythematosus (SLE) is a systemic inflammatory autoimmune disease predominantly affecting women. The prevalence of lupus is estimated at 12.5–78.5 cases per 100,000 population in Europe and the USA with a female:male ratio of around 9:1.[1] In the UK SLE is approximately 2.5 times more common in South Asian and 5–6 times more common in Afro-Caribbean individuals.[2] Due to the rarity of SLE it is difficult to accurately determine the incidence, but it has been estimated to be between 2.0 and 7.6 cases per 100,000 population/year.[1] The aetiology and immunopathogenesis of SLE have been extensively reviewed elsewhere.[4] This review will focus on advances in the management of SLE in terms of both the disease itself and its associated co-morbidities. SLE is one of a small number of truly multisystem disorders. The heterogeneous nature of the disease can result in delayed diagnosis and cause considerable difficulty in the design of robust clinical trials. There is no diagnostic test specific for SLE and as such the diagnosis remains a clinical one, relying on a combination of clinical and laboratory features. The 1992 Revised American College of Rheumatology (ACR) Classification Criteria, while developed to aid trial design, offer a useful aide-mémoire to the rheumatologist of some of the more common features of SLE (Table 1).[6,7] Newer criteria have only recently been published but are likely to be more widely used in the future [8] It is interesting to note that, in addition to differences in disease prevalence, marked ethnic variation in organ involvement has also been reported; for example, when compared to Caucasian lupus patients Afro-Caribbean patients have an increased risk of renal disease while antiphospholipid syndrome (APS) is less common , A wide spectrum of autoantibodies can be found in patients with SLE and are often associated with specific clinical features. Antinuclear antibodies (ANA) are found in 98% of SLE patients but are non-specific. The presence of anti-double-stranded DNA (dsDNA) is highly specific for SLE but they are only present in around 70% of cases.[9] Other autoantibodies reported in patients with SLE include anti-Smith, anti-ribosomal P and anti-proliferating cell nuclear antigen (PCNA).[11] Of all these antibodies, it is only dsDNA that has been shown to be pathogenic (for lupus nephritis)[12] – the others appear to be biomarkers for the presence of an autoimmune state.

Mortality in SLE

There has been a significant reduction in mortality among lupus patients over the last 50–60 years; the 5-year survival is now estimated at around 95%. This does of course still mean there is an unacceptably high mortality in this condition affecting younger women. In the largest observational study to date (of c.9500 lupus patients) increased mortality was seen in female patients, particularly within the first year following diagnosis. This early peak in mortality, which is commonly due to lupus disease activity and infection, is followed by a second later peak chiefly due to cardiovascular disease (CVD).[11]

Identification of 'high-risk' patients

No universal prognostic factor has been identified, but some clinical features of SLE are associated with a worse prognosis. In a study by Lopez et al of 350 lupus patients, older age, higher disease activity and pre-existing organ damage were all independently associated with premature death. In addition, renal disease (identified either at biopsy or by measurement of serum creatinine) and thrombocytopenia are associated with increased mortality. Perhaps most importantly, it is increased lupus disease activity overall that should alert the rheumatologist to the fact that the patient is at risk of a poor outcome.

Morbidity in SLE

The clinical course in SLE can vary markedly from relatively mild symptoms through to life-threatening multi-organ disease. A thorough assessment of lupus patients is important to clearly identify active disease and the presence of organ involvement. Disease activity scoring systems have been developed primarily for use in research studies in order to try to capture activity in this heterogeneous disease (reviewed in Griffiths et al). Although developed for use in research studies, these scoring systems offer a useful framework for the treating physician.

Global scoring systems such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) provide a single total activity score, with serious manifestations (e.g. neurological disease) weighted more heavily. Recent updates to SLEDAI include SELENA-SLEDAI (Safety of Estrogens in Lupus Erythematosus: National Assessment-SLEDAI) and SLEDAI-2K, both of which aim to capture *ongoing*rather than just new or recurrent activity.[12]

The British Isles Lupus Assessment Group (BILAG) index offers a more comprehensive approach to the assessment of lupus disease activity. Rather than generating a global activity score, the BILAG-2004 index classifies activity, over a 4-week period, according to 9 different organ systems. Furthermore, rather than using an arbitrary definition of disease activity the benchmark is set against whether or not the signs or symptoms would prompt an escalation of therapy. It is important when using indices such as BILAG that only features due to SLE activity per se (and not damage or other conditions) are recorded.

Against a background of a cluster of negative randomised trials (see below) new scoring systems to capture therapeutic response in SLE are being developed. These response indices, analogous to an ACR or European League Against Rheumatism (EULAR) response in rheumatoid arthritis, aim to quantify changes in disease activity in clinical trials. The SLE Responder Index (SRI) comprises a reduction in SELENA-SLEDAI score of $\geq$4 points, no new BILAG 'A' or more than 1 new 'B' score, and no significant worsening in Physician's Global Assessment (PGA) score. This composite scoring system has thus far only been used in the clinical trials of belimumab. The development of sensitive and reproducible scoring systems will be essential for the conduct of more robust clinical trials.[12]

Clinical assessment of the lupus patient

In the assessment of symptomatic patients consideration should be given as to whether the clinical features are due to:

- Lupus disease activity (i.e. a lupus flare)
- Other lupus-related pathology, e.g. thrombosis or vasospasm
- Irreversible organ damage
- Non-lupus causes, e.g. infection, atherosclerosis, other autoimmune diseases or drug-related adverse events.

It is important to remember that other diseases (e.g. infection) can co-exist in the SLE patient and can be worsened by a lupus flare, resulting in 'dual-pathology'. An accurate diagnosis therefore relies on interpretation of symptoms against a background of probability. For example, haematuria and proteinuria are more likely to be due to a urinary tract infection rather than lupus nephritis. Indeed, concomitant infections are one of many co-morbidities common in SLE and are discussed in detail below. The Systemic Lupus International Collaborating Clinics Damage Index (SLICC-DI) allows damage to be recorded and quantified as a score between 0 and 46.[27] Unlike the measures of disease activity *all* damage is scored from the time of diagnosis of SLE onwards, regardless of whether or not it can be attributed to lupus.

Discussion:

Management of lupus: no major organ involvement

The general principle of management of SLE is analogous to that of other inflammatory disorders: suppression of inflammation in an attempt to prevent organ damage. The intensity of therapy is therefore dictated by the severity and site of organ involvement, and the overall prognosis for specific organ involvement. The management of SLE is summarised in Figure 1.

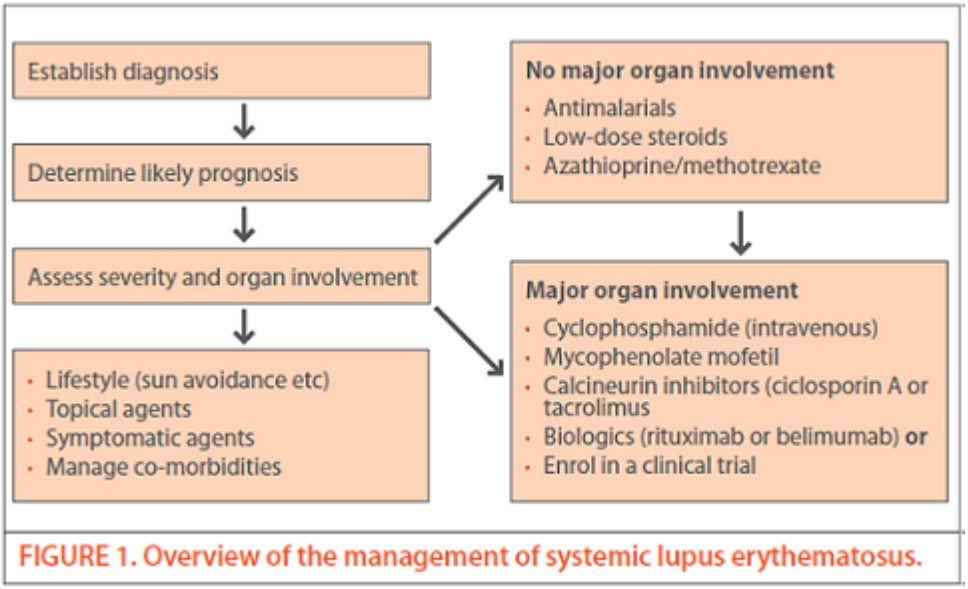

FIGURE 1. Overview of the management of systemic lupus erythematosus.

Non-organ-specific symptoms in SLE are common and include marked fatigue, arthralgia, myalgia, fever, weight-loss and mood changes (often low mood and depression). These can be severe enough to significantly impair a patient's quality of life. Management of these symptoms, particularly fatigue, is often challenging as the causes are multifactorial and no specific therapies exist. These symptoms will to some extent be improved by increasing overall control of the disease. Fatigue and chronic pain are therefore common in SLE, although there is evidence that

the prevalence of fibromyalgia itself is lower than would be expected.[13] In mild–moderate lupus, musculoskeletal and mucocutaneous features are likely to dominate the clinical picture. Common manifestations include mucosal ulceration (typically oral and nasal), scarring alopecia, non-erosive arthropathy (Jaccoud's arthropathy) and skin rashes (malar rash, discoid lesions and other photosensitive rashes). Oral corticosteroids at low–moderate doses and antimalarial therapy are the mainstay of management of mild–moderate disease, using the lowest dose of steroids to adequately control the symptoms. Higher-dose steroids and steroid-sparing agents are used when this approach is insufficient to control the disease. In addition, steroid and antimalarial agents can be important adjuvant therapy to reduce the risk of flare in patients with more severe disease.

UV protection

Exposure to sunlight is a recognised precipitant of a lupus flare. Patients often have photosensitive rashes, or may experience a worsening of systemic symptoms in response to ultraviolet (UV) radiation. Lupus patients should be advised to avoid sitting in direct sunlight and to use physical protection from the sun (e.g. long sleeves, hats and sun-protective clothing) where appropriate. Diffusers on low-energy light bulbs and fluorescent light sources may also be of help. High-factor sunblock (ideally sun protection factor (SPF) ≥50) is also recommended and should be applied regularly. Sunlight avoidance may, however, partly contribute to the increased prevalence of vitamin D deficiency in patients with SLE.[34] Although the clinical relevance of low vitamin D in SLE with regard to immunological function is currently under investigation, vitamin D deficiency is of course an established risk factor for poor bone health, including the development of osteomalacia and osteoporosis.[14]

Antimalarial therapy

Hydroxychloroquine (HCQ) (up to 6.5 mg/kg daily) has been shown to be very effective in the management of mucocutaneous disease, serositis and fatigue. It should be noted that prolonged use of chloroquine phosphate (but to a lesser extent HCQ) can lead to the development of retinopathy.[37] In 2009 the Royal College of Ophthalmologists issued good practice guidelines for the use of antimalarial therapy by rheumatologists and dermatologists.[38] In the absence of pre-existing retinal disease routine ophthalmological review is not recommended. In more refractory cases, or if ocular toxicity is a concern, mepacrine has also been used with good effect, although it can result in a dose-dependent yellow discoloration of the skin. HCQ and mepacrine can also be efficacious in combination. The therapeutic options for treatment of cutaneous lupus have been extensively reviewed by Kuhn et al. Importantly, HCQ use has also been associated with a reduction in overall mortality in lupus patients.[15]

Corticosteroids

Systemic corticosteroids remain a keystone in the management of SLE, particularly when a rapid response is desirable. The response of moderately active lupus to steroid therapy is such that if effectiveness alone were the only consideration then other agents would rarely be needed. Low doses (e.g. 5–10 mg daily) are often sufficient for mild disease, but can be increased to 0.5 mg/kg where the disease is moderately active. Corticosteroid therapy is, however, associated with significant unwanted effects and hence long-term high or moderate doses are undesirable.[41]The therapeutic aim should therefore be to maximise benefit while minimising steroid-related harms. Steroid-sparing therapies such as azathioprine (AZA) can therefore be used in order to reduce the cumulative exposure to steroids. EULAR guidelines for the management of steroid therapy in rheumatic diseases were published in 2007 and cover issues such as risk stratification, monitoring and management of complications of glucocorticoids.

Immunosuppressant agents

Azathioprine (AZA) (1–3 mg/kg) is the most commonly used steroid-sparing agent for the management of patients with SLE. The effective metabolism of AZA is dependent on normal thiopurine methyltransferase (TPMT) activity. Patients should therefore be screened for a homozygous deficiency of TPMT (present in 1 in 300 of the population) which results in an extremely high risk of bone marrow suppression. In homozygous-deficient patients AZA should be avoided. Patients with heterozygous deficiency should have their 'target' AZA dose adjusted downwards by approximately 50% and any further dose adjustments should be carefully monitored. In patients with inflammatory arthritis methotrexate (MTX) is often beneficial in controlling synovitis and may also reduce cutaneous disease.[45]The effect of MTX on disease activity appears to be rather modest, but there is clinical trial evidence that MTX can allow more rapid and greater steroid withdrawal. Sulfasalazine is usually avoided in SLE due to its association with drug-induced lupus. The evidence for this association is, however, limited to case reports and has not been clearly demonstrated in larger cohorts.[16]

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