Review

Treatment of systemic lupus erythematosus

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Abstract

The treatment of systemic lupus erythematosus (SLE) is mainly based on a number of “traditional” drugs such as corticosteroids, antimalarials, azathioprine and cyclophosphamide. However, this scenario is rapidly changing due to the introduction of new compounds. Some of these new agents have been successfully used in other diseases, while others are being specifically designed to interfere with the immune abnormalities seen in SLE.

As our knowledge on the mechanisms of immune response increases, new drugs that can interfere with T and B cell interaction and activation, production of anti-dsDNA autoantibodies, immune-complexes deposition and cytokine activation have been developed and some of these are now under investigation in SLE. Although initial data regarding their safety and efficacy are encouraging, caution must be taken before these drugs are considered as the treatment of choice for specific SLE manifestations. Specifically, controlled clinical trials with sufficient number of patients are necessary. If the promising results already available are confirmed, the use of these drugs might represent the keystone in the future management of SLE and other autoimmune diseases.

Keywords: Systemic lupus erythematosus; Anti-dsDNA autoantibody; Autoimmune diseases

1. Introduction

Systemic lupus erythematosus (SLE) is a multi-system disease with an extremely variable clinical picture, characterized by a wide variety of active clinical manifestations, by an alternating course of flares and remissions and by the possible presence of chronic sequelae of the disease itself and/or treatments received. Taking all these aspects into account, it appears that each patient has their particular disease, thus a single therapeutic approach to SLE is almost impossible.

Over the last two decades, several combinations of drugs used to control disease activity have led to a dramatic improvement in the prognosis of SLE patients [1,2]. After the introduction of immunosuppressive drugs, lupus patients now achieve a 10-year survival rate of 85% [2]. Along with improvements in prognosis of the disease, new aspects have gained the attention of the clinicians, such as the risks related to long-term cytotoxic or corticosteroid therapy, the presence of co-existing conditions such as diabetes mellitus, hypercholesterolemia or hypertension, the management of sequelae of the disease such as end-stage renal disease and many other factors that together may have a great impact in the quality of life and the long-term prognosis of SLE patients [3].
The management of SLE is becoming more complex as the number of aims increases (Table 1) and is now undergoing rapid changes. These changes can be attributed to three main reasons. Firstly, the improvement of medical practice and clinical research in the administration and management of “traditional” drugs (corticosteroids, azathioprine, cyclophosphamide), which is leading to a refinement of the existing protocols, with better results and less toxic effects. Secondly, the use in SLE of drugs already used in other medical conditions. Lastly, the development of new drugs specifically designed to interfere with different phases of the immune response. To summarise these concepts in economical terms we could say that we are facing incremental the first two and radical the third changes in the treatment of SLE.

In this review, we will examine the drugs used to obtain control of disease activity. We will start with the data available on the traditional therapeutic armamentarium used in the treatment of SLE, and then analyse the new therapeutic approaches, in an attempt to highlight the role that each drug has or might have in the near future.

2. The “traditional” armamentarium

Antimalarials and immunosuppressive drugs, along with anti-inflammatories (both steroidal and non-steroidal), have been the basis of treatment of SLE over the past 30 years [4].

2.1. Antimalarials

Antimalarial drugs are extensively used in the treatment of the articular and mucocutaneous manifestations of SLE [5,6]. Regarding the latter, chloroquine and hydroxychloroquine (HCQ) have been successfully combined with quinacrine to treat severe cutaneous SLE [7,8]. Antimalarials can also control other manifestations of SLE, such as fatigue and serositis [6], and recently their beneficial effect on the lipid profile of lupus patients has been shown [9,10].

In 1991, the Canadian Hydroxychloroquine Study Group [11] reported a 6-month multicentre, placebo-controlled, double blind, randomized study of the effect of withdrawing HCQ in 47 patients with stable SLE. In the results, patients randomized to placebo were 2.5 times more likely to develop an SLE flare than those who remained on HCQ. Though most flares were mild, the frequency of severe flares was also higher in the placebo group, approaching statistical significance (p = 0.06). The same group has been retrospectively evaluated after 3 years of follow-up, with the purpose of evaluating the long-term efficacy of HCQ to prevent major flares in quiescent SLE. Fifty percent of the patients randomized to placebo vs. 28% of those receiving HCQ presented a major flare [12]. However, the difference was not statistically significant due to small sample size.

In 1996, Meinao et al. [13] reported the results of a 12-month, double-blind, placebo-controlled trial with chloroquine diphosphate, 250 mg/day, in 24 patients with mild SLE. Patients treated with placebo had an estimated risk of reactivation 4.6 times greater than those in the antimalarial group, and the prednisolone dose at the end of the study was also statistically higher in the placebo group.

Taken together, all these data support the clinical belief that antimalarials have a long-term protective effect against disease flares in SLE, acting as “disease-modifying agents”. They are also considered safe and well tolerated drugs. A recent report published in 1999 showed that, among 156 SLE patients treated with antimalarials, side effects caused the discontinuation of the drug in only 11% of cases [14]. The clinical experience also suggests that HCQ has a good safety profile for the mother and baby and can be used during pregnancy [15].

2.2. Azathioprine

Azathioprine (AZA) is used for the treatment of a wide spectrum of SLE manifestations [5,16]. The majority of published data come from patients with
lupus nephritis (LN), in whom the drug has been mostly used in sequential protocols after an induction phase with cyclophosphamide [17–19]. Data on its efficacy as first choice drug in the treatment of diffuse proliferative glomerulonephritis (DPGN) are controversial. However, AZA has proved to be efficacious in the treatment of DPGN in association with pulse steroids [20]. Furthermore, in a recent retrospective paper, prednisolone 1 mg/kg/day and AZA up to 2.5 mg/kg/day have been associated to outcomes similar to those obtained with pulse cyclophosphamide in a group of 26 lupus patients with DPGN [21].

The use of AZA to treat cutaneous, haematological and other manifestations or as a steroid-sparing agent, although widely accepted, is mostly empirical or based on small case series [22]. A further advantage of this drug is that it can be safely used during pregnancy, although it is not recommended during breast-feeding [23].

2.3. Cyclophosphamide

Although cyclophosphamide (CYC) is considered as the standard treatment for major organ involvement in SLE [4], most studies in SLE patients are focused on LN [24–30]. CYC is generally accepted as the treatment of choice for proliferative LN. However, due to the small number of controlled clinical trials and the small size of the groups studied, the debate on the optimal therapeutic protocol is still open.

Initial controlled studies of CYC in LN, which date back to the 1970s, failed to show a significant difference between oral CYC and prednisone alone [29], although less renal scarring was found in patients treated with immunosuppressive regimens [30]. Subsequent studies carried out at the US National Institute of Health (NIH) have proved intravenous CYC superior to steroids alone in the long-term maintenance of renal function—76% of patients treated with i.v. CYC vs. 37% of patients treated with prednisone alone [25–27].

The most widely used CYC regime consists of monthly pulses of 1 g/m² during 6 months, followed by quarterly pulses for 2 additional years, or at least 1 year after the achievement of remission [27,28]. Corticosteroid, either prednisone or pulse methylprednisolone, are also given. However, major concerns have been raised on the side effects of this regime, such as infections, premature ovarian failure and potential for malignancy, which are seen with the long-term use of CYC, being strongly associated with the cumulative dose (Table 2) [28,31].

Although the efficacy of long (2 years) and short (6 months) CYC courses in preserving renal function have not been shown to be statistically different, short courses have been less effective in preventing exacerbations of LN [27]. Studies analysing the frequency of renal flares after therapy with CYC have showed rates ranging from 7% to 46%, thus suggesting that some additional maintenance treatment may be required after the suspension of this drug [32–34].

For all the above reasons—high toxicity of long courses and more reactivations with short courses—new approaches have been proposed. These include weekly low-dose pulses of 0.5 g. of CYC until control of disease activity is achieved. CYC is then changed to a monthly schedule and rapidly discontinued and followed by maintenance treatment with AZA. The rationale for this schedule is that a short but frequent iv CYC regime may be as effective in inducing remission but less toxic than the higher dose regimens, while AZA could maintain remission once this has been achieved [18]. In a retrospective study, this schedule has proved efficacious in preserving renal function [18]. A randomised controlled trial comparing this regime with the NIH’s is currently in progress, and their results are expected shortly.

Treatment failures are observed in 15–35% of patients treated with pulse CYC [35]. The duration of renal disease before the start of treatment, high

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<th>Table 2</th>
<th>Side effects of cyclophosphamide therapy in different protocols</th>
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<tr>
<td>Major infections (%)</td>
<td>5</td>
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<tr>
<td>Amenorrhea (%)</td>
<td>38</td>
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<td>Cervical dysplasia (%)</td>
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*Long course.

*Short course.
serum creatinine at the time of renal biopsy, hypertension, and chronic lesions on renal histology, have been found as negative prognostic factors for response to treatment. For this reason, active nephritis should be promptly and aggressively treated, while a careful balance between the possible benefits and risks of side effects is particularly important in patients with advanced chronic changes before starting CYC treatments. Finally, pregnant patients must be delivered before starting CYC for the teratogenic potential of the drug [23].

3. The “new” therapeutic approaches

Although most of the drugs in this section are frequently used in other medical conditions, their use in SLE is relatively new. Therefore, published data mainly consist of uncontrolled studies and small case series. For this reason, the majority of these drugs should be viewed as rescue therapies rather than first line agents for the management of SLE until new clinical studies are available.

3.1. Cyclosporin A

Cyclosporin A (CsA) is a drug widely used in solid organ transplantation that acts by selectively and reversibly inhibiting T-cell mediated responses. Data available on the use of CsA in SLE suggest that this drug may be efficacious in controlling disease activity in a variety of disease manifestations [36–44]. The use of CsA at doses of 2–4 mg/kg/day has resulted in the reduction of disease activity and steroid requirements in patients with lupus resistant to other immunosuppressive drugs [36,38,39]. Recent reports have shown that very low dose CsA (1 mg/kg/day) might be sufficient to control some SLE manifestations such as thrombocytopenia [40,41].

In LN, CsA at a dose of 3–6 mg/kg/day is associated with reduction of proteinuria [36,37,42–44] and preliminary data also suggest that this drug may improve histological lesions [42–44]. In a pilot study of membranous nephropathy in 10 patients, repeating renal biopsies in five patients revealed a decrease in the number of fresh deposits [43]. In 1998, Tam et al. [44] reported the results of a prospective open study of long-term CsA in 17 patients with type IV nephritis. On repeating renal biopsy at 12 months, the authors observed that all the patients had changed to a type II glomerulonephritis, with a significant reduction in activity but no changes in chronicity indices.

The major side effects associated with the use of CsA have been hypertension (40–100% of patients), hypertrichosis (8–30%) and gingival hypertrophy (10–18%), while no significant increase in serum creatinine or signs of CsA nephrotoxicity have been found in the renal biopsies in lupus patients [42,43]. This makes a big difference with transplant recipients, probably due to the smaller doses of CsA used in SLE.

According to all of the above, and although further prospective data are mandatory, CsA might become an important drug to control minor organ involvement in SLE. It may also have a role in major organ involvement, especially proteinuric nephritis, in refractory cases or as maintenance therapy in sequential protocols. It may also be used as a second-line agent after AZA in selected cases during pregnancy [23].

3.2. Methotrexate

Methotrexate (MTX), at doses up to 15–20 mg/week, is being increasingly used in the treatment of serositis, cutaneous and articular manifestations of SLE. However, while the efficacy of MTX in the treatment of various autoimmune diseases, particularly rheumatoid arthritis, is already established by controlled studies, its use in SLE is based on case series [45–47] and only one small randomised placebo-controlled study [48].

In this study, 41 patients with active, non-life-threatening SLE were included [48]. Twenty patients were treated with MTX, 15 or 20 mg/week, and 21 patients received placebo. After 6 months, MTX-treated patients had less active SLE and needed lower doses of prednisone than controls. Arthritis and rash were the manifestations more likely to respond. Side effects, mainly dyspepsia and increase in hepatic-enzyme serum levels, were observed in 70% of patients, although none had to be withdrawn for these reasons. It is interesting to note that patients with renal insufficiency were excluded.
This study has confirmed the results of previous uncontrolled series [45–47]. Therefore, the main indications for MTX in lupus patients are severe arthritis and skin rash unresponsive to corticosteroids or antimalarials. MTX must be avoided during pregnancy [23].

3.3. Mycophenolate mofetil

As CsA, mycophenolate mofetil (MMF) is a drug developed for immunosuppression in organ transplantation. MMF has proved to suppress the development of autoimmunity and to prolong lifespan in the female B/W mouse model of SLE [49]. Thus, its use in human SLE, especially LN, has been proposed.

Data available in the literature, coming from the experience of five groups [50–54], seem promising. The daily doses of MMF have ranged between 1000 and 3000 mg, and the follow-up periods between 1 and 24 months. Most patients had resistant forms of proliferative LN or other severe manifestations of the disease, unresponsive to other immunosuppressive agents. In general, MMF has resulted in improvement of the symptoms and decrease in proteinuria. However, complete remission has been uncommon, and most patients with LN continued to have some degree of proteinuria.

This drug seems to have a good safety profile. Side effects have been few and not severe, only two patients being withdrawn for pancreatitis and severe febrile pancytopenia. However, despite this encouraging data, MMF should still be considered in selected patients with severe SLE manifestations unresponsive to other more conventional treatments.

3.4. Autologous bone marrow transplantation

Allogeneic stem cell transplantation (SCT) has demonstrated a therapeutic potential in animal models of autoimmune disease. Furthermore, adjuvant arthritis and experimental allergic encephalomyelitis cure by means of total body irradiation followed by autologous hemolymphopoietic SCT has been achieved [55]. The mechanism by which autologous bone marrow or peripheral SCT could improve autoimmune diseases would be the substitution of self-reactive T cells by others that are tolerant to self antigens.

Based on these observations, autologus bone marrow or peripheral SCT has been used in the treatment of some autoimmune diseases such as multiple sclerosis, scleroderma, refractory autoimmune thrombocytopenic purpura and SLE. Few patients with lupus have been treated so far, with good results in terms of disease control and survival [56–62]. Immunoablative chemotherapy without SCT has also been tried with success in some SLE patients, adding some controversy regarding the optimal approach [63].

The main limitation to these techniques is the identification of the patients suitable for SCT, since the risk of this treatment is relatively high, with a mortality in the range of 3% to 5% [64]. Guidelines for the inclusion of patients in these still investigational protocols have been developed [65]. Basically, only patients with very severe, uncontrolled disease and without permanent organ damage must be considered for this procedure.

3.5. Dapsone

Dapsone (4,4'-diaminodiphenylsulfone) is a drug used in the treatment of dermatitis herpetiformis and as an anti-mycobacterial drug in leprosy. A number of case reports and small series on the use of dapsone in SLE have been published. Oral doses of 25–100 mg daily have been shown to be effective in vasculitic lesions, bullous LE, subacute cutaneous lupus, oral ulcers and severe leukopenia and thrombocytopenia [66–69].

The main side effects of dapsone are hematological (hemolysis) and neurological (polyneuritis), thus, a careful monitoring is needed. This drug should be considered as a second-line treatment, mostly in cases of cutaneous lupus resistant to conventional therapies.

3.6. Thalidomide

The first data on the use of thalidomide in SLE date back to the early 1980s [70]. In this first report, cutaneous manifestations of lupus resistant to HCQ responded to high doses of thalidomide (300 mg/ day). A series of 60 patients with discoid lupus was published in 1983 [71]. These authors used 400 mg/day with a rate of response in the range of 90%.
Several groups have published their experience during the last 10 years [72–79]. In general, response rates have remained high, even though the doses of thalidomide used have been lower than in the past, usually between 50 and 200 mg/day. In this sense, low doses have shown to be as effective as higher ones.

On the other hand, side effects have been frequent in most studies, neuropathy being the most troublesome. It has been reported in 21–50% of patients and may be irreversible [80]. The precise mechanisms of thalidomide-induced nerve damage are not well established. Although a dose-dependent mechanism has been suggested, individual susceptibility is an important factor, since some patients develop symptoms soon after starting treatment [80]. Of note, relapse after thalidomide withdrawal is also frequent, ranging between 35% [73] and 80% [79].

Clinical use of thalidomide should be reserved for patients with severe skin lesions unresponsive to other treatments such as antimalarials and MTX. Women on thalidomide must ensure reliable contraceptive measures. The lowest dose possible should be used, and frequent monitoring of nerve conduction must also be performed, with the aim of detecting early and reversible nerve damage.

3.7. Dehydroepiandrosterone (DHEA)

Sex hormones may have a role in the etiopathogenesis of SLE. A possible therapeutic role of dehydroepiandrosterone (DHEA), a weak androgenic adrenal steroid, has been hypothesised. In a double-blind, placebo-controlled, randomized trial, published in 1995, 28 female patients with mild to moderate SLE were treated with DHEA 200 mg/day or placebo for 3 months. Although results did not reach a statistical significance, patients taking placebo showed a lower decrease in disease activity, a higher steroid dose and a high incidence of lupus flares than those treated with DHEA [81]. Similar results have been obtained in a long-term prospective, non-controlled trial, of treatment of SLE with DHEA at 50–200 mg/day [82].

The beneficial effect of DHEA in severe SLE, manifested primarily by nephritis, serositis or hematological abnormalities has not been demonstrated in a second randomised-controlled study [83]. Also, side effects of DHEA, mainly acne, hirsutism and irregular menses, while not life-threatening, can be troublesome in young women with SLE.

3.8. Bromocriptine

Prolactin might have a role in the immune response and SLE activity [84]. On the basis of these considerations, bromocriptine, a selective inhibitor of prolactin secretion, has been proposed to be beneficial in some autoimmune diseases.

This hypothesis has been investigated in two prospective, double-blind, randomised studies, one against placebo [85] and the other against HCQ [86]. In the first study [85], 66 patients, treated with bromocriptine, 2.5 mg/day, or placebo, have been followed for 12.5 months; no differences have been observed among the two groups in disease activity scores or number of flares, although bromocriptine decreased the mean number of flares/patient/month. In the second study [86], in 24 patients with active disease, bromocriptine showed the potential to suppress disease activity in SLE with results comparable to HCQ.

On the basis of these data it appears that bromocriptine has little effect on disease activity. On the other hand, it seems to be a safe drug, with headaches and nausea being the main side effects observed.

3.9. Nucleoside analog (fludarabine and cladribine)

Fludarabine and cladribine (2-chloro-2'-deoxy-adenosine) are nucleoside analogues that act specifically on lymphocytes. A recent pilot study has suggested the efficacy of a single iv infusion of cladribine to maintain LN in remission [87]. However, other authors have reported failure in inducing SLE remission, and even SLE reactivation by cladribine [88,89]. Fludarabine has been used anecdotally in two patients with SLE [90,91]. Thus, no specific recommendations can be done on the basis of these reports.

3.10. Tacrolimus

Tacrolimus has a mechanism of action very similar to CsA. The only data available so far in patients
with SLE are confined to three patients with severe cutaneous vasculitis refractory to other therapies [92]. Two patients responded to the drug, while the third did not. Hypertension developed in all three patients and some degree of renal failure in two.

4. The future prospective

The future of the treatment of SLE is represented by new drugs that are specifically designed to interfere with the different phases of the immune response (Table 3). These drugs are now under careful evaluation for their efficacy and safety. In this section, we comment on the data available for those drugs under more advanced evaluation.

4.1. Anti-CD40 ligand antibodies

The interaction between CD40 on B cells and CD40 ligand (CD40L) on activated T helper cells is required for normal antibody production. Monoclonal antibodies that block CD40:CD40L interaction would block B cell differentiation and could induce tolerance. A monoclonal antibody anti-CD40L has proved to be efficacious in reducing anti-DNA antibodies production, controlling renal disease and prolonging survival in New Zealand Black × New Zealand White lupus-prone mice [93].

Preliminary data from a phase I single-dose, dose-escalating trial with a humanised anti-CD40L monoclonal antibody, in 23 patients with SLE have shown that the drug is well tolerated, with mild to moderate side effects, mainly asthenia, dizziness, nausea and headache [94]. On the other hand, a second study was recently stopped due to the occurrence of thrombotic events in some recipients of the drug.

4.2. DNase

DNase is an enzyme that catalyzes the hydrolysis of extracellular DNA. It has been proposed that DNase might prevent the deposition of immune complexes containing DNA and promote their removal from the tissues.

On the basis of these considerations, a randomized, placebo-controlled trial has been performed to evaluate the safety and efficacy of recombinant human DNase (rhDNase) at doses of 25 μg/kg (n = 8) or 125 μg/kg (n = 6) in patients with LN [95]. Serum dsDNA antibodies, complement levels (C3 and C4), circulating immune complexes, serum cytokine profiles and serum markers of disease activity did not change significantly during the treatment period in any of the groups. Immune complex deposition in skin biopsies was also unchanged in the different treatment groups. Therapy with rhDNase was well tolerated and no neutralising antibodies to rhDNase were observed. Further studies with bigger samples should evaluate the efficacy of this drug in the future.

4.3. LJP 394

LJP 394 is designed to specifically reduce the anti-dsDNA antibody production. One single i.v. administration of the drug is associated with a rapid decrease of anti-dsDNA antibody levels which remain low for as long as 4 weeks after administration. As the increase of serum levels of anti-dsDNA antibodies has been correlated to an increased risk of flares, the efficacy of this drug in preventing the occurrence of renal flares in patients with history of LN is under investigation [96]. A recent Phases I–II study in four women with stable SLE [97] showed a decrease of anti-DNA levels shortly after the infu-

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Table 3
The future prospective: new drugs under evaluation in SLE

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<th>Drug</th>
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<td>Anti-B7 monoclonal antibody</td>
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<tr>
<td>Methimazole</td>
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<td>Anti-complement C5 mAb</td>
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<td>CTLA-4Ig</td>
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<td>Anti-CD40 ligand monoclonal antibody</td>
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<td>LJP 394</td>
<td>Phase II/III</td>
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sion of the drug. Adverse effects were mild, mainly headache and insomnia. Clinical efficacy is yet to be established.

4.4. Bindarit

Bindarit [2-(1-benzyl-indazol-3-yl) methoxy-2-methyl propionic acid] is an immunomodulatory agent that interferes with the acute phase response. Studies on animal models of SLE have shown that the development of the disease is inhibited by the continuous administration of the drug. In NZB/W animals, this drug reduced the frequency of renal disease and proteinuria and caused a delay in the appearance of anti-dsDNA and antinuclear antibodies [98]. Bindarit is safe and well tolerated in normal subjects, elderly volunteers and in patients with RA.

In a pilot study carried out in 10 SLE patients with inactive LN, bindarit, 600 mg twice daily, induced a significant reduction of urinary albumin secretion and urinary IL-6 [99]. A randomized placebo-controlled trial of the efficacy of bindarit vs. methylprednisolone in active LN has been recently concluded and its results are expected shortly.

5. Conclusions

Nowadays, the treatment of SLE is mainly based on the use of “traditional” drugs, such as corticosteroids, antimalarials, azathioprine and cyclophosphamide. However, this scenario is rapidly changing due to the introduction of new drugs. Some of these new agents have successfully been used in other diseases, while some others are being specifically designed to interfere with the immune abnormalities present in SLE.

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