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The comparison between different therapies of Systemic Lupus Erythematosus

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Abstract. The immune system has three basic functions: defense, surveillance and homeostasis. It helps us monitoring and timely eliminate mutant cells and distinguishing between "alien" components to maintain self-stability. However, once it loses these abilities, it could cause the autoimmune disease. In this article, I mainly discuss about the Systemic Lupus Erythematosus (SLE), a type of autoimmune diseases which is mediated by type III hypersensitivity. SLE patients suffer from chronic inflammatory responses, leading to tissue damage and organ dysfunction. Therefore, purpose of therapeutic schedule is to inhibit the overactive immune system and relieve the inflammatory response. Nowadays, there are three major therapies: Glucocorticoids (GC), immunosuppression agents and belimumab. Glucocorticoids suppresses inflammatory responses and generate anti-inflammatory factors. Immunosuppression agents can not only control SLE and raise the survival rate of long-term prognosis for SLE patients. Belimumab inhibits the survival of B cells by obstructing the interaction between soluble B cell activating factor (BAFF or BLys) and receptors on B cells. This action promotes the apoptosis of auto-reactive B cells, leading to a decrease in auto-antibodies present in the serum. With the development of biotechnology, more and more advanced treatments have emerged and brings new hope to SLE patients.

Keywords: Systemic Lupus Erythematosus (SLE), autoimmune disease, belimumab

1. Introduction

In about the 4th to 5th century BC, doctor Hippocrates met a special patient whose face looked like it was bitten by a wolf. Due to the limitations of medical treatment, this could only be treated as a strange skin disease. The terrible illness has not gone away but continued for more than 2000 years and today it is called Systemic Lupus Erythematosus (SLE). The term "Lupus" originates from Latin and translates to "wolf," while "Erythematosus" refers to the reddening of the skin.

SLE is an autoimmune disease and like most diseases, SLE is the result of both genetics and environment. If a person with a susceptibility gene gets sunburned under excess UV light, the DNA in cells will be badly damaged causing cell apoptosis, releasing nuclear materials which include the damaged DNA. The susceptibility gene affects his immune system to recognize the nuclear antigens as foreign things and it also makes the person cannot get rid of the apoptosis bodies as well as others. Eventually, an abundance of antigen-antibody complex accumulates within his body and disseminates to various organs including joints, skin, brain, lungs, kidneys, and even the heart via the bloodstream,

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resulting in localized inflammation and subsequent tissue damage. Type III hypersensitivity, also known as immune complex-mediated hypersensitivity, occurs when soluble immune complexes are deposited on the basement membrane of various capillaries, leading to complement activation and involvement of effector cells like neutrophils. This process ultimately results in inflammatory reactions and tissue damage, either locally or systemically. Some patients generate antibodies that target healthy cells, leading to the manifestation of symptoms associated with type II hypersensitivity reactions. This immune response occurs when IgG or IgM antibodies bind to specific antigens on the surface of cells, ultimately resulting in cell lysis or tissue damage with the involvement of complement, phagocytes, and NK cells. Besides the sunlight, some chemical medicines and hormonal factors especially estrogen can also induce SLE.

Nowadays, there are 3 main treatments for SLE. They are glucocorticoids (GC), immunosuppression therapy and biologicals such as belimumab. GC, also known as glucocorticoid, is a steroid hormone that is produced by the zona fasciculata of the adrenal cortex. Its primary function is to regulate the synthesis and breakdown of sugar, fat, and protein. Additionally, it plays a crucial role in suppressing immune responses, reducing inflammation, counteracting toxicity, and mitigating shock. However, it will produce a risk of serious adverse effects such as cataracts, osteoporotic fractures, and diabetes mellitus when taken for longer periods or at higher doses [1].

There are 4 main kinds of immunosuppressants: 1) immunophilin binding drugs 2) cytostatic drugs 3) anti-lymphocyte antibodies 4) monoclonal antibodies [2]. The immunophilin-binding drug works mainly through the formation of a drug-immunophilin complex and to restrain the transcription activity of IL-2 [3]. When it comes to cytostatic drugs, they principally hinder the proliferation of B cells and T cells by slowing the rate of DNA replication [4]. Finally, are the anti-lymphocyte antibodies and monoclonal antibodies. They both bind to the surface glycoprotein of mature B and T cells or just T cells to trigger apoptosis thus achieving immune-suppression [5].

Finally, we will discuss biologicals, specifically belimumab. Belimumab, developed by GlaxoSmithKline (GSK), is the first biological agent in the world approved for treating SLE. This recombinant IgG1 λ monoclonal antibody works by preventing the binding of soluble BLyS to receptors on B cells, leading to the inhibition of B cell survival and increased apoptosis of auto-reactive B cells, ultimately decreasing auto-antibodies in the bloodstream. It also does not affect late-stage cells (such as memory B cells or long-lived plasma cells), so the body's immunity is still preserved [1-2].

At present, with the development of science and technology, The survival rate for individuals with SLE has shown a marked improvement. Up to 95% of patients are alive at 5 years and approximately 85% of patients who diagnosed early could survive for 10 years and 75% for 20 years. Therefore, except for continuing searching more effective therapy, it is important to consider the well-being of patients with SLE when assessing their quality of life. This will help to promote the holistic approach and draw the distance close between a patient and a physician [6].

2. Application of glucocorticoids in systemic lupus erythematosus

Glucocorticoids (GC) are an extremely essential kind of regulatory molecules. It has a crucial function in controlling the body's development, growth, and metabolism, serving as the primary regulatory hormone in the body's stress response. Studies have shown that one of the most remarkable functions of GC is a large dose of GC can produce rapid, powerful and nonspecific anti-inflammatory effects. It diffuses into the cytosol and binds with the glucocorticoids receptor (GR), The GC-GR complex proceeds to enter the nucleus in order to interact with the target gene promoter, thereby triggering gene transcription. This leads to the production of anti-inflammatory substances while impeding the production of inflammatory substances. Additionally, it hinders the attraction and engulfment of monocytes, neutrophils, and Mϕ in the inflamed tissue. In addition, the second major effect of GC is that it can exert immunosuppression. Firstly, it hampers the phagocytosis and processing of antigen of macrophages. Low doses mainly inhibit cellular immunity and high dose can inhibit the conversion process from B cells to plasma cells, reduce antibody production and interfere with humoral immunity. All the above prominent effects show that GC can well match the treatment needs of SLE.

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GC can play a role through either the genomic or non-genomic pathways.

The genomic pathway commences by combining GC with the cytosolic-GC receptor (cGR). Once formed, the GC-cGR complex gains entry into the nucleus of activated B cells, subsequently inhibiting the activity of transcription factors activator protein (AP-1) and nuclear factor kappa-B (NF-κB). Consequently, the production of pro-inflammatory cytokines like IL6 and TNF is diminished, effectively regulating the inflammatory response. But there is a fly in the ointment, the GC-cGR concentration in the nucleus increases continuously, the trans-activation soon comes into play, which should take major responsibility for most of the adverse effects of GC such as enhancing gluconeogenesis, insulin resistance, skin atrophy and bone resorption. Unfortunately, like two sides of a same coin, trans-activation tightly connects with the genomic way. With the increasing activation of the genomic pathway, the intensity of side effects associated with GC can also escalate.

The non-genomic pathways does not influence gene expression directly, but it leads to the inactivation of the phospholipase A2 (PLA2), reduction of lymphocyte activity and the reduction of of ATP production via block the trans-membrane cycling of calcium and sodium plus [7].

Studies have shown that low doses of GC (≤7.5mg/day of prednisone or equivalent) saturated <50% cGC, which means the genomic pathways is only half initiated. The anti-inflammatory strength is minimal, however, the occurrence of negative effects is also minimal. At this moment, the non-genomic pathways are in the inactive state. Reaching high doses of prednisone (>30 to ⩽100mg/day) results in nearly 100% saturation of receptors, leading to maximum gnomic-mediated anti-inflammatory and toxic effects when exceeding 30 mg of prednisone daily. Hormone therapy is typically unnecessary for patients with mildly active SLE. However, in cases where the disease is not effectively managed with hydroxychloroquine or non-steroidal anti-inflammatory drugs, low-dose hormone therapy (prednisone, ⩽10 mg/d or equivalent doses of other hormones) may be considered. For patients with moderately active SLE, it is recommended to use moderate doses of prednisone (0.5-1mg • kg-1 • d-1) or equivalent doses of other hormones. In situations where controlling the disease quickly proves challenging with a medium dose of corticosteroids, a combination of immunosuppression agents and an appropriate increase in glucocorticoid dose can be utilized. This approach helps to reduce the cumulative dose of corticosteroids and minimize the risk of long-term adverse reactions. In the case of severely active SLE patients, the recommended treatment involves the standard dose of prednisone (1mg • kg-1 • d-1 prednisone or equivalent dose of other hormones) combined with immunosuppression agents. The dosage of corticosteroids will be adjusted once the disease stabilizes.

Although GC is the most widely used clinically and effective anti-inflammatory and immune inhibitor, but it also brings many severe side effects such as osteoporosis which can cause irreversible damage to our body.

During the initial year of GC treatment, osteoclastic activity is stimulated due to the overexpression of receptor activator of NFκβ ligand and macrophage colony-stimulating factor, resulting in decreased bone density through excessive resorption. The suppression of osteoprotegerin production further enhances osteoclastogenesis. Although this effect is temporary, the long-term impact of GCs becomes more pronounced over time. Significant bone loss in trabecular bone-rich regions increases the risk of hip and vertebral fractures. Evidence of bone mass reduction can be observed within three months of treatment initiation, particularly with high doses and prolonged therapy. Marrow fatty mass and fat cell enlargement induced by GCs can lead to intraosseous hypertension. Fat accumulation in the endovascular system can cause ischemia, potentially resulting in sequestra formation, subchondral stress fractures, collapse, and degenerative arthritis. Except for osteoporosis, other side effect also involved hyperglycemia/diabetes mellitus(DM), adrenal insufficiency, skin disorders and ophthalmic alterations. Therefore, patients under GC treatment should;

- Measure the blood pressure, metabolic profile and weight at first;
- Live a healthier life and take part in some regular physical activities;
- Monitor blood sugar every year every month after the start of treatment;
- Regularly assess the cardiovascular risk;

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- Pay attention to symptoms of adverse effects during treatment [8].

3. Application of immunosuppression therapy in systemic lupus erythematosus

As we all know, immunosuppression is a class of drugs that can inhibit the activity of the immune system. There are four main kinds of non-glucocorticoid immunosuppressants: Immunophilin-binding drugs, cytostatic drugs, anti-lymphocyte antibodies, and monoclonal antibodies.

First, let us talk about the immunophilin binding drugs. After administration of the drug, it will enter the cytosol of T cells and combine with the immunophilin to form the drug-immunophilin complex. 1. The interaction between Complex and an intracellular protein known as calcineurin is crucial for the production of interleukin-2 (IL-2), an essential pro-immune chemokine that enhances the function, development, and specialization of T cells. However, when the drug is introduced, the expression of IL-2 is blocked due to the lack of calcineurin, resulting in the inhibition of T cells and ultimately causing immunosuppression.

A cytostatic drug, the second type mentioned, possesses the ability to impede cell division. Its primary objective is to curtail the growth of B cells and T cells by inhibiting DNA replication, which is achieved through a specific pathway.

The third is the anti-lymphocyte antibodies. Alemtuzumab serves as a prime illustration of an anti-lymphocyte antibody. It combines with the surface glycoprotein CD52, which is extensively present on the surface of B and T cells, as well as to a lesser degree on natural killer (NK) cells and other leukocytes. Upon binding with CD52, the antibody initiates cell apoptosis through antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Consequently, the elimination of B cells and T cells facilitates the achievement of immunosuppression.

The final one is the monoclonal antibody. Monoclonal antibodies are highly uniform antibodies created by a single B-cell clone that target a specific epitope. These drugs function by binding with lymphocytes to inhibit their differentiation or induce cell apoptosis. Researchers from Charité – Universitätsmedizin Berlin and DRFZ successfully treated two systemic lupus erythematosus patients with daratumumab, a targeted CD38 human monoclonal antibody. CD38 surface protein is a common plasma cell marker. In lupus patients, elevated levels of this marker can also be found in other active immune cells like memory T lymphocytes. This discovery highlights CD38 as an ideal target for SLE treatment. The new therapy was administered to two lupus patients experiencing symptoms such as heart and kidney inflammation and anemia due to antibodies. Weekly daratumumab injections for four weeks resulted in rapid and significant symptom improvement, which has been sustained for several months. The patients' serum auto-antibody levels have notably decreased.

However, long-term use of immunosuppression agents may increase the risk of infection and cancer because immune inhibitors will weaken the immune system response ability. Some immunosuppressants may cause liver and kidney damage. The liver injury caused by immunosuppressants is a highly intricate process, with variations in the mechanism depending on the type of immunosuppressant used. In this study, it was discovered that the primary causes of liver injury are hepatic lipid peroxidation, apoptosis of liver cells, abnormalities in hepatic drug metabolism enzymes, and gene polymorphism. Patients need regular liver and renal function tests to detect and manage possible injuries in time. In addition, long-term use of immunosuppression agents may cause other side effects such as headache, insomnia, muscle pain, nausea, vomiting, diarrhea, etc.

4. Some advanced therapies in systemic lupus erythematosus

4.1. Belimumab

BLyS, a crucial B cell survival factor, belongs to the tumor necrosis factor (TNF) ligand family and exists in two forms: soluble and membrane-bound. It plays a significant role in the proliferation and differentiation of B cells. Research has demonstrated that the upregulation of BLyS in vivo is closely associated with the development of SLE. Elevated BLyS levels can lead to the production of auto-antibodies by B cells, exacerbating the SLE condition. BLyS interacts with three receptors: BLyS

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receptor 3 (BR3/BAFF-R), trans-membrane activator-1 and calcium modulator and cyclophilin ligand-interactor (TACI), and B cell maturation antigen (BCMA). Studies have highlighted the essential role of BLyS in B cell survival. B cells lacking BLyS were found to be arrested at the T1 phase and deficient in marginal zone (MZ) B cells, follicular B cells, T-independent (TI), and T-dependent (TD) humoral immunity. However, BLyS deficiency did not affect bone marrow cells, B1 cells, and T1 B cells. BR3-deficient mice exhibited a similar phenotype to BLyS-deficient mice, indicating that BR3 is the primary regulator of B cell survival. B cells from BCMA-/-mice were developing normally and had both TI and TD humoral immunity. BCMA regulated plasma cells survival. During plasma cell development, the expression of BCMA was up-regulated, which was very essential for plasma cell survival [9]. TACI-/-mice appeared autoimmune symptom and specific activation of TACI can induce the apoptosis of B cells [10]. What's more, TI-2 response was impaired, which shown TACI was a negative regulation factors of B cell activation and promote TI - 2 immune response [11].

In patients with SLE, an excess of BLyS provides a survival signal for auto-reactive B cells that should undergo apoptosis, resulting in the continuous production of auto-antibodies, leading to tissue inflammation and damage. Belimumab is a fully human monoclonal antibody (IgG1) that competitively binds soluble BLyS to TACI, BCMA, and BR3. This leads to a decrease in B cell survival due to the lack of abundant BLyS, resulting in reduced antibody production. A preclinical study showed that mice expressing the exogenous human protein and treated with belimumab had decreased spleen weight and serum IgA levels, indicating a reduction in auto-reactive B cells. Nonclinical data suggest that anti-BLyS treatment does not affect secondary immunity, preserving memory B cells and long-lived plasma cells [12]. Belimumab can be considered a "stabilizer" of SLE. Results from three phase III studies consistently demonstrated the superior short-term efficacy and safety of belimumab in SLE patients. BEL110751 and BEL110752 are two phase III randomized, double-blind, placebo-controlled trials with similar designs. The former was a 76-week study primarily conducted in North America and Western Europe, while the latter was a 52-week study conducted in South America, Eastern Europe, Asia, and Australia. Both trials met the primary endpoint of the SRI (SLE Responder Index) at week 52, with the belimumab group showing significantly higher SRI compared to the placebo group (50.6% vs 38.8%, $p< 0.0001$) [13-14].

4.2. Stem cell treatment

Stem cells possess the unique ability to proliferate limitlessly, differentiate in multiple directions, provide hematopoietic support, regulate the immune system, and self-replicate. They serve as excellent "seed" cells for repairing damaged tissues and organs. Mesenchymal stem cells (MSCs) act as "trainers" in the management of systemic lupus erythematosus (SLE), adjusting various imbalanced immune cells to prevent them from attacking the body's own tissues. Over 1500 SLE patients worldwide have undergone MSCs treatment, with the majority receiving allogeneic MSCs transplantation. Notably, 60.5% of patients achieved complete remission after one year of allogeneic MSCs therapy, leading to significant reductions in urinary protein levels and British Isles Lupus Assessment Group (BILAG) scores. After four years, 50% of patients maintained clinical remission, with a 94% survival rate and a low recurrence rate of 23%. The efficacy rate for severe and refractory SLE reached 60%, reducing the 5-year mortality rate from 35%-45% to 16%. No severe adverse reactions or transplantation-related deaths were reported. A retrospective study involving 404 patients with autoimmune diseases, including 178 SLE patients (44.1%), demonstrated the safety and efficacy of allogeneic MSCs transplantation. These findings highlight the potential of MSCs, particularly allogeneic MSCs, as a promising biological treatment for SLE, offering hope for improved patient outcomes in the future.

5. Conclusion

Regrettably, despite the current advancements in technology, a definitive cure for SLE and other autoimmune diseases remains elusive. This is primarily because our understanding of the underlying causes, such as environmental factors and pathogenesis, is still incomplete.

Current immunomodulatory drugs for autoimmune diseases such as glucocorticoids and immunosuppression are broad-acting, non-disease-specific, and often cause side effects such as infections and malignant diseases. All of these drugs have a common characteristic, that is, they have a wide range of action but do not have their disease-specific. In contrast to the individualized therapies that have made their way into oncology research, it seems like the world does not attach importance to autoimmunity diseases. Although the advent of belimumab and MSCs have bring new hope for patients, belimumab cannot save critically ill patient's life. Therefore, researchers need to conduct molecular and clinical experiments on SLE patients urgently to develop new drugs.

Due to the rapid advancements in medical technology and scientific research, up to 95% of patients now experience a 5-year survival rate, a significant increase from the 50% rate seen in the 1950s. About 85% of patients with early diagnosis survive for 10 years, and 75% to 20 years. In patients with SLE, typical facial erythema and rash often make patients feel ugly and affect their moods, such as sadness, depression, fear or anxiety [15]. At the same time, we should also pay attention to the mental health of patients and give them positive support and encouragement!

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