

Therapeutic Perspectives in Systemic Lupus Erythematosus

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Abstract: Prognosis in systemic lupus erythematosus (SLE) has improved markedly in the last 40 years. From mortality rate which was higher than 50% after 5 years of SLE diagnosis in the 60's to a more than 90% survival after 10 years in the more recent prospective studies [1]. This is probably due to a number of reasons, including a better knowledge of the disease (earlier and easier diagnosis, assessment of new subsets) and an improved general healthcare (new antibiotics or better drugs to treat hypertension or hyperlipidemia, development of intensive therapy units), but also to the introduction of non-specific anti-inflammatory drugs, immunosuppressors and immunomodulators (steroids, cytostatics, intravenous gammaglobulins). Future challenges are to improve the quality of life of these patients and to reduce even more the mortality - the current mortality is still 3-4 times higher than expected for the similar age and gender population. In order to achieve these objectives, three main goals should be addressed: 1) to improve the use of some drugs already available; 2) to introduce some drugs in the clinical practice that are currently in phase I-III trials; and 3) to increase the basic research in order to discover targets for new selective immunomodulators.

1. IMPROVEMENTS IN THE USE OF SOME DRUGS ALREADY AVAILABLE

Currently available drugs for SLE allow a relatively good control of disease activity in most patients, but with a higher incidence of side effects. Among the measures that should be widely implemented in order to correct this problem, are: a) administration of the lowest doses of steroids that are necessary to control the "inflammatory" manifestations of the disease and avoidance of their use for other manifestations without a clear inflammatory nature (i.e. thrombosis, fatigue, arthralgia, asymptomatic rise in the levels of autoantibodies); b) use of non-steroidal anti-inflammatory drugs, antimalarials and some immunosuppressive agents, such as azathioprine and methotrexate that allow the tapering of steroid doses; c) systematic association of gastrointestinal protective agents when anti-inflammatory drugs are used as well as calcium and vitamin D when steroids are administered; d) active surveillance of the appearance of infections, specially tuberculosis or those produced by opportunistic agents; e) strict control of blood pressure and lipid levels and the early use of anti-hypertensive or lipid-lowering drugs when necessary; f) administration of lower doses of cyclophosphamide for the treatment of lupus nephropathy, such as the regimen recommended by the "Euro-Lupus Nephritis Trial" (6 fortnightly pulses of 500 mg) that allows a similar control of nephropathy at short [2] and long-term [3], but with less side effects than the classical regimens from the National Institutes of Health [4]; g) substitution of chloroquine by hydroxychloroquine; h) administration of ovarian protective agents, such as the synthetic agonists of gonadotrophin-releasing hormone [5], in young women treated with cyclophosphamide; and i) spreading of the use of intravenous gammaglobulins as an effective alternative drug but with less side effects (although more expensive) of

high doses of steroids and cyclophosphamide for life-threatening conditions (pulmonary haemorrhage, severe thrombocytopenia, catastrophic antiphospholipid syndrome...) [6]. These measures should be accompanied by the elaboration and wide use of clinical guidelines following the postulates of the evidence-based Medicine [7].

2. INTRODUCTION IN THE CLINICAL PRACTICE OF SOME DRUGS THAT ARE CURRENTLY IN PHASE I-III TRIALS

There are currently ongoing several phase I-III therapeutic trials in the European Union and the United States that follow, basically, three types of strategies against SLE: a) to modulate the function of B lymphocytes and other cells of the immune system with more selective immunosuppressive agents (mycophenolate mofetil [8, 9], tacrolimus [10], leflunomide [11]), monoclonal antibodies (mAb) against CD40L [12], CD-20 [13], C5b [14], or interleukin (IL)-10 [15] and androgenic hormones (dehydroepiandrosterone) [18]; b) to reconstitute the immune system (autologous or allogenic hemopoietic stem cell transplantation) [19]; and c) to deplete the immune system of immunocompetent cells (immunoablation with cyclophosphamide) [20] (Table 1). The preliminary results are encouraging, specially for some difficult cases.

Among the new experimental drugs, it is worth to mention the following agents:

1. Anti-CD40L mAb: CD40 and its ligand (CD40L) are the members of the tumour necrosis factor (TNF) superfamily and their interaction is essential for T and B cell co-stimulation. Anti-CD40L mAb block this interaction and T-B cell co-stimulation thus avoiding B cell activation [12].
2. Anti-BLyS mAb: These antibodies block B lymphocyte stimulator (BLyS) that is also a member of the TNF superfamily that plays a crucial role in the regulation of maturation and development of B cells [21].

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Table 1. Novel Therapies for SLE

Immunosuppressants	Mycophenolate mofetil Tacrolimus Leflunomide
Androgenic hormones	Dehydroepiandrosterone
Blockage of costimulatory pathways	Anti-CD40L mAb CTLA4-Ig Anti-4-1BB (CD137) mAb
Blockage of B cell maturation and differentiation	Anti-CD20 mAb (rituximab) Anti-CD22 mAb (epratuzumab)
Anticomplement	Anti-C5b
Anticytokine therapy	Anti-BlyS mAb Anti-IL-10 mAb
T and B cell tolerance	LJP 394 LJP1082
Immunoablation	High-dose cyclophosphamide
Stem cell transplantation	Autologous Alogenic

- Anti-4-1BB (CD137) mAb: They are directed against another member of the TNF superfamily (CD137) that also participates in the co-stimulation [22].
- CTLA4Ig: This drug is obtained by the fusion of the extracellular domain of the CD152 (CTLA4) molecule and the IgG Fc domain; it blocks the union of that molecule with the B7 ligand of the antigen presenting cells, thus avoiding T-B cell co-stimulation [23].
- Anti-CD20 mAb (rituximab): These antibodies are directed against the CD20 antigen located at B cells precursors and mature B cells, but disappear when these cells differentiate into plasm cells [13].
- Anti-CD22 mAb (epratuzumab): These humanized antibodies block the CD22 antigen located at mature B cell surface [24].
- Anti-C5b mAb: These antibodies block C5b complement factor thus avoiding the formation of the membrane attack complex (C5b-9) [14].
- Anti-IL-10 mAb: IL-10 induces SLE activation and administration of these antibodies decreases this activation [15].
- LJP 394: This drug is composed by 4 double chain oligonucleotides linked to a polyethylenglycol non-immunogenic substrate that induces tolerance to ds-DNA in B cells, thus making a decrease in the synthesis of anti-dsDNA by B cells [16].
- LJP 1082: This is another bioconjugate drug that contains 4 copies of the first domain of the human recombinant γ_2 -glycoprotein I (key protein in the pathogenesis of the antiphospholipid syndrome) linked to a tetravalent substrate of polyethylenglycol; this drug induces tolerance against γ_2 -glycoprotein I, thus decreasing the synthesis of antibodies directed against this protein [17].

Besides these specific therapies against SLE activity, several associated problems that these patients commonly

present (i.e thrombotic events related to the antiphospholipid syndrome) should benefit from other experimental drugs. These include new antiaggregants such as the glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban, eptifibatide, lamifiban) [25] and anticoagulants such as the selective inhibitors of activated factor X (fondaparinux, ximelagatran) [26].

3. MORE BASIC RESEARCH IN ORDER TO DISCOVER TARGETS FOR NEW SELECTIVE IMMUNOMODULATORS

The time between recognition of new target molecules, the development of drugs against these targets and the introduction in the clinical practice of these drugs has been reduced during the last years but it is rarely lower than 10-15 years. Some molecules that can be of interest for the development of new drugs for SLE and other autoimmune diseases are TNF, interferon, T cell transforming growth factor receptor and signal transducer and activator of transcription (STAT) molecules 3 and 4, among others [27].

Independently of the future perspectives in SLE therapy, complexity and heterogeneity of this disease will require to individualize treatment [28]. Therefore, clinical characterization of SLE patients will continue as the central hallmark in the management of these patients.

REFERENCES

- Cervera R, Khamashta MA, Font J, *et al.* and European Working Party on Systemic Lupus Erythematosus. Morbidity and mortality in systemic lupus erythematosus during a 10-year period. A comparison of early and late manifestations in a cohort of 1, 000 patients. *Medicine (Baltimore)* 2003; 82: 299-308.
- Houssiau FA, Vasconcelos C, D'Cruz D, *et al.* Immunosuppressive therapy in lupus nephritis. The Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002; 46: 2121-2131.
- Houssiau FA, Vasconcelos C, D'Cruz D, *et al.* Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from the long-term follow-up of the Euro-Lupus Nephritis Trial. *Arthritis Rheum* (in press).
- Austin HA III, Klippel JH, Balow JE, *et al.* Therapy of lupus nephritis. *N Engl J Med* 1986; 314: 614-619.
- Blumenfeld Z, Shapiro D, Shteiberg M, Avivi I, Nahir M. Preservation of fertility and ovarian function and minimizing gonadotoxicity in young women with systemic lupus erythematosus treated with chemotherapy. *Lupus* 2000; 9: 401-405.
- Gómez-Puerta JA, Cervera R, Font J. Clinical utility of intravenous immunoglobulins in autoimmune diseases. *Inmunología* 2003; 22: 287-293.
- Font J, Cervera R, Ramos-Casals M, Espinosa G, Jiménez S, Ingelmo M. *Guías clínicas 2004 - Diagnóstico y tratamiento de las enfermedades autoinmunes sistémicas.* MRA Ediciones, Barcelona, 2003.
- Chan TM, Li FK, Tang C, *et al.* Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med* 2000; 343: 1156-1162.
- Contreras G, Pardo V, Leclercq B, *et al.* Sequential therapies for proliferative lupus nephritis. *N Engl J Med* 2004; 350: 971-980.
- Yoshimasu T, Ohtani T, Sakamoto T, Oshima A, Furukawa F. Topical FK506 (tacrolimus) therapy for facial erythematous lesions of cutaneous lupus erythematosus and dermatomyositis. *Eur J Dermatol* 2002; 12: 50-52.

- [11] Remer CF, Weisman MH, Wallace DJ. Benefits of leflunomide in systemic lupus erythematosus: a pilot observational study. *Lupus* 2001; 10: 480-483.
- [12] Huang W, Sinha J, Newman J, *et al.* The effect of anti-CD40 ligand antibody on B cells in human systemic lupus erythematosus. *Arthritis Rheum* 2002; 46: 1554-1562.
- [13] Silverman GJ, Weisman S. Rituximab therapy and autoimmune disorders. Prospects for anti-B cell therapy. *Arthritis Rheum* 2003; 48: 1484-1492.
- [14] Strand V. Monoclonal antibodies and other biologic therapies. *Lupus* 2001; 10: 216-221.
- [15] Llorente L, Richaud-Patin Y, García-Padilla C, *et al.* Clinical and biologic effects of anti-interleukin-10 monoclonal antibody administration in systemic lupus erythematosus. *Arthritis Rheum* 2000; 43: 1790-1800.
- [16] Furie RA, Cash JM, Cronin ME, *et al.* Treatment of systemic lupus erythematosus with LJP 394. *J Rheumatol* 2001; 28: 257-265.
- [17] Cockerill KA, Smith E, Jones DS, *et al.* *In vivo* characterization of bioconjugate B cell toleragens with specificity for autoantibodies in antiphospholipid syndrome. *Int Immunopharmacol* 2003; 3: 1667-1675.
- [18] van Vollenhoven RF, Park JL, Genovese MC, West JP, McGuire JL. A double-blind, placebo-controlled, clinical trial of dehydroepiandrosterone in severe systemic lupus erythematosus. *Lupus* 1999; 8: 181-187.
- [19] Tyndall A, Passweg J, Gratwohl A. Haemopoietic stem cell transplantation in the treatment of severe autoimmune disease 2000. *Ann Rheum Dis* 2001; 60: 702-707.
- [20] Brodsky RA, Petri M, Smith BD, *et al.* Immunoablative high-dose cyclophosphamide without stem-cell rescue for refractory, severe autoimmune disease. *Ann Intern Med* 1998; 129: 1031-1035.
- [21] Cheema GS, Roschke V, Hilbert DM, Stohl W. Elevated serum B lymphocyte stimulator levels in patients with systemic immune-based rheumatic diseases. *Arthritis Rheum* 2001; 44: 1313-1319.
- [22] Sun Y, Chen HM, Subudhi SK, *et al.* Costimulatory molecule-targeted antibody therapy of a spontaneous autoimmune disease. *Nat Med* 2002; 8: 1404-1413.
- [23] Daikh DI, Wofsy D. Cutting-edge: reversal of murine lupus nephritis with CTLA4Ig and cyclophosphamide. *J Immunol* 2001; 166: 2913-2916.
- [24] Juweid M. Technology evaluation: epratuzumab, Immunomedics/Amgen. *Curr Opin Mol Ther* 2003; 5: 191-198.
- [25] Hirsh J, Weitz JI. New antithrombotic agents. *Lancet* 1999; 353: 1431-1436.
- [26] Shulman S, Wahlander K, Lundstrom T, Clason SB, Erikson H, Thrive III. Investigators. Secondary prevention of venous thromboembolism with the direct thrombin inhibitor ximelagatran. *N Engl J Med* 2003; 349: 1713-1721.
- [27] Davidson A, Diamond B. Autoimmune diseases. *N Engl J Med* 2001; 345: 340-350.
- [28] Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, *et al.* Systemic lupus erythematosus: Clinical and immunological patterns of disease expression in a cohort of 1000 patients. *Medicine (Baltimore)* 1993; 72: 113-124.