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SLE - Update Ethiopathogenesis Leading to Biological Therapy

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Abstract

Systemic lupus erythematosus is a chronic, autoimmune disorder which may have even fatal consequences, particularly if it affects vital organs of the human body. It is typically manifested by inflammation of various organ systems. The course of the disease includes sporadic flare-ups, or relapses, which may lead to irreversible damage of the organs. The focus is on the suppression of clinical symptoms, inhibition of the formation of autoantibodies induce remission, preventing relapse and irreversible organ damage while maintaining the best possible quality of life for the patient. The traditional treatment of SLE include corticosteroids, cyclophosphamide and cyclosporine A, in severe forms are widely used in addition to azathioprine and high doses of immunoglobulins. In recent years, intensive research into the pathogenesis of SLE appeared other potential targets for therapeutic intervention.

Keywords

Systemic lupus erythematosus, Etiopathogenesis, Conventional and biological treatment

Introduction

Similarly as in other autoimmune diseases, etiology of SLE is still a subject of various hypotheses. SLE is actually a rather more complex immune system disorder. Abnormal function, regulation and interaction of immune system cells (T lymphocytes, B lymphocytes, macrophages, and dendritic cells) lead to deposition of the developing immune complexes and subsequent damage of tissues and organs. The most realistic seems to be the hypothesis on apoptosis disorders resulting in exposure of and structural changes in cellular organelles that are not under normal conditions in contact with the immune system [1]. In case of SLE it concerns primarily the structure of the cell nucleus, the most prominent of which are chromatin components and their complexes. It has been proved that autoantibodies to these apoptotic products are important both in pathogenic and diagnostic terms. They include mainly antibodies to double-stranded DNA (dsDNA) and anti-nucleosome antibodies [2-5]. During development of the disease there probably take place interactions between abnormal immunological structures (e.g. hyperactive B-cells) and the systems (e.g. complement) that subsequently culminate in damage to tissues and clinical manifestation. It has been found out that increased disease activity involves or impairs also the mechanisms of cellular immunity. The common feature is damage to vascular walls ranging from arterioles up to medium-sized blood vessels, including the venous system. A characteristic finding in the damaged organs is the presence of fibrinoid and hematoxylin bodies, sometimes also lymphoid hyperplasia and infiltration. Recently detected vascular changes include non-inflammatory vasculopathy involving arteries and veins, which is induced by antiphospholipid antibodies. SLE is a chronic autoimmune disease with very diverse clinical course, affecting any organ. Due to a large clinical variability which is given by a wide range of abnormalities, SLE therapy is dictated by activity of the disease and the type of organ involvement. Treatment includes preventing flares and permanent organ dam-

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age, respond rapidly to flares and stop progression of the disease.

Non-Specific Anti-Inflammatory or Immunosuppressive Therapy

Treatment of SLE has traditionally involved non-specific anti-inflammatory or immunosuppressive medications.

Non-steroidal anti-inflammatory drugs (NSAIDs) are usually able to suppress episodic arthritis, arthralgia and increased temperature, although they are not as efficient as glucocorticoids and cannot manage more severe SLE forms. In SLE, a higher incidence rate of hepatotoxicity and nephrotoxicity after NSAIDs was reported as compared to other rheumatoid diseases, as well as rare cases of aseptic meningitis. NSAIDs should be indicated with caution in patients with active nephritis and renal failures.

Currently, antimalarials (AMs), mainly hydroxychloroquine (HCQ) and chloroquine, are considered as key medications in SLE treatment and are used either as a monotherapy or in combination with corticosteroids and immunosuppressive drugs, such as mycophenolate, azathioprine and cyclophosphamide which improve survival of SLE patients [6]. According to the study published by Nørgaard, et al. [7], the use of AMs in Denmark has increased in the recent 10 years, with 50.2% of SLE patients receiving AM therapy in the course of the disease and up to 75% of patients being treated with AMs within one year of establishment of SLE diagnosis. AM therapy was commenced usually earlier in male SLE patients than in females. In addition, the authors found out during a 10-year follow-up that these patients had less comorbidities as compared to patients who did not use AMs at the beginning of the treatment [8].

Hydroxychloroquine at a dose of 200-400 mg/day may have a positive effect in the treatment of lupus erythema, photosensitivity, arthralgia, arthritis, hair loss and general weakness, associated with SLE, as well as in the treatment of the discoid and subacute cutaneous lupus erythematosus. After administration of hydroxychloroquine's, skin lesions may improve as early as within several days, but joint-related symptoms get better as late as after 6-10 weeks. These medications are not effective in case of increased temperature, hematopoiesis disorders and involvement of vital organs of the body [9]. Recent studies have confirmed that antimalarials have an antithrombotic effect and play an important role in prevention of atherosclerosis (both early and late) [10,11].

Indications for general administration of glucocorticoids include a high inflammatory activity (fever, humoral activity, and autoantibody activity), life-threatening SLE manifestations, such as glomerulonephritis, CNS involvement, vasculitis, thrombocytopenia and hemolytic anemia. Long-term treatment with glucocorticoids contributes to development of atherosclerosis indirectly, by increasing the number of risk factors (hypertension, hypercholesterolemia, hypertriglyceridemia, DM, obesity, homocysteinemia), or directly by damaging vascular walls [12,13]. In the Hopkins´ cohort the SLE patients had 3-4 common risk factors for atherosclerosis. Hypertension occurred mainly in patients with renal disorder, hyperlipidemia in patients with active SLE, in patients with cardiolipin antibodies - low levels of HDL, apo A1, and high VLDL levels and in patients treated with glucocorticoids - high levels of TG, cholesterol and LDL [14].

Intravenous methylprednisolone pulse therapy is used in SLE in life-threatening conditions, such as rapidly progressive renal failure, acute manifestations of CNS involvement and severe thrombocytopenia. Intravenous infusions of 500 mg of methylprednisolone in 0.9% physiological solution or 5% dextrose solution are administered for more than 30 minutes every 12 hours, for the period of 3-5 days, or in a single 1000 mg dose in 24 hours - a total of three infusions. In patients with hypertension it is possible to administer methylprednisolone in 5% glucose solution with a small dose of insulin (8 u.). Patients whose condition does not improve after this dose, probably do not respond to corticosteroids, and alternative therapeutic procedures must be considered. After completion of the pulse therapy, patients receive oral prednisone at a dose of 20-60 mg/day according to the momentous condition. The prednisone dose may be gradually reduced, based on a favorable clinical finding. Most of these conditions require combination of glucocorticoids with cytostatic drugs [15].

Immunosuppressive preparations are used mainly in patients with involvement of visceral organs, who do not respond to glucocorticoid therapy, do not tolerate it, and require high maintenance doses of glucocorticoids or when the disease repeatedly reactivates during this therapy. The dose is adjusted individually in order to prevent toxic manifestations, a hematopoiesis disorder in particular. After suppression of the disease, the lowest possible effective dose of the preparation is used. Objective evidence of improvement of the condition may appear after 2-12 weeks of the therapy. In this context it is necessary to take into account the potential short-term effect of immunosuppressant and the risk of development of malignancies (lymphoma, leukemia) in its long-term administration.

Azathioprine

At the beginning of the therapy, 1.5 mg/kg/day of azathioprine is administered either in one or two doses. At 8-12-week intervals the dose may be increased with a good tolerance to a maximum of 2.5 mg/kg/day, where a disorder of hematopoietic or elevated AST, ALT, and GGT activity [16]. The azathioprine dosage is reduced by 60-75% if azathioprine is administered simultaneously with allopurinol which blocks its metabolic degradation.

Cyclophosphamide

At the beginning of the therapy it is administered

orally at a dose of 1.0-1.5 mg/kg in the morning. With a good tolerance, the dose may be increased to a maximum of 2.5 mg/kg/day. Patients must be instructed to drink plenty of fluids with the drug, to empty frequently the urine bladder, mainly before going to bed, in order to reduce the risk of hemorrhagic cystitis. Sometimes intravenous cyclophosphamide pulse therapy (0.5-1.0 g/m^2) at monthly intervals is preferred. This therapy may provide better results as compared to glucocorticoids. Its disadvantage is a frequent incidence of infectious complications and increased frequency of malignant diseases. According to EULAR and ACR recommendations, classes III, IV and V. LN should be treated with cyclophosphamide or mycophenolate mofetil in combination with a higher dose of corticosteroids for six months which should result in decrease in proteinuria and correction of serum complement levels confirming a good response to the therapy [17-19].

Cyclosporine

A. It is used in SLE with associated renal disorder or involvement of other vital organs of the body in case of:

- resistance to other immunosuppressants,
- adverse effects of other immunosuppressants,
- persisting anemia, leukopenia and thrombocytopenia associated with the underlying disease, with a simultaneous administration of glucocorticoids.

Dosage, monitoring of therapy and adverse effects of cyclosporine A are the same as in case of RA. Cyclosporine A reduces clinical as well as autoantibody activity of SLE [20]. The dose is 2.5-5 mg/kg/day.

High-dose intravenous immunoglobulin therapy (IVIg) is a method of choice in SLE with lupus nephritis resistant to immunosuppressive therapy, in SLE with antiphospholipid syndrome and repeated miscarriages (this therapy may be used also during pregnancy), in SLE with thrombocytopenic purpura and in case of severe infectious complications in SLE and other systemic connective tissue diseases. The dose is 400 mg/kg/day administered for five consecutive days. Sugisaki, et al. [21] and Lin, et al. [22] have reported that in resistant forms of SLE glomerulonephritis, IVIg are successfully used to suppress glomerulonephritis (clinical finding) as well as to improve the biopsy finding. Type IV glomerulonephritis in SLE transformed in two patients into type II b and in one patient into type III; in two patients the biopsy finding did not change. Based on overall evaluation the author concludes that IVIg pulse therapy is effective in about a half of the group of SLE patients with glucocorticoid- and immunosuppressant-resistant forms of lupus glomerulonephritis and is particularly useful in treatment of type IV glomerulonephritis in SLE. The clinical effect in the form of decrease of proteinuria becomes evident during 7-14 days and lasts for up to 6 months. In addition, according to the experience of Lin, et al. [22], serum C3, C4 levels and CH50 hemolytic activity also increased. This phenomenon we consider also in other successful immunomodulatory therapeutic procedures as a signal of improvement of glomerulonephritis [23,24]. Silvestris, et al. [25] administered lower immunoglobulin IgG doses with anti-8.12 idiotype specificity and achieved a provable decrease in anti-dsDNA activity together with reduction of proteinuria. Finally, Francioni, et al. [26] pointed out to the possibility of the use of this therapy in SLE, and confirmed the potential for improvement of renal finding, correction of thrombocytopenia, increase of serum haemolytic complement and C3 and C4 components.

Our results [27] correspond to those of the above mentioned authors and indicate that IVIg may be used in resistant forms of glomerulonephritis, in order to overcome the period of activity, to suppress resistance and to convert the therapy of glomerulonephritis in SLE to classic immunosuppressive or immunomodulatory treatment.

There is a possibility to use IVIg also in antiphospholipid syndrome associated with repeated cerebral infarctions [28]. Finally, Ben-Chetrit, et al. [29] suggested administration of IVIg in refractory pleuritis in SLE which was unresponsive to the therapy of high-dose glucocorticoids with azathioprine. Sherer, et al. [30] reported a case of a 59-year-old patient with SLE who developed during glucocorticoid therapy a severe cardiac dysfunction with left ventricular ejection fraction reduced to 20%. Coronary artery blood flow was normal, and as a result the presence of myocarditis was suppressed. After administration of high doses of IVIg, cardiac function improved, ejection fraction increased in several days and one month after administration of IVIg the condition did not exacerbate. Karim, et al. [31] report successful outcomes of IVIg treatment in patients with SLE, where exacerbation was associated with the accompanying sepsis.

On the horizon are new targeted therapies specifically designed to block pathways involved in disease pathogenesis. To date, specific biologic agents for SLE have targeted the B cell, given the importance of autoantibodies in driving the pathogenesis. However, other promising therapeutic targets have emerged, including the plasmacytoid dendritic cell (pDC)-type I interferon (IFN) pathway. The most advanced therapeutics targeting the IFN pathway are monoclonal antibodies (mAbs) that block type I IFNα or its receptor, IFNAR; the latter has commenced a phase III clinical trial.

B-Cell Depletion or Modulation

SLE is characterized not only by polyclonal hyperactivity of B lymphocytes, but also by a significant disorder of their homeostasis. It has been proved that B lymphocytes are not only passive antibody producers, but they play a key role in autoimmune processes through unconventional mechanisms including antigen presen-

tation and modulation of other immunocompetent cells. Therefore B lymphocytes have become the center of attention in search for new therapeutic options. The targeted therapy to influence B lymphocytes is focused on depletion of B lymphocytes by blocking receptors on B lymphocytes, inhibition of costimulatory receptors, inhibition of production of cytokines having effect on B lymphocytes and elimination of auto reactive B lymphocytes.

SLE patients have a reduced number of B lymphocytes in peripheral blood, but their abnormal phenotype indicates a marked activation of these cells. It has been found that the number mainly of naïve B lymphocytes (CD27-cells) is significantly reduced, while the number of memory cells ($CD27^+$ B cells) is increased [32]. Polyclonal hyperactivity of B lymphocytes plays an important role in SLE pathogenesis. Increased attention is paid not only B lymphocytes, but also to factors influencing survival of B lymphocytes. They include mainly BLyS-BAFF-R interaction which is decisive for survival of B cells. In case of disorder, autoreactive or polyreactive B lymphocytes might display increased survival resulting in impairment of their apoptotic removal. The primary source of BLyS secretion are dendritic cells which can be often found in mucosa and skin [33]. As SLE manifests itself by skin and mucosal changes, it may be reasonably hypothesized that hyperactivity of dendritic cells may be involved also in the increase of BLyS serum levels in SLE patients. The preparation able to inhibit selectively the biological activity of soluble BLyS and thus leading autoreactive B lymphocytes to apoptosis is the monoclonal anti-BAFF/LyS antibody [34]. Only two biologic agents, both B-cell-targeted mAbs, have entered clinical practice in SLE. The first of these is rituximab, a mAb targeting CD20 and second monoclonal antibody (mAb) is belimumab, which targets BAFF, a B-cell survival factor.

Belimumab is a fully human monoclonal IgG antibody binding soluble BLyS and inhibiting its binding to TACI, BCMA and BAFF-R. Its half-life is 11-14 days. The latest results of a multicentric, randomized, double-blinded, placebo controlled study conducted at 90 centers in 13 countries in Asia, Latin America and Eastern Europe has proved efficacy, safety and tolerability of belimumab in combination with standard treatment of patients with seropositive SLE [35]. Treatment with belimumab had also a corticosteroid-sparing effect, reducing the use of steroids by more than 50%. At the same time it reduced the incidence of significant relapses and markedly normalized the levels of C3, C4 complement components and anti-dsDNA antibodies. The incidence of adverse effects in 52^{nd} week of the therapy was comparable with the placebo group. The results of this study have confirmed a safe profile and efficacy of belimumab in terms of SLE control in a wide range of patients; inhibition of soluble BLyS by belimumab shows a new way to management of this severe autoimmune disease.

Atacicept is a chimeric molecule with the extracellular domain of TACI, which binds both BAFF and APRIL, a proliferation-inducing ligand fused to the constant region of human IgG1. The arm of the trial that demonstrated a potential advantage was discontinued early owing to an increased risk of infections [36].

CD20 is a receptor on the immature, naïve and memory B cells, but is not found on early pro-B cells and plasma B cells [37]. Rituximab - anti-CD20 monoclonal antibody - is a chimeric monoclonal antibody which was first used in the year. 1997 for the treatment of non-Hodgkin's lymphomas [38] and causes selective short-term depletion of [39]. Two recent randomized controlled trials have evaluated the use of rituximab in patients with SLE - Explorer (the Exploratory Phase II/III SLE Evaluation of Rituximab) [40] and LUNAR [41] (the Lupus Nephritis Assessment with Rituximab). Therapy with rituximab was well tolerated in patients. Studies have shown significant improvement LN evaluated by BILAG score, decrease levels of complement C3 and anti- dsDNA.

Ocrelizumab - another anti-CD20 monoclonal antibody. The trial - BELONG [42] was suspended early due to the detection of severe infection [43] and ocrelizumab has not been studied further.

CD22 is surface receptor on mature B cells. Epratuzumab, humanized anti-CD22 mAb, similar to the anti-CD20 MAb, is associated with the depletion of B cells, but can affect by down-regulation of B-cell receptor signaling by inhibiting the CD22 membrane molecule.

Treatment with Epratuzumab was well tolerated in patients with improvement in disease activity [44-46].

Interferons - Several studies heave elucidated the critical role of type I interferon - inducible genes in pathogenesis of SLE [47]. Studies of expression profiles of interferon signature genes have shown that patients with SLE typically exhibit increased regulation of IFN I genes, resulting in higher production of IFN I. A higher IFN I production has been reported also in association with gene polymorphisms in these patients. Expression of these gene modifications is, however, conditioned by the presence of SLE-specific autoantibodies. Based on this, the "gene + autoantibody = high IFN I" model has been proposed [48].

In patients with incomplete SLE (meeting less than 4 ACR diagnostic criteria), interferon signature may be a predictive marker of further progress of the disease. Comparison of autoantibody production with expression profiles of interferon signature genes in patients with incomplete SLE also revealed a significant correlation of a high-degree expression of these genes with the panel of IgG class antibodies (primarily antibodies to dsDNA, RNP, SS-A and SS-B). Low degree of their expression was observed in patients with predominating production of IgM class autoantibodies [49]. About half of patients with severe SLE showed dysregulated expres-

sion of genes in the IFN pathway as compared to healthy controls [50].

Garcia-Romo, et al. [37] described a new link between nucleic acid-recognizing antibodies and type I IFN production in SLE. Increased production and/or bioavailability of IFN-α and associated alterations in dendritic cell homeostasis have been linked to lupus pathogenesis. The authors have shown that mature SLE neutrophils are primed in vivo by type I IFN and die upon exposure to SLE-derived anti-ribonucleoprotein antibodies, releasing neutrophil extracellular traps (NETs). These complexes are produced by activated neutrophils which, similarly as in case of sepsis, form NETs and trigger activation of immature plasmacytoid dendritic cells in a Toll-like receptor 9 (TLR9) manner. In these patients, antibodies were found to DNA, as well as to microbial peptides present in NETs. It may be hypothesized that these complexes may also serve as autoantigens activating B lymphocytes. Circulating neutrophils of SLE patients release more NETs as compared to the healthy controls. In some SLE patients, degradation of NETs is impaired by inhibition of DNase I enzyme and by antibodies to NETs [38].

Besides participating in the activation of dendritic cells, the role of TLR 9 in the pathogenesis of SLE remains controversial. Both TLR7 and TLR9 are expressed by pDCs and activation initiates the release of type I IFN, although TLR7 and TLR9 act in parallel on different subsets of autoantibodies. MyD88 is a common adaptor protein present in most TLR signaling [51]. Because both TLR7 and TLR9 utilize this protein, MyD88 is an excellent target to intervene in the abnormal signaling in SLE [52].

Alternate therapies that target type I IFN are the anti-IFNα mAb, ASG-009, which was well tolerated and effective in neutralizing a 27 IFN gene signature in a phase I trial [53] and an IFNα kinoid (IFN-K) vaccine composed of IFNα2b coupled to a carrier protein [54].

Sifalimumab, mAb against INFα - reduced baseline moderate to severe SLE mucocutaneous involvement, as well as decreased arthritis and fatigue scores. It did not improve serological markers of active disease, such as dsDNA and complement levels. INFα blocking therapies entered phase II clinical trials and show promising results in moderate to severe SLE [55]. Rontalizumab, a human-

Table 1: New drugs for systemic lupus erythematosus tested in clinical trials (APRIL: A proliferation-inducing ligand; BLyS: B-lymphocyte-stimulator protein; ICOS: Inducible costimulator; JAK: Janus kinase; mAb: Monoclonal antibody).

Drug	Mechanism of action
Blisibimob	Inhibition of B lymphocytes (BLyS blocking)
Abatacept (CTLA4-Ig)	T lymphocyte costimulation blocking (CD28/B7 interaction)
AMG 577	T lymphocyte costimulation blocking (by ICOS inhibition)
AMG 811	IFN-γ activity blocking (anti-IFN-γ mAb)
Anakinra	Cytokine blockade, human recombinant IL-1 receptor antagonist
Anifrolumab	IFN-α activity blocking (anti-IFN-α receptor mAb)
Atacicept	Inhibition of B lymphocytes (BLyS-APRIL blocking)
CDP 7657	Blockade of T cell co-stimulation (CD40L)
Epratuzumab	Inhibition of B lymphocytes (anti-CD22 mAb)
Glutathione	Antioxidant (*N*-acetylcysteine)
IFNa Kinoid	IFN-α vaccine
JAK 116439	T lymphocyte costimulation blocking (by JAK inhibition)
Laquinomod	Immunomodulatory agent (synthetic tolerogen)
Lupizor	Immunomodulatory agent (synthetic tolerogen)
MEDI-570	T lymphocyte costimulation blocking (by ICOS inhibition)
NNC 0152	IFN-α activity blocking (anti-IFN-α mAb)
Ocrelizumab	Inhibition of B lymphocytes (anti-CD20 mAb)
Rapamycin	mTOR inhibition
Rituximab	Inhibition of B lymphocytes (anti-CD20 mAb)
Rontalizumab	IFN-α activity blocking (anti-IFN-α mAb)
Sifalimumab	IFN-α activity blocking (anti-IFN-α mAb)
Sirukumab	Cytokine blockade (anti-IL-6 receptor mAb)
SM 101	Fcγ receptor modulation
Tabalumab	Inhibition of B lymphocytes (BLyS blocking)
Tocilizumab	Cytokine blockade (anti-IL-6 receptor mAb)
Vitamin D	Immunomodulatory agent

ized IgG1 anti-interferon α (anti-IFN-α) monoclonal antibody, was used in patients with moderate-to-severe SLE. A phase II trial found rontalizumab to be safe; however, it failed to meet efficacy endpoints [56].

A recent randomized controlled trial of a mAb against INFγ (molecule AMG 811) used in subjects with mild to moderate SLE showed dose dependent modulation of INF gene expression and reduction of the inflammatory protein linked to the prediction of future flares and level of disease activity [57].

IFNγ receptor deletion inhibited autoantibody production in SLE and nephritis. **Anifrolumab**, monoclonal antibody against the type I interferon (IFN) receptor that inhibits the activity of all type I IFNs, significantly reduced disease activity compared with placebo across multiple clinical endpoints [58].

Conclusion

A combined therapy using various biological agents may increase success rate of interventions into the network of impaired immune mechanisms associated with SLE. Multiple studies dealing with SLE diagnosis and treatment have produced ample data that must be systematically reviewed and incorporated in recommendations for use in everyday practice. Many other biological agents with various mechanisms of action are or will be shortly introduced in clinical trials focused on SLE. The aim of all research is to find out as much about failures not only the immune system in SLE. There are still unanswered questions despite the ever emerging knowledge in the etiopathogenesis of SLE. Over the next few years we will continue to test the effectiveness of many new therapeutic agents based on obtained new knowledge about the etiopathogenesis of SLE and search targeted therapeutics with few side effects (Table 1). Analysis of clinical manifestations of SLE patients, taking into account gender-specific features, will continue to be also in future the key issue in the choice of appropriate treatment of SLE patients.

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