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Systemic Lupus Erythematosus

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Abstract:

Systemic lupus erythematosus (SLE) is autoimmune disease in which the body's immune system mistakenly attacks healthy tissue in many part of the body. The SLE is chronic inflammatory disease that has protean manifestations and follows a relapsing and remitting course. More than 90% of cases of SLE occur in women, frequently starting at childbearing age. Common symptoms include painful and swollen lymph nodes, feeling tired, and a red rash which is commonly in the face. SLE can occur in up to 20% of patients 50 years of age or older. SLE affects almost every system in the body, with varying degrees of severity. Recent advances in our understanding of the genetic, molecular and cellular basis of autoimmune diseases and especially SLE have led to the application of novel and targeted treatments. This article reviews the general approach to the therapy of SLE, focusing on current approved therapies .(1)(3)

Introduction:

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with heterogeneous clinical manifestations and disease course. It is characterized by the dysregulated innate and adaptive immune pathways and the development of anti-nuclear antibodies. The term "lupus" is most often used to describe a more severe form of the condition called systemic lupus erythematosus (SLE). The current treatment approach includes antimalarials, steroidal and non-steroidal anti-inflammatory agents and immunosuppressive drugs,. there is a dramatic improvement in the prognosis for SLE patients, treatment On the horizon are new targeted therapies specifically designed to block pathways involved in disease pathogenesis.

Symptoms of lupus:

SLE can cause a wide range of symptoms, depending on the areas of the body affected. The most common symptoms are:

•Rashes – particularly on the face, wrists and hands

•Fatigue (extreme tiredness).

•Joint pain and swelling.

-Most patients presented with symptoms of fatigue, typical rash and\or musculoskeletal symptoms, May include headache or lymphadenopathy **(**cervical or axillary**)** patients may present with pericarditis. (3)

Discussion:

1 - Investigation

Diagnosis of systemic lupus erythematosus (SLE) requires documentation of multisystem involvement and the presence of antinuclear antibodies. In almost all cases of SLE, these autoantibodies are detected at significant titer with a sensitive screening test such as the fluorescent antinuclear antibody test. After other diagnostic possibilities, such as rheumatoid arthritis, have been excluded, several laboratory tests (hematocrit determination, complement tests, anti-native DNA assays) are available to monitor the response to therapy.

Systemic inflammation direct treatment:

1. Antimalarials-Hydroxychloroquine

Antimalarials remain as first line treatment for patients with mild SLE along with nonsteroidal anti-inflammatory drugs. Hydroxychloroquine is effective in the treatment of mild SLE manifestations as well as in preventing the occurrence of new mild SLE manifestations, but it is ineffective in preventing the occurrence of severe SLE manifestations.

2. Corticosteroids:

Glucocorticoids are the mainstay of treatment in SLE, especially at the beginning of a flare. They have strong anti-inflammatory effects on both acquired and innate immune pathways. They inhibit B and T cell responses and effector functions of monocytes and neutrophils.

3. Cyclophosphamide:

Pulse cyclophosphamide (CTX) defined the standard of care for lupus nephritis for many years and is usually used in conjunction with corticosteroids.

The comparison of "mini-pulse" CTX with conventional pulse CTX therapy (National Institutes of Health (NIH) trials) showed no difference in efficacy between the groups, CTX is also used with corticosteroids in patients with severe neuropsychiatric involvement.

4. Methotrexate (MTX):

Methotrexate is a folic acid analogue and a potent competitive inhibitor of dihydrofolate reductase (DHFR), and acts by inhibition of both DNA and RNA synthesis. MTX has a role in the management of resistant arthritis and skin disease in SLE as a steroid-sparing agent. It does not have a role in the treatment of SLE patients with major organ involvement.(2)

2 - Investigation

Renal biopsies:

The 2012 American College of Rheumatology (ACR) guidelines for lupus nephritis recommend renal biopsy for all cases of active, previously untreated lupus nephritis, unless contraindicated. Renal biopsy is used to confirm the presence of lupus nephritis; to aid in classification of systemic lupus erythematosus (SLE) nephritis based on the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification
cardiac MRI (CMR) provides an excellent alternative to clinical assessment, electrocardiography, and echocardiography for diagnosing SLE myocarditis.

Treatment

Approximately 30 novel agents are currently being evaluated in phase II/III clinical trials for the treatment of SLE, lupus nephritis and cutaneous lupus In phase III trials, agents include those targeting the interferon (IFN) pathway, , T-cell signalling and B-cell signalling.

IFN pathway inhibitors

Rationale

, a member of the type I IFN family, promotes the stimulation and differentiation of various immune cells, including the differentiation of autoreactive B lymphocytes to immunoglobulin-secreting plasma cells,

Mouse models indicate that type I IFN receptor deficiency reduces lupus-like symptoms.

Anifrolumab:

Anifrolumab binds to and neutralises the IFN-α receptor, in effect blocking type I IFN-dependent cell signalling.

In patients with moderate-to-severe SLE who did not have active or severe lupus nephritis, a significantly greater percentage of patients receiving anifrolumab 300 mg every 4 weeks achieved response at week 24

In addition, after 1 year of treatment, anifrolumab patients achieved significantly greater rates of improvement in rash, alopecia and joint manifestations

T-cell and B-cell signalling inhibitors

Rationale:

Patients with SLE have autoreactive T cells, and concentrations of both $CD4^+$ T-helper cells and $CD3^+CD4^-CD8^-$ T lymphocytes are elevated in patients with SLE, supporting the production of autoantibodies.

Central and peripheral B-cell tolerances to self-antigens are defective in SLE

resulting in the promotion of autoreactive B-lymphocyte differentiation to pathogenic memory and plasma cells.

Rituximab:

anti-CD20 monoclonal antibody that is considered a treatment option in published guidelines for patients with lupus nephritis who are not responsive to first-line therapy.

In a pilot study of 50 patients with lupus nephritis, 90% of patients achieved complete or partial response by a median time of 37 weeks when treated with two doses of rituximab (1 g) and methyl prednisolone (500 mg).(4)

3 - Investigation

1. Complete blood count(CBC) : Leukopenia, lymphopenia, anemia, Thrombocytopenia:
• Prolonged partial activated thromboplastin (aPTT).
2. Serum creatinine : Kidney affection.
3. Urinalysis:
• Low serum albumin, persistent proteinuria.
• Red and white cell cast.

Other laboratory test:
1. ESR or CRP : Elevated due to increase activity of infectious process.
2. Complement level : Decrease C3 and C4 in active SLE.
3. Liver function test : Mildly elevated in acute SLE.
4. Creatine kinase assay : Increase in myosities and overlap syndromes.

Anti-cytokine therapy:

Tumor necrosis factor (TNF) and anti-TNF therapy.

TNF is a cytokine that exerts several functions in the immune system and can either promote or reduce autoimmunity. TNF concentration is increased in sera of SLE patients and is associated with disease activity.

The short term use of TNF blockade might be safe and effective in some SLE patients, especially those with lupus nephritis.

Anti-IL-10**:**

IL-10 is the first cytokine successfully blocked in SLE. IL-10 is increased in serum of patients with SLE and is associated with disease activity

In an open study, a single dose of mouse anti-IL-10 mAb There was improvement in cutaneous lesions, joint symptoms and disease activity. Prednisone dose was also decreased. The beneficial effect lasted 3–6 months. All patients developed antibodies against the mouse mAb. Currently, there are no studies with humanized anti-IL-10 mAb.

Anti-IL-1**:**

IL-1 can be increased by TNF and by autoantibodies to dsDNA. Serum IL-1 level is increased with lupus disease activity. There are two small trials of IL-1 receptor antagonist Anakinra in patients with SLE and severe lupus polyarthritis, both of which showed beneficial effects. there was a transient improvement of arthritis but no effect on muscle pain.

Statins:

Statins inhibit the production of proinflammatory mediators such as TNF-α, IL-1β, IL-6, IL-8, RANTES, monocyte chemotactic protein 1 (MCP-1), IL-17, cyclooxygenase 2, and nitric oxide by T cells and antigen-presenting cells.

Statins may also play an important role in prevention of cardiovascular diseases in SLE patients.

A 1-year trial with atorvastatin demonstrated a decrease in cholesterol levels, proteinuria, and rate of progression of chronic kidney disease in SLE patients with lupus nephritis.(5)

Conclusion:

In this review article, the general approach to treatment of SLE, focusing on current approved therapies, ongoing clinical trials, , novel approaches that has a potential to be used in the future are discussed in detail. Advances in our understanding of the mechanisms of SLE have offered better drug targets for treatment. Biomarkers which will help us to identify SLE disease and disease activity earlier are urgently needed.

References:

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