The Future of Treatment for Systemic Lupus Erythematosus

Donato Alarcón-Segovia MD MS PhD

Department of Immunology and Rheumatology, National Institute of Medical Sciences and Nutrition Salvador Zubirán, Mexico City, Mexico

Abstract

The future promises good news for the treatment of systemic lupus erythematosus, some of which can already be foreseen. Increased knowledge on genes that participate in the predisposition, pathogenesis, pharmacogenetics of, and protection against this disease may permit intervention at this level. Also, better understanding about the role of sex hormones has allowed trials of weak androgens or prolactin inhibitors. New immunomodulators or immunosuppresors may enable more precise treatment at the immunoregulatory level, and greater knowledge on the disturbance of circuits has already provided hints and even allowed trials of anti-interleukin-10 antibodies, an IL-10 decreasing agent, tolerance-induction strategies or intervention at the level of T cell co-stimulation, as well as immune ablation with subsequent stem cell transplantation. Autoantibodies can be removed, controlled by means of anti-idiotypes, which are blocked from reaching their target antigen or uncoupled from the tissues they have reached. All these treatment strategies will gradually become decanted in order to achieve the optimal treatment of SLE, which may turn out to be its cure.

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Systemic lupus erythematosus is an autoimmune disease with a complex etiology and pathogenesis. That it is autoimmune became apparent with the discovery of both the LE cell phenomenon and the fact that antinuclear antibodies participate in its occurrence. That its etiology and pathogenesis are complex has gradually been unraveled, but is still open to surprises.

Early in the course of knowledge about SLE, it came to be considered as a rare and uniformly fatal disease. Both of these concepts have changed considerably with improved awareness, better prognosis, prolonged remission, and markedly decreased mortality [1,2]. Its treatment, however, is still less than ideal – being either empirical or based on the notion of abating the hyperactive immune system for its control. This results in considerable morbidity, to the point that the current mortality of SLE patients relates more to this drug-related morbidity (e.g., infection) than it does to the autoimmune disease itself. However, despite the shortcomings posed by the incomplete knowledge on the etiology and pathogenesis of SLE, there is evidence that the future holds great promise for its treatment. The purpose of this paper is to review the new avenues of treatment for SLE that can be foreseen on the basis of such, albeit incomplete, knowledge.

In an attempt to put some order into the complexity of the multiple factors that participate in the causation of SLE we have divided it into three levels: a) etiology – where genetic, environmental and hormonal factors participate; b) etiopathogenesis – where immunoregulatory circuits lead to autoimmune disease mechanisms, particularly to the production of pathogenic autoantibodies; and c) pathogenesis proper – where these autoantibodies cause disease by forming immune complexes, by direct interaction with cells or tissues, or by causing dysfunction, including immune dysfunction [3].

New forms of treatment

The etiology level

The genetics of SLE are complex and involve the participation of multiple genes in predisposing for the disease and/or determining or modulating its manifestations. Much of the information regarding this has arisen from studies in murine models of SLE, but fine genomic mapping has lately led to knowledge about the human counterpart. Some genes seem to participate in ameliorating or even preventing disease (e.g., perforin, *fas*, *Ea***d**), some of them depending on major histocompatibility complex haplotypes (e.g., *Ea***d**) [4–6]. The possibility of intervening by inserting or deleting genes awaits better definition of the role of the various genes involved not only as soloists but in concert.

Other genes may influence disease by causing deficiencies that permit autoimmunity to arise. Dnase-1 deficiency, for instance, by permitting persistence of undigested nucleosomes may contribute to or even directly cause a lupus-like disease in mice [7]. There has been recent evidence that Dnase-1 treatment may ameliorate disease in lupus mice, although this has been contested [8,9]. Also, Dnase-1 deficiency has been shown to occur in SLE patients [10].

There are genes that may influence the behavior of drugs currently used in the treatment of SLE patients. Multi-drug

IL = interleukin
SLE = systemic lupus erythematosus

resistance-1 gene encodes a membrane glycoprotein called P-glycoprotein, a pump molecule that transports hydrophobic drugs (including corticosteroids) and toxins outside the cell, thereby inhibiting their therapeutic or toxic effects. In a preliminary study, the mean percentage of lymphocytes from SLE patients having high P-glycoprotein activity was found to be increased as compared to controls [11]. In addition, P-glycoprotein activity was found to be lower in patients whose response to treatment had led them to disease remission, than in those whose disease remained active. Inasmuch as there is potential drug intervention to abrogate P-glycoprotein activity (e.g., verapamil), this is an avenue of treatment currently being explored.

Hormonal factors that participate in the etiology of SLE can also be pharmacologically modified. Increased prolactin levels can be modified with bromocriptine, and decreased androgen function due to production of weaker androgens can be reversed with dihydroepiandrosterone. The latter form of treatment has been tested but its effects are still undefined [12]. The effects of estrogens on autoreactive B cells are partially mediated through prolactin [13] and can be favorably influenced by simultaneous treatment with bromocriptine [14,15].

The immunoregulatory level

The immune dysregulation that leads to SLE is particularly complex, but it has been gradually dissected. While it is at this level that most current therapeutic strategies act, such as immunosuppressors and corticosteroids, they are still rather unselective, with the effect of causing considerable risks, particularly of infection but also of possible neoplasia. Among the new therapeutic strategies are new more selective immuno-suppressors, such as those inhibiting lymphokines (cyclosporin or FK 506), those suppressing lymphokine signal transduction (rapamycin or leflunomide), those that affect lymphocyte differentiation (15-deoxyperguealin), and those that inhibit nucleoside synthesis (mizorbine, brequinar or mycophenolate mofetyl) [16]. Most of these have been tested only in animal models of SLE where they have shown promise. Cyclosporin A, leflunomide and mycophenolate mofetyl have already been used in SLE patients with encouraging results. However, unlike the current immunosuppressors, the benefit of longtime experience with their use is lacking.

A more specific form of treatment would be that of inducing tolerance to autoantigens to which there is autoreactivity [17]. This can be achieved in several ways: by administering an autoantigen via a tolerizing route, be it mucosal or dermal, or by administering it in a tolerogenic form (e.g., soluble IV or intraperitoneal, alone or coupled to MHC, as an altered peptide ligand or as an aggregated immunoglobulin chimera) [18]. In addition, tolerance can be induced by administering antigen-specific T cells in an immunogenic form. Oral tolerance has been attempted in the treatment of various autoimmune diseases. It has been tested in NZBxNZW F1 mice orally admin-

istered a rat-kidney extract that would theoretically include the putative kidney antigen of SLE autoantibodies. The kidney extracts were given three times a week for 5 weeks and then weekly until 6 months of age. This treatment resulted in decreased anti-dsDNA antibody levels, less kidney damage and prolonged survival, as compared to control mice. It also caused a decrease in the expression of IL-4 and IL-10 [19].

A new way of causing specific B cell tolerance for treatment of SLE has recently been developed with much ingenuity. A triethylene glycol plate was coupled by 4 double-stranded DNA epitopes of 20 base pairs each. This compound, named LJP-394, with a molecular weight of 54 kD would bind anti-dsDNA surface immunoglobulin of anti-dsDNA-producing B cells without participation of T cell help, thus resulting in apoptosis of those B cells. Its weekly administration to SLE patients with anti-dsDNA and a history of renal flares was able to reduce new renal flares and limit the requirement for high cortisone or cyclophosphamide treatment, as compared to matched controls. This reached particular significance in patients whose anti-dsDNA antibodies were of high affinity for the dsDNA epitopes present in LJP-394 [20].

Systematic study of immunoregulatory circuits in patients with SLE has pointed to the role of increased expression and production of IL-10 by their B cells and monocytes [21]. SCID mice injected with mononuclear cells from SLE patients produced human immunoglobulin within one month, including anti-dsDNA antibodies. Injection of these animals with a monoclonal antibody to IL-10 caused a marked fall in their anti-dsDNA levels while their injection with an anti-IL-6 mAb had an irregular effect on the levels of these autoantibodies. The specificity of the effect of anti-IL-10 became apparent when it was shown that it caused little fall in total immunoglobulin levels [22]. Treatment of patients with refractory SLE by means of 20 mg injections of anti-IL-10 murine mAb daily for 21 days resulted in marked improvement, beginning during the administration of the mAb and lasting throughout the 6 months of follow-up. There were falls in disease activity indices as well as a decrease in prednisone requirements. The disease was inactive by the end of 6 months in five of six patients thus treated. Although all six patients developed antibodies to the mAb, this form of treatment had no untoward effects [23]. Use of a humanized or, better, a human anti-IL-10 mAb produced in mice transgenic for immunoglobulin genes could permit longer term or repeated treatment of SLE patients.

The striking effect of anti-IL-10 mAb supports the important role of this cytokine in the immunoregulatory disturbance in SLE patients. Therefore, other ways of decreasing the production of IL-10 have been sought. The immunomodulatory agent AS-101, an organotellurium compound, has been found to act primarily by decreasing the production of IL-10 [24]. In an early study we showed that it can correct *in vitro* a number of functions of mononuclear cells from SLE patients [25]. The

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MHC = major histocompatibility complex

dsDNA = double-stranded DNA
mAb = monoclonal antibody

functions thus corrected were later found to be altered as a result of the increased production of IL-10 [21,22]. In subsequent studies AS-101 was found to decrease the spontaneous IL-10 production by mononuclear cells from SLE patients *in vitro* [26]. Systemic injection of AS-101 to SCID mice transplanted with SLE mononuclear cells significantly decreased their serum human IL-10 levels, with a concurrent decrease of their anti-dsDNA and anti-Sm levels. In the NZB/W F1 mice model, AS-101 significantly increased serum tumor necrosis factor alpha and increased interferon gamma, while decreasing serum IL-10; these changes were accompanied by a decrease in anti-dsDNA and anti-ssDNA levels. Continuous treatment of NZB/W F1 mice with AS-101 for 6 months protected 70% of the mice from the development of proteinuria and resulted in reduced immune complex deposition with little glomerular hypercellularity and mesangial expansion. It is thus apparent that this non-toxic substance may constitute an important future form of treatment for SLE [26].

Intervention at the level of T cell co-stimulation has also been attempted by administering a humanized anti-CD40-ligand mAb to SLE patients [27]. Results of a phase II trial [27] were equivocal, although another study showed a marked reduction of both anti-DNA antibody levels and anti-DNA-producing B cells [28]. Other attempts at this level of T cell co-stimulation have been made by utilizing CTLA4, a product of T cell activation that is fused to modified CH2-CH3 domains of immunoglobulin-G that no longer bind Fc receptors (CTLA4Ig) [29]. This soluble fusion protein binds B7.1 and B7.2 with much higher affinity than CD28 and is thus an efficient competitive antagonist of B7/CD28 co-stimulatory interaction. Injection of an engineered adenovirus that expresses murine CTLA4Ig results in long-term serum expression of this protein. This caused inhibition of T cell-dependent B cell maturation in NZB/W F1 with resulting delayed disease onset, milder glomerular disease, abrogation of anti-DNA antibodies in most animals and prolonged survival, as compared to controls [29].

A more drastic but clearly promising intervention at this level is immune ablation, usually achieved by extreme suppression, followed by substitution or rescue with allogeneic or autologous bone marrow or peripheral hemopoietic stem cells with the aid of hemopoietic growth factors [30]. There have been encouraging anecdotal reports of this approach to treatment of severely ill SLE patients. In one patient who received this treatment at the time of an active flare of SLE, the disease became quiescent for the first time in 13 years and remained in remission for over a year [31]. Immunoablative treatment without subsequent stem cell transplantation has been, on occasion, sufficient to achieve remission.

The pathogenic autoantibody level
The third level in the pathogenesis of SLE is where autoantibodies meet their antigens and, in so doing, cause disease.

This can occur by several mechanisms: a) by the formation of circulating immune complexes that come to rest at various sites and cause complement-mediated damage; b) by direct interaction of autoantibodies with cells or tissues causing their deletion or local damage, respectively; and c) by their interference or alteration of cell functions, including the causation of apoptosis by penetrating into cells [31].

Therapeutic intervention at this level can have several modalities, some of which are already being explored. One of them contemplates the removal of autoantibodies – whether indiscriminately by means of plasmapheresis, a method that has been of little success in SLE, or selectively by passage through affinity columns laden with the corresponding antigen, a method that has still to find its adequate application. A somewhat different approach is that of utilizing an immuno-globulin-binding peptide that interferes with Fc-gamma receptor recognition [33]. Injection of this peptide to MRL/*lpr* mice resulted in markedly decreased proteinuria, absent or little glomerular changes, and prolonged survival.

Another approach could be the deletion of autoantibodies by injecting or promoting the development of anti-idiotypic antibodies that block them. The beneficial effects of intravenous immunoglobulin are probably based on the presence of natural anti-idiotypic antibodies to pathogenic autoantibodies. Two more direct approaches could be the administration at the time of relapse of either plasma or isolated immunoglobulins, obtained at the time of remission. There have been indications that healthy relatives from lupus patients may also have such anti-idiotypic antibodies, and some attempts have been made to use their plasma to treat their ill relatives (unpublished observations). Anti-idiotypic antibodies to anti-DNA can also be raised by means of idiotypic vaccination with murine anti-dsDNA mAb [34].

A form of treatment that has already shown promise in animal models of SLE is by target distraction. This is accomplished by injecting a substance of similar charge to that of a self-antigen that is bound to a tissue due to its charge. This strategy has been used by injecting heparin, similarly anionic to DNA, which would therefore compete with it for binding at the glomerular basement membrane [35]. Uncoupling of immune complex deposition in the kidneys of MRL/-*lpr*/*lpr* mice has also been achieved by treatment with high dose granulocyte colony-stimulating factor [36].

Conclusion

From this review it is apparent that the future augurs well for the treatment of SLE patients. Some of the promises, or others that will undoubtedly emerge, may someday bring about a cure for this disease. In the meantime, better understanding of the etiology and pathogenesis of SLE will bring us closer to that end.

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Correspondence: Dr. D. Alarcón-Segovia, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vasco de Quiroga 15, 14000 Mexico DF, Mexico. Phone: (52-2) 573-1127/1193, Fax: (52-5) 513-2921, email: avilla@aztlan.innsz.mx