Review

The future of the treatment of systemic lupus erythematosus

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ABSTRACT

Despite recent advances, patients with systemic lupus erythematosus (SLE) still experience considerable morbidity and mortality. To try and improve their prognosis, varied novel biological interventions and immune manipulations are being developed. They may hold promise in particular for patients whose disease is organ-threatening and refractory to conventional treatment.

In addition, awareness of the tendency of lupus patients to develop accelerated atherosclerosis as well as newly gained insights into the underlying mechanisms, may lead to better control of risk factors, earlier diagnosis of prevalent cardiovascular disease and more effective treatment. Infections also remain a significant threat that may be amenable to improved preventive measures. Evidence related to a better management of lupus patients by specialists, the need to address the impact of commonly associated stress and depression and other significant developments are also presented and discussed.

Introduction

With improved diagnosis and modern evidence-based treatment of systemic lupus erythematosus (SLE), a dramatic improvement in patient outcomes could be expected. This did not entirely happen. Side by side with the increasing incidence of lupus (1), several recent epidemiological studies still reveal standardized mortality ratios (ratio of observed to expected deaths) of 3.3 – 4.7 for all patients (2, 3), and the figures may be higher for certain subsets such as blacks, and patients who are older than 50 or have renal dysfunction, thrombocytopenia or high SLE disease activity index score (SLEDAI) on presentation (4, 5). Thus, some patients with SLE have a considerably compromised long-term survival (e.g. ten-year survival of ~80% and 15-year survival of < 66%) (1, 6), and SLE-related deaths were still common in the late nineties (7). This is a disturbingly high mortality, especially considering that most patients are diagnosed in their third decade (3) and that approximately one third of deaths from SLE occur among persons younger than 45 years (7). Moreover, a considerable burden of morbidity is associated, that is not reflected in these data but has a significant detrimental effect on patients' quality of life (8). Will future therapies improve these outcomes ? In order to answer that we will need to address newly acquired insights into the pathogenesis and treatment of the three main causes of lupus mortality – disease activity, cardiovascular disease and severe infections (3, 4, 9, 10).

Better insight into the pathogenesis and course of SLE, and controlled studies of treatments - have already led to improved clinical outcome during the last decade (11). Furthermore, initial animal experiments suggest that angiotensin inhibition may further ameliorate glomerular damage beyond its hemodynamic effect (12). Nevertheless, severe organ-threatening lupus that is refractory to standard treatment (based on IV cyclophosphamide and corticosteroids) still poses a major problem. Over the last few years several dozens of lupus patients have been treated with nonspecific immunoablation followed by autologous hematopoietic stem cell transplantation (HSCT). High-dose chemotherapy is used to eradicate the autoreactive clone and then HSCT should allow bone marrow reconstitution with normal cells and normal immune system. Initial results are encouraging. Although treatment-related mortality of about 10% was encountered, the majority of patients improved and maintained immunosuppressive-free survival over >1 year of follow up (13, 14). Better selection of patients and earlier treatment before the develop-

ment of irreversible organ failure may further improve results. However, patient selection is complex and the influence of HSCT on long-term outcome is unknown (15). Randomized controlled trials are currently under way that will hopefully clarify the potential of HSCT in severe SLE.

Many other strategies of harnessing the deranged immune response in SLE patients have been proposed. They should be particularly helpful in those patients at high risk because of severe disease, adverse drug reactions or both. Many different approaches directed at the etiology level, the autoantibodies or the immunoregulatory level are being extensively studied in murine models of SLE, then examined in patients (Table I) (16-45). Detailed discussion of these approaches is beyond the scope of this manuscript, but a few deserve a separate mention. One important mode of intervention is to deplete B cells or the pathogenic antibodies that they produce. Anecdotal evidence suggests that SLE patients who had a nearly complete loss of B cells are very likely to go into complete remission (46). Indeed, B lymphocyte depletion using anti-CD 20 monoclonal antibodies (Rituximab, MabThera) in conjunction with other immunosuppressive therapies has also proved useful in some severely affected patients (28), but thusfar, accumulated experience does not amount to much more than a few case reports (29). Early results are encouraging in that 9 of 13 SLE patients with refractory disease responded (47) and several abnormalities in peripheral B cell homeostasis may show a remarkable resolution (48). Another notable method involves BLyS, a B cell stimulatory molecule that is among the newly described TNF ligands and receptor superfamily members. It binds to B cell receptors and is a potent inducer of B cell activation, survival and immunoglobulin production. Significant elevations of BLyS commonly found in SLE patients suggest that it may be a target for intervention. Using BLyS antagonists to inhibit of the interaction of BLyS with its B cell receptors has been shown to suppress disease in lupus mice and initial tests in patients are under way (30, 31). B cell tolerization by LJP 394 – an immunogen consisting of four dsDNA oligonucleotides attached to a non-immunogenic PEG platform is another important option. LPJ 394 binds B cells without T cell activation resulting in their apoptosis and reduced anti-dsDNA antibody production (24). A randomized controlled trial of 230 SLE patients treated with LJP 394 or placebo over 76 weeks has confirmed its ability to prevent or delay renal flares and showed the drug to be well tolerated (25). Another approach is based on inhibiting the binding of pathogenic lupus autoantibodies to their target by using a laminin-derived peptide that competes with the binding of these antibodies to the kidney. This approach has been shown to prolong survival significantly in murine lupus (49).

The activation of B cells depends not only on the recognition of the specific

Table I. Suggested potential interventions for SLE treatment.

	Intervention *	Stage#
The etiology level		
Genetic manipulation	Inserting 'ameliorating' genes (e.g. perforin, fas, Ead) or deleting harmful genes (e.g. Dnase-1) (16)	? MM.
Hormonal manipulation	Dihidroepiandrosterone (DHEA) to increase androgens or tamoxifen (anti-estrogen) or bromocriptine to counteract prolactin (17-19)	MM. RCT
Complement suppression	Antibody to C5 (anti-C5b) to inhibit complement membrane attack complex C5b-9 or complement C3 inhibitor (20,21)	MM. ? EH
The autoantibody level		
Removal of pathogenic antibodies	Plasmaphersis (no clear benefit); Immunoadsorption on affinity columns with varied antigens (22)	EH.
Deletion of pathogenic antibodies	Blocking anti-idiotypic antibodies (23) or B-cell tolerization by LJP394 (24,25)	MM.; EH RCT
Introducing alternative targets	Injecting a substance of similar charge to DNA (e.g. heparin) (26) or a similar structure to the target antigen (e.g. laminin-peptide) that competes for tissue binding	MM.
Uncoupling of immune-complex deposition	High dose G-CSF (27)	MM.
Depletion of antibody-producing B cells	Anti-CD 20 (28, 29)	EH.
Blocking B cell activation	Anti-BLyS (30, 31)	MM.; EH
The immunoregulatory level		
Immunosuppressive agents	Cyclosporine-A, tacrolimus (FK506), mycophenolate mofetil (MMF) (32##), leflunomide (33,34), etc. MMF + renal thromboxane A2 inhibitor	EH. MM.
Long-lasting CD4 depletion	Total lymphoid irradiation (35)	H.
Induction of T cell tolerance	Vaccination with peptides (36) derived from Vh region of anti-DNA antibodies, oral administration of kidney extract, etc.	MM.
Targeting cytokines pivotal in SLE	Anti-IL-10 (or AS-101) (37) Interferon-α ? (38) Tumor necrosis factor-α ? (39) Chemokines ? (40) IL-4 ? (41)	MM. (EH.)
Interference with T-cell co-stimulation	Anti-CD 40 ligand and (or) CTLA4 (42, 43) Anti-CD 154 (44) Anti- CD 137 (45)	MM. EH.

* The above-mentioned classification is somewhat oversimplified since many interventions act in more than one way.
# MM: murine models; (E)H: (early) human trials; RCT: randomized controlled trial.
Also refs. 77,91.

antigen but also on B-T cell interaction of co-stimulatory surface molecules. Among these the interaction of T cell CD-40 ligand and CTLA-4 with the CD-40 and B7 receptors expressed on the B cell surface are required for B cell activation. Antibodies against CD-40 ligand and the CTLA-4 immunoglobulin fusion protein have been shown to block T cell activation and T dependent B cell function and to suppress autoantibody production and renal disease in lupus mice (42, 43). The anti CD-40 ligand antibodies have been tested in early clinical trials in SLE. A trial of one product was terminated prematurely due to the development of thromboembolic events and a trial with a second product was stopped as no improvement in disease activity was observed. CTLA-4Ig was found to suppress disease in lupus mice and was well tolerated in human clinical trials in the treatment of rheumatoid arthritis and psoriasis, but has not yet been tested in human SLE. A short course of a combination of CTLA-4Ig with an anti-CD-40L antibody was found to prolong survival of B/W lupus mice but has not been tested yet in a clinical trial.

The success of anti-TNF antibodies in inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease has led to attempts to treat SLE by antagonists to various cytokines that participate in the inflammatory process. It is noteworthy however, that SLE differs from most other autoimmune diseases where TH1 cells are the major pathogenic cells. Anti-TNF antibody treatment is associated with the induction of anti-DNA antibodies and even clinical SLE (50), whereas suppression of IL-10, a classical anti-inflammatory cytokine in other diseases, has been shown to be beneficial in the management of refractory SLE. Nevertheless, a recent small open trial demonstrated that TNFα blockade in moderately active SLE might be beneficial: remission of arthritis or nephritis could be achieved by infliximab and although autoantibodies increased, there were no associated adverse events (51), leading the investigators to suggest that larger controlled trials are warranted. All varied experiments intensively pursued by many laboratories and clinical centers (Table I) will certainly be the focus of significant advances in the foreseeable future.

Among the causes of death of lupus patients, cardiovascular mortality has emerged as a prominent problem, especially in patients with longstanding disease. For example, looking at 407 mortality cases among 1671 SLE patients studied over a median period of 11 years in four large series, 107 patients (25%) died as a result of a vascular event, mostly acute myocardial infarction and sudden cardiac death (3, 9, 10, 52). Cardiovascular morbidity is also significant and symptomatic coronary artery disease, stroke that is unrelated to central nervous system lupus and peripheral vascular disease can all be found and often occur in relatively young patients whose risk may be 50 times that of controls in the Framingham Offspring Study (53, 54). Once a myocardial infarction or stroke develops in the context of SLE, in-hospital mortality of about 19% was reported (54), vs. 9–9.4% in controls (55). Since accelerated atherosclerotic cardiovascular disease (ASCVD) appears to underlie most of these cases, an intensive effort aimed at an early diagnosis and treatment, and more importantly – prevention, is justified (56). This should apply to most patients since sensitive techniques (such as stress thallium myocardial perfusion imaging or ultrasonographic determination of carotid intimal medial thickness) may detect asymptomatic ASCVD in as many as a third of the patients with SLE (57, 58).

The pathogenesis of the vascular disease of SLE is imperfectly understood, but three main factors have been implicated. They include a high prevalence of 'traditional' risk factors (RF) for atherosclerosis, including hyperhomocysteinemia, and possibly also the detrimental effects of prolonged corticosteroid treatment with substantial cumulative doses (59). However, a recent study of large cohorts showed a rate of vascular events that was >7 times that expected by the patient's traditional RF alone, suggesting the importance of lupus itself in atherogenesis (60). This observation was strongly supported by a remarkably careful study of 197 patients and the same number of matched controls. The impressive premature occurrence and high prevalence of atherosclerosis in lupus were confirmed and related primarily to disease duration, disease damage and under use of cyclophosphamide (61). SLE patients who had developed ASCVD had higher disease activity and their blood tests show stronger acute-phase response and the frequent presence of antiphospholipid antibodies (aPL), including some that cross-react with oxidized low-density lipoprotein (ox-LDL) (57, 62). Thus, systemic inflammation, as reflected by raised serum concentrations of CRP and fibrinogen, represents a major independent RF for cardiovascular events (63) and should be suppressed as effectively as possible. In addition, over 30% of patients with SLE may have aPL that have been associated with valvular disease and recurrent cerebral and cardiac events. These may either be embolic or related to macrovascular or microvascular atherothrombosis. APL cross-react with phospholipids in ox-LDL, a modified product of LDL exposure to oxidative stress in the sub-endothelium, facilitating its uptake by macrophages, an immune response in the atheroma and a vicious cycle of plaque progression (64, 65). This hypothesis is supported by many observations (66) and taken together (22), optimal suppression of lupus activity. is likely also to decrease the risk of ASCVD. To try and avoid worsening of RF, a sparing use of corticosteroids should be attempted, as well as the addition of hydroxychloroquine (59), which has myriad beneficial activities and few possible adverse effects. At the same time, RF should be comprehensively evaluated, monitored and aggressively treated setting low treatment goals reminiscent of those recently advocated for patients with diabetes (67). For patients at high risk of vascular complications, early noninvasive testing for subclinical ASCVD as well as primary prevention with aspirin and statins should be considered (56). These recommendations are currently lacking supporting evidence and may have to

Table II. Management of postulated risk factors for atherosclerotic cardiovascular disease in SLE @.

Aggressive reduction of traditional risk factors @@
Hypertension/LVH (goal: blood pressure < 130/80 mmHg; ACE inhibitors or β-blockers may be the preferred drugs).
Obesity (goal: BMI < 25 Kg/m^2)
Diabetes mellitus (goal: HbA1C ≤ 7%)
Dyslipidemia LDL (goal: probably < 100 mg/dl) HDL (goal: > 45mg/dl for men, > 55 mg/dl for women) Triglycerides (goal: < 150 mg/dl) Lipoprotein(a) (goal: < 30 mg/dl)
Smoking (mandatory cessation using nicotine replacement and group programs)
Sedentary lifestyle (goal: physical activity of ≥ 30 minutes/day, 3 times/week)
Menopause (Estrogens may exacerbate SLE and HRT may increase cardiovascular events, especially over the first year of treatment and have additional adverse effects)
Alcohol (avoid excessive consumption; encourage light to moderate intake?)
B-vitamins and folic acid
To be used in all patients where increased serum levels of homocysteine are detected.
Disease activity and prednisone use
• Attempt to suppress disease activity, monitoring clinical & biochemical markers • Use the smallest effective prednisone dose; try to limit dose increases to the shortest period possible • Use steroid-sparing agents whenever possible, especially hydroxychloroquine • New biological therapies for SLE?
Antiphospholipid antibodies
If criteria of lupus-associated aPL syndrome and a history of thrombosis are present – consider anticoagulant treatment with warfarin, for life
Pharmacological primary (and secondary)-prevention measures @@@
Aspirin, low-dose
Statins
Antioxidant vitamins?

@ Recommendations are derived from extrapolation from data on patients at increased risk of ASCVD and vascular events; currently, there are no specific data on the effects of aggressive risk factor reduction in patients with SLE.
@@ Patient education is an integral part of the management program, as is dietary counseling.
@@@ None are currently based on sufficient data in patients with SLE; statins may reduce vascular events even in patients with low-normal LDL but with elevated CRP levels; antioxidants have not yet proven efficacy in the prevention of vascular events in non-lupus patients, and data in SLE are limited.

be modified once more data becomes available. However, patients with the antiphospholipid (Hughes) syndrome who have had a thrombotic event are at a high risk of recurrence and have been shown to benefit from chronic warfarin treatment (68). The results of a study of primary prevention in SLE patients with aPL are eagerly awaited. Current recommendations for the management of postulated RF for premature ASCVD in lupus patients are summarized in Table II.

Infections complicating the course of SLE are also an important target of future improved care. Overall data indicate an intrinsic risk for infection that is further enhanced by immunosuppressive therapies. Patients with active disease are especially affected by impaired phagocytic function, functional hyposplenism and hypocomplementemia. Moreover, SLE patients who were homozygous for mannose-binding lectin (MBL) variant alleles had a four-fold increase in the incidence of infections (69). In the future, MBL genotyping may be used to assess the risk of infections during treatment of SLE (70). It is estimated that 50% of lupus patients will suffer at least one severe infection during the course of their illness (71), and infections remain the third most common cause of mortality in SLE despite availability of highly effective antibiotics (3, 9, 10). Serious infections in SLE are mostly bacterial and due to *Salmonella* spp. and other Gram-negative organisms, *Streptococcus pneumoniae* and *Staphylococcus aureus* (3, 9), but activation of latent *M. tuberculosis* (TB) and opportunistic infections such as *Pneumocystis carinii pneumonia* (PCP) and Nocardia spp. infections have also been well described, particularly in patients receiving > 20 mg prednisone/day for long periods (71, 72). Cyclophosphamide is another strong risk factor. Failure to make an early diagnosis and initiate appropriate antibiotic treatment remains the most common avoidable error (71, 73).

With the notorious difficulty of diagnosing acute infection as opposed to disease activity in these patients, a different approach should be adopted. A combination of improved patient health literacy regarding this complication, early referral to specialist care of patients who report new symptoms and a low threshold of initiating antibiotic treatment in suspected cases may decrease morbidity and mortality alike. In addition, two techniques may prove useful, although they await proof of efficacy in randomized controlled trials. *First*, immunizations are generally safe in patients with SLE (74) and most patients immunized can expect effective protection (75). Therefore, an intensive immunization program, repeated at frequent intervals may have important advantages for the patient. Second, patients who have to be treated with substantial doses of prednisone for many weeks may benefit from TB prophylaxis if they are PPD positive (76) as well as from prophylactic cotrimoxazole. The latter can be expected to decrease the incidence of PCP, *Nocardia* and possibly other infections (71). Again, as in the amelioration of cardiovascular risk, effective suppression of disease activity using new treatments, which are more specific and steroid-sparing, may afford a much better long-term outlook for patients with this complex and many-faced illness. Notably, initial data suggests that infectious complica-

tions may be less frequent in patients treated with mycophenolate mofetil than in those who get cyclophosphamide (77).

Three points of general importance should be recognized. *First,* no direct comparison of the management of SLE patients by specialists and primary care physicians has been performed. Nevertheless, the rarity of prolonged remissions and the high frequency of flares (60-80% per year) (78), the importance of effectively suppressing disease activity with as little adverse drug reactions as possible and the recognition that significant vascular, renal and cognitive damage may develop without symptoms – all strongly suggest that all patients with lupus had better be treated and followed by rheumatologists (79). *Second,* as in other chronic diseases, the impact of psychological variables on lupus patients appears to be considerable, but is often disregarded. A link between emotional stress and the appearance or flare of lupus is well recognized, albeit based mostly on case reports. In contrast, the effects of SLE on patient's psychological distress and quality of life have been well studied and found to be substantial. Health status measures have been found to be greatly impaired and comparable to those of severe medical illnesses (8). About 40% of patients remain highly distressed over time (80) and depression is also commonly found (81). Evidence from studies of patients with chronic diseases other than lupus suggests that such distress or depression may have an important adverse effect on patient's compliance, coping, quality of life and even disease progression (82). In SLE however, we could find very few randomized controlled trials studying the effect of behavioral interventions on patient outcomes. Brief supportive-expressive group psychotherapy improves adaptation and coping (83) and a brief cognitive-behavioral treatment was associated with short-term improvement in pain and psychological dysfunction (84). A graded exercise program may alleviate fatigue in many patients (85). Other safe, simple adjuvant treatments that showed effect in early trials include dietary supplementation with omega-3 fish oils (86) and UVA-1 cold light (87). The high prevalence of osteoporosis or osteopenia in SLE (about two-thirds of the patients) (88) also merits attention and suggests the need for trials of antiosteoporotic treatments (89) and a consideration of the problem in each patient. Further studies are needed which will hopefully focus on these aspects (80) and support appropriate interventions to improve patients' well-being and prognosis.

Third, current treatment of SLE is better informed and evidence-based than it was in the past (90, 91). However, although intravenous cyclophosphamide as given in the NIH protocol is considered by most rheumatologists as the "standard of care" for lupus nephritis, there is no FDA approved immunosuppressive agent for SLE. The data has not been considered sufficient evidence to obtain an FDA label for cyclophosphamide treatment for this indication. Looking for potentially less toxic immunosuppressive agents, mycophenolate mofetil (MMF) has been tested in a few, but promising, clinical trials. In two recent non-blinded studies MMF was found to have at least equivalent efficacy compared with intravenous (IV) cyclophosphamide in proliferative lupus nephritis and to offer safer and more efficatious maintenance therapy, than long-term IV cyclophosphamide (77, 92). Importantly, the American College of Rheumatology response criteria for SLE have been validated and standardized (93), enabling a well-founded evaluation of new therapies and comparisons between different trials.

Clearly, our understanding and treatment of SLE have improved considerably over recent years and many varied options for more specific interventions are being rapidly developed. However, for a truly dramatic change in patient well-being and survival, we need not only to identify efficient and safe therapies but also to observe their efficacy in long-term randomized controlled trials and this takes a long time. Until then, treatment of patients with lupus by experienced rheumatologists, based on up to date evidence and with special attention to the modifiable risks of infections, accelerated ASCVD, osteoporosis and the psychological burden of a serious chronic illness may improve outcomes of patients with this complex and multifaceted disease.

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