International Immunopharmacology 72 (2019) 218–223

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

Therapeutic advances in the treatment of SLE

Ali Mohamed[a,1], Yongjian Chen[a,1], Haijing Wu[a], Jieyue Liao[a], Bo Cheng[b,*], Qianjin Lu[a,**]

[a] Department of Dermatology, The Second Xiangya Hospital of Central South University, Hunan Key Laboratory of Medical Epigenomics, 139 Middle Renmin Road, Changsha, Hunan 410011, China
[b] Department of Dermatology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian, China

ARTICLE INFO

Keywords:
SLE
Monoclonal antibody
IL-2
Lupus nephritis

ABSTRACT

In recent years, the research on the pathogenesis of systemic lupus erythematosus (SLE) has been deepened, from the level of histopathology to the cellular and molecular biology, thus promoting the progress of SLE drug therapeutics. In March 2011, the United States Food and Drug Administration (FDA) approved the humanized monoclonal antibody, Belimumab for the treatment of SLE and put an end to the dilemma of no new drug available to SLE for more than half a century. On the other hand, the continuous evidence-based medical information has enabled rheumatologists to have a more comprehensive and depth understanding of the application of SLE traditional therapies, further improve the treatment strategy of SLE and put forward higher requirements for treatment goals. At the same time, advances in therapies have significantly improved survival rate of the patients, and the importance of long-term complications such as early-onset atherosclerosis and cardiovascular events has become increasingly apparent as a new challenge. In view of the hot issues of SLE clinical treatment, this paper introduces the research progress in recent years.

1. Introduction

Systemic lupus erythematosus (SLE), also known as lupus, is an autoimmune disease in which the body's immune system mistakenly attacks healthy tissue in many parts of the body [1]. The disease has highly variable course with vague and unpredictable symptoms that can vary from person to person. The main symptoms are skin rashes, sun sensitivity and joint aches. Most people with lupus will never experience all the symptoms and no two individuals seem to experience identical symptoms. Hence, the management is complex and treatment involves preventing flares and reducing their severity and duration when they occur. While treating lupus, clinicians aim to reduce inflammation in tissues and improve quality of life. Survival of patients has dramatically improved over the last 50 years, possibly owing to earlier diagnosis and more appropriate treatment schemes [2]. However, SLE patients still display a 4.6-fold higher standardized mortality rate compared with general population [3]. In recent years, the use of several therapeutic agents in the management of SLE has increased and plenty of clinical trials have highlighted both the potential and the pitfalls in the development of such agents. In view of these clinical trials and hot issues of SLE clinical treatment, this paper introduces the research progress in recent years.

2. Classic therapy

SLE is a kind of highly heterogeneous disease [4,5]. The performance of each patient is different. The light is only the lesion of the skin joints. In severe cases, there will be blood system damage, visceral damage, and even the central nervous system, and neuropsychiatric lupus [6–8]. Throughout the history of SLE treatment, human beings appear very small in front of unknown diseases, and the 5-year survival rate is only 30% in 1930s. Since 1950s, glucocorticoids have been gradually applied to the treatment of lupus, and the 5-year survival rate has increased to 50% [9]. With the increase of experience in hormone use and the guidance of evidence-based medicine, we now emphasize the individualization of hormone therapy and the selection of different doses of hormones according to the different activity levels of patients [10–12].

Glucocorticoids (here in after referred to as “hormones”) are still the first-line treatment options for SLE. Due to their extensive anti-inflammatory and immunosuppressive effects, glucocorticoids play an irreplaceable role in the treatment of SLE involving vital organs and

* Corresponding author.
** Correspondence to: Q. Lu, Department of Dermatology, The Second Xiangya Hospital of Central South University, 139 Middle Renmin Road, Changsha, Hunan 410011, China.
E-mail addresses: chengbo630415@126.com (B. Cheng), qianlu5860@csu.edu.cn (Q. Lu).
[1] These authors have contributed equally to this work.

https://doi.org/10.1016/j.intimp.2019.03.010
Received 18 August 2018; Received in revised form 4 March 2019; Accepted 5 March 2019
Available online 16 April 2019

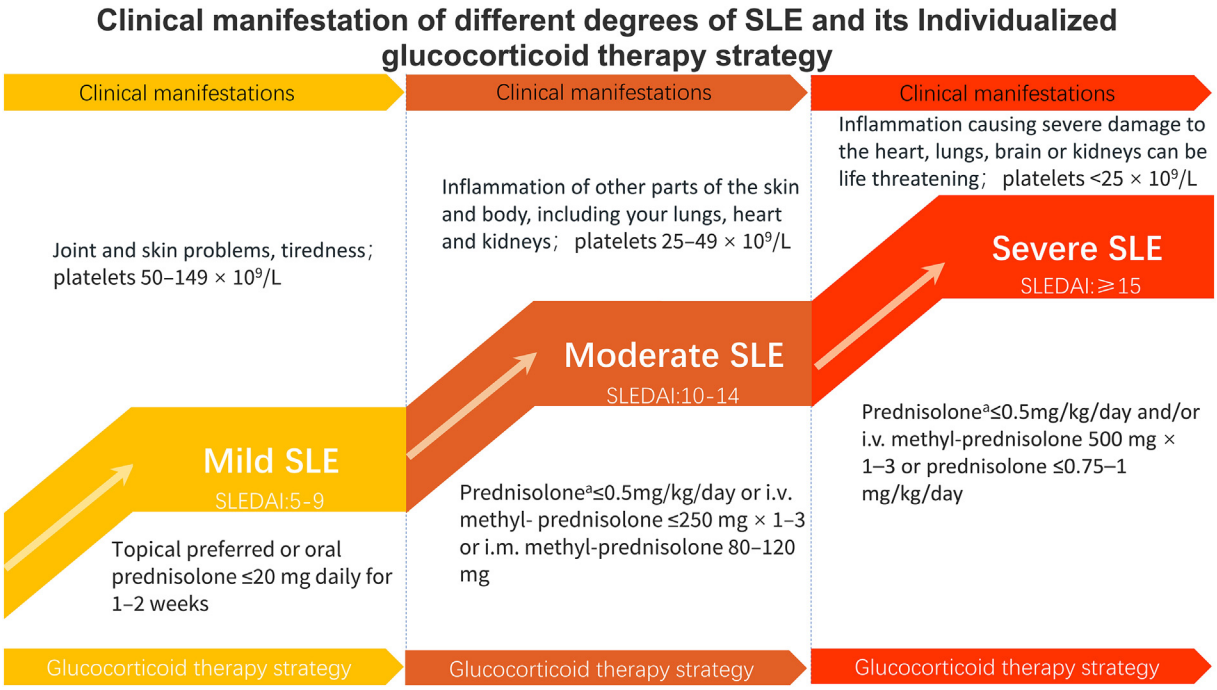

Fig. 1. Clinical manifestation of different degrees of SLE and its Individualized glucocorticoid therapy strategy Abbreviation: I.v. = intravenous injection; I.m. = intramuscular injection; IA = intraarterial injection; [a] = the lowest effective dose of prednisolone or other CSs should be used at all times.

acute diseases. However, the dose required is high enough to have adverse effects. Moreover, the disease has relapse and remission course, which requires the patient to remain on maintenance therapy for long duration. But the maintenance dose and course of treatment differs from doctor to doctor. This may be the reason why steroids have not yet reached a standard protocol for SLE treatment. Clinical manifestation of different degrees of SLE and its Individualized glucocorticoid therapy strategy is summarized in Fig. 1 [13].

The choice of immunosuppressive agents should be based on available evidence-based medicine and depending on the activity of SLE and the involved organs. For example, cyclophosphamide (CPA) and mycophenolate mofetil (MMF) are useful for lupus nephritis and other severe lupus, methotrexate and azathioprine (AZA) for moderately active SLE and arthritis, hydroxychloroquine for mild lupus, lupus skin lesions and anti-phospholipid syndrome patients. In addition, more and more new immunosuppressive agents are gradually being introduced for SLE treatment such as leflunomide, cyclosporine and tacrolimus, which provide more options for treatment. We should also consider the patient's tolerance and the side effects of each immunosuppressant when choose immunosuppressive agents, such as the inhibitory effect of CPX on ovarian function (especially for children and adolescent women). Many studies show that the combination of immunosuppressive agents and steroids can reduce steroid dosage. A long-term prospective observational study show that [14], a total of 40 patients with lupus nephritis (LN) are induced at maintenance doses of hormone therapy and is divided into ≥ 20 mg/d and < 20 mg/d, 2 groups are given CPA 500–1500 mg/m^2 per month infusion therapy. A result at 24 months, the overall complete remission rate is 62.5%. After a mean follow-up of 10.4 years, there is no significant difference in the risk of relapsed between the two groups. In another study, 18 patients with SLE (types III, IV, and type IV LN) are infused intravenously with rituximab and methylprednisolone twice during the induction period, only to MMF as maintenance treatment without corticosteroids. The results show that 1 year after the complete remission rate of 78%, and hormones with CPA or MMF regimen were similar [15]. These studies show that the full application of immunosuppressive agents and even bio-targeted drugs help to reduce or even stop the use of hormones while keeping the stability of the disease.

3. Advanced therapy

3.1. Monoclonal antibody

With the development of the research on the pathogenesis of SLE, researchers have tried to intervene in the occurrence and development of SLE from different molecular pathways for therapeutic purposes. The promotion of the concept of transformation medicine makes new biological targeting drugs to emerge. This field will be the hotspot and breakthrough hope of SLE treatment. There are various mechanisms of biological agents in clinical trials, including > 20 kinds of B cells, T cells, interferon I, Toll like receptors, and inflammatory/chemokines [16]. Due to the over-activation of B cells and the massive production of autoantibodies, which are prominent features of SLE, biological therapy targeting B cells has naturally become a researcher's focus. As mentioned above, rituximab, a human and mouse chimeric anti-CD20 monoclonal antibody, has been widely tried and has high hopes of the drug, many literature reports of rituximab in the treatment of refractory SLE such as the central nervous system, kidney and blood system involvement and vasculitis effectively. In a systematic review of relevant studies from 2002 to 2007, 171 (91%) of 188 patients with severe or refractory SLE treated with rituximab achieve a significant benefit in at least one of the clinical manifestations, 91% of LN patients have a response to treatment, patients with anti-dsDNA antibody titer decreases significantly. 32% of patients have adverse reactions, the most common side effect is opportunistic infections (26%) [17]. However, a large, controlled clinical study (LUNAR study) is followed by negative results. After reflection, the researchers believe that the research design is too strict for the baseline patients and the end point is not likely to produce the expected results. Which may have led to no expected results. In this study, a considerable proportion of SLE patients benefit from the treatment of rituximab which also prompts researchers to continue to search for new anti B cell targets. Belimumab is another biological agent targeting B cells and its mechanism is binding to B lymphocyte stimulating factor and inhibiting B cell growth and differentiation.

Drawing lessons from previous LUNAR design studies, two controlled clinical trials of Belimumab (BLISS-52 and BLISS-76), which strictly define the baseline dose of steroids and use a combination of clinical endpoints, give encouraging positive results: Belimumab improves the clinical symptoms, serological and renal function parameters of active SLE and prevents SLE recurrence with good tolerability [18,19]. The drug is approved for sale in the United States in 2011. However, the efficacy of bevacizumab is modest and not organ-specific. In the future, a randomized controlled clinical study of the SLE specific system (such as LN) is needed to further clarify the benefit in a population. Abatacept, another costimulatory pathway inhibitor, is a fusion protein of the Fc fragment of human IgG1 and CTLA4 on T cells, which can inhibit T cell activation. Abatacept has been used in rheumatoid arthritis, long-term follow-up show that its efficacy is significantly higher than placebo. T cell activation is a key link in the pathogenesis of glomerulonephritis. Studies on the mouse model of lupus show that the drug can reduce urinary protein and prolong survival. Epratuzumab, another promising drug targeted for the treatment of SLE, is a fully humanized monoclonal antibody that binds to CD22 molecules on the surface of B cells and inhibits circulating B-cell activation signaling pathways. Two clinical studies have shown that Epratuzumab has a therapeutic effect on SLE, which can improve BILAG score and the quality of life of patients and contribute to reduce the use of steroids.

3.2. Anti-interferon (IFN)-alpha monoclonal antibody

In recent years, the pivotal role of the IF interferon (IFNα) pathway in the pathogenesis of SLE has gradually been revealed. IFα levels are elevated in serum from patients with SLE, while high levels of IFNα promote the maturation of myeloid dendritic cells and present their own antigens to further activate T cells. IFNα also decreases the activity of regulatory T cells to induce an autoimmune response. In addition, enhancing the role of the Toll-like receptor 7/9 signaling pathway in dendritic cells can produce more IFNα. Currently, biological agents targeting the IFNα pathway include three types: (1) monoclonal antibodies to IFNα such as Sifalimumab, Rontalizumab, and AGS-009; (2) vaccines that induce the production of anti-IFNα antibodies such as IFNα-Kinoid; (3) Toll-like receptor inhibitors such as IMO-3100 and DVll79.

Among those monoclonal antibodies which targeting interferon I and its receptors, the most anticipated is AstraZeneca lupus drug-Anifrolumab, and this is a monoclonal antibody targeting type I interferon receptor and has been developed for the treatment of moderate to severe systemic lupus erythematosus. In 2015, Anifrolumab reach the primary and secondary goals of its Phase II clinical study, significantly reducing lupus disease activity at multiple endpoints compared with placebo [20]. However, this experimental drug fails to meet its main goal in a late-stage clinical study. There is no statistically significant reduction in SLE disease activity (assessed by the SLE Responder Index 4, SLE4) after 12-month treatment of Anifrolumab compared with the placebo group [21].

There are some unclear questions about the treatment of the IFNα pathway. One of the evaluation indicators for monitoring the activity of IFNα activity is ELISA method. However, the determination of IFNα concentration repeatability is poor, and IFNα function test results are not satisfactory. The recent discovery of type I interferon signature (Type I interferon signature) is the determination of IFN Specific induction of gene expression products, studies have shown that its level and SLE disease activity is closely related to the hope that anti-IFN targeted therapy can be a reliable indicator. Another problem is the concern about the increased risk of infection and tumor after suppression of IFNα, which requires further study [22]. Fig. 2 will show algorithm for therapeutic of SLE.

3.3. Low-dose IL-2

There is an immune imbalance in patients with systemic lupus erythematosus, mainly manifested by immune imbalance between effector and regulatory CD4+ T cells [23,24]. The researchers have found that low doses of IL-2 can regulate CD4+ T cell subsets and treat systemic lupus erythematosus. Patients with refractory or relapsed systemic lupus erythematosus activity (SLEDAI) > 8 are treated with low-dose IL-2, the clinical symptoms and test indexes improves a lot and systemic lupus erythematosus response index is up to 89.5% in 12 weeks. The researchers reveal that the mechanism of low-dose IL-2 endogenously inhibits the overactive immune response in patients with systemic lupus erythematosus and reduces the attack of autoantibodies on organ tissues [25]. Scientists from Shanxi Medical University of China use low-dose IL-2 for 127 of 225 SLE patients, 50 WIU per day for 5 days. After treatment, clinical and immunological assessments are conducted again. The results show that low-dose IL-2 selectively regulate Tregs abundance and induce immune tolerance to improve clinical symptoms [26]. The treatment of refractory systemic lupus erythematosus relies on the combination of high dose glucocorticoids and immunosuppressive agents, but most of the patients are ineffective and have serious side effects [26,27]. Researchers in the Department of Rheumatology, the Second Hospital of Shanxi Medical University find that refractory SLE is associated with a decrease in the number of Treg, independent of the number of Th17. Treatment with low doses of IL-2 in combination with rapamycin reduces the dose of glucocorticoids and DMARDs [28,29]. Therefore, the true meaning of this treatment lies in the down-regulation of the overactive immune system through multiple immune mechanisms. This major discovery will bring a new concept to the diagnosis and treatment of clinical immune diseases and has a milestone significance.

4. Treatment strategies for mild lupus erythematosus

Mild lupus accounts for a large proportion of SLE, and it may be transformed into severe disease, and its treatment should not be ignored. In recent years, the importance of antimalarial drugs, such as hydroxychloroquine, is becoming more and more important. Numbers of lupus cohort observations show that hydroxychloroquine has a unique role in preventing renal involvement, and improving LN remission rate, lowering blood lipid, preventing thrombosis, reducing SLE recurrence rate and mortality, and can also be used for SLE in pregnancy. Hydroxychloroquine has many advantages. Therefore, it is called “SLE's background therapy” and that all SLE patients should be treated with hydroxychloroquine without taboos. The problem is that even in phase III clinical studies for the treatment of lupus drugs, the use of hydroxychloroquine is only 70%. Due to the long-term use of hydroxychloroquine as a medication for the maintenance of the disease, the compliance of the patients is particularly important. A French study measure 143 patients taking hydroxychloroquine 400 mg/d for more than a half year and the plasma concentration, find that if the < 200 μg/L, which means that patients have not taken medication [30]. Further show that 96% of patients with hydroxychloroquine serum concentration > 1000 μg/L had no relapse. Dehydroepiandrosterone (DHEA) may have a role in the treatment of mild lupus, and two double-blind placebo-controlled studies have shown to improve the condition, contribute to steroids reductions and increase bone mineral density [31,32]. DHEA can be metabolized into estrogen, and there are concerns about the safety of the application in postmenopausal women. Non-steroidal anti-inflammatory drugs (NSAIDs) commonly are used in the treatment of mild lupus fever, arthritis and other symptoms. Considering the adverse effects on the kidneys, attention should be paid to COX. 2 inhibitors of cardiovascular side effects, long-term, high-dose NSAIDs should be avoided. Serological activities and clinical stability (SACQ) are one of the problems faced by doctors in the treatment of mild lupus: patients have no clinical evidence of any long-term

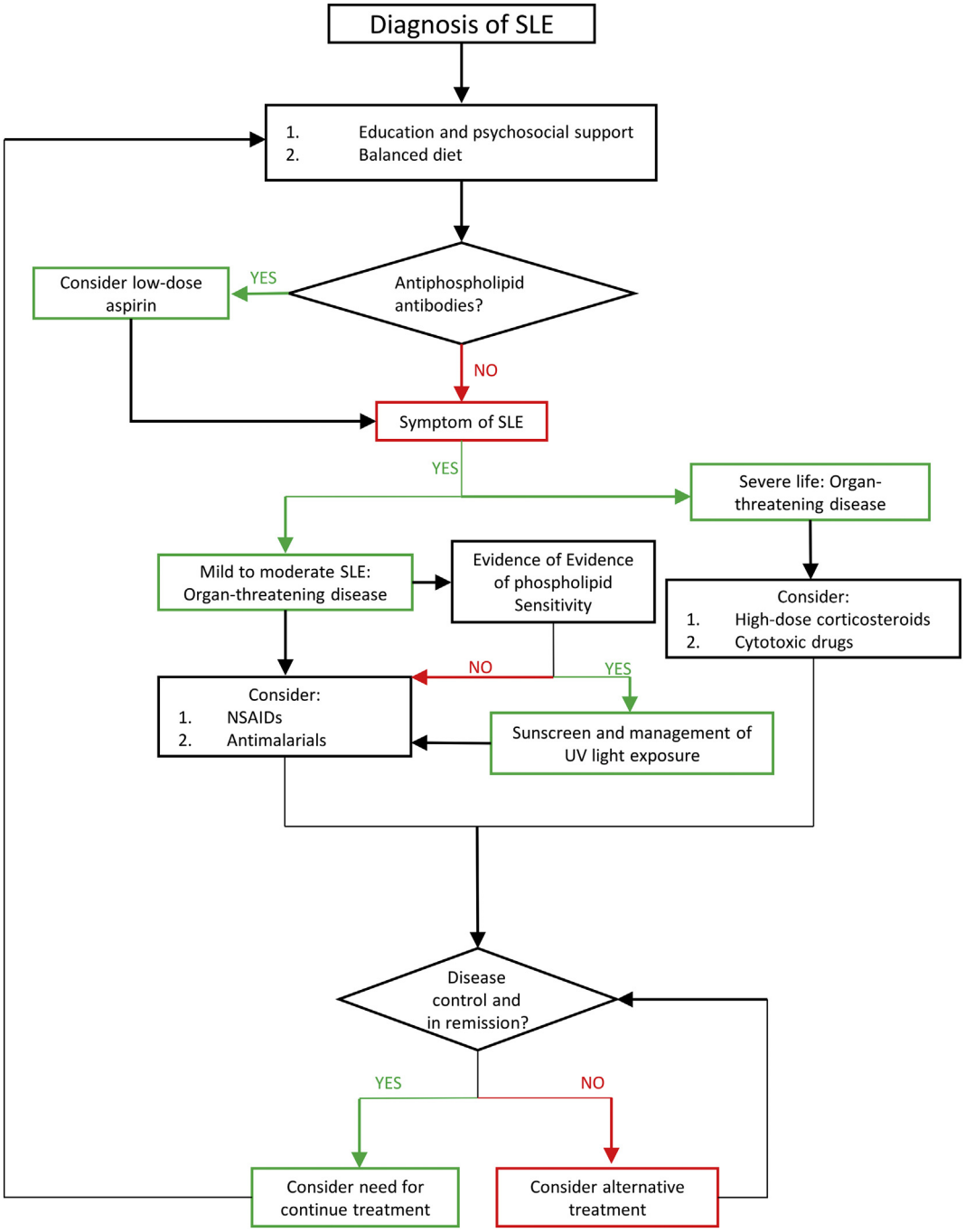

Fig. 2. The general arrangement for treatment of SLE.

evidence of visceral involvement, but serum complement has not been able to recover normal and/or anti-dsDNA antibodies persistent positive. A ten-year follow-up study of 757 patients in the Hopkins Lupus cohort finds that 33% of all patients have remission, and the risk of relapse was still higher in patients with serum complement and anti-dsDNA antibody-negative. But in the end such patients with abnormalities of serological activity should be treated with stronger immunosuppressive therapy? How long should be treated? Intensive steroid and immunosuppressive therapy in the end are to improve the long-term prognosis of patients or increased Risk of Toxicity? It is still unknown. A 10-year observation of one such group of SLE patients in the Canadian lupus cohort find that only 3.6% of patients developed kidney disease and the organ damage index (SDI) of patients with SACQ was significantly lower than both clinical and serological indexes, the researchers believe that for SACQ patients reasonable diagnosis and treatment strategy is to increase the monitoring frequency rather than directly increase the treatment intensity [33].

5. Progress in the treatment of lupus nephritis

In recent years, LN is the hot topic of evidence-based medicine. Treating LN is the main target of SLE treatment. In 2012, both the United States and Europe update the guidelines for the treatment of LN and determine that the goal of LN is to achieve complete remission, including a proteinuria/creatinine ratio of < 50 mg/mmol (proteinuria < 0.5 g/24 h) and normal renal function [34]. Partial renal remission (with a $> 50\%$ reduction in proteinuria and normal or near normal kidney function) is an acceptable outcome only if none of the

treatments can achieve complete remission or the patient cannot tolerate the toxicity of the drug. The best therapeutic target in initial treatment should be up to 6 months, no later than 12 months.

The United States and European guidelines further establish the status of MMF as a first-line treatment for proliferative LN. During the induction period, a number of clinical studies confirm that the efficacy of MMF (2–3 g/D) is equivalent to CPA, and the risk of any adverse reactions (such as infection) is lower. Therefore, the total cost of treatment may be lower, and it is more suitable for patients with fertility requirements [35]. In the maintenance phase, MMF (1–2 g/d) has become the standard treatment as AZA. ALMS studies have shown that MMF is more effective than AZA in maintenance dose and has no role in induction therapy; any ethnicity or geography can well tolerate with relatively few serious adverse events [36]. It should be noted that in view of the adverse reactions occurring in the ALMS study, the recommended dose of MMF in the Asian population is relatively small (2 g/d) while the recommended dose of ALMS for type III or IV LN with a significant increase in crescentic glomerulonephritis or serum creatinine is 3 g/d. In addition to the traditional high-dose regimen (0.5 to 1 g/m^2 month), intravenous infusion, 6 times, followed by every 3 months for a total of 2 treatment cycles for CPA in the induction phase). In recent years, Europe has proposed a low-dose program (2 weeks, 0 .5g/intravenous infusion, a total of 6 times). Studies have shown that low-dose regimens are comparable in efficacy to conventional high-dose regimens and have a lower risk of serious infections and gonadal suppression. The 10-year follow-up study showed a similar incidence of both regimens and end-stage renal disease [37]. Most patients should be initially treated with CPA or MMF for 6 months unless there is clear evidence of worsening (proteinuria or serum creatinine ≥50%) at 3 months. For initial treatment with CPA (high dose or low dose regimen), if treatment fails after 6 months, consider switching immunosuppressants to MMF and vice versa.

In some patients with severe LN and refractory LN, the risk of developing end-stage renal disease is not significantly reduced. Most randomized controlled trials do not include or even avoid such patients, and the definition of these two types of LN in the literature is not clear and uniform, so it is difficult to integrate data analysis. Hence, treatment of severe LN and refractory LN remains a major challenge for physicians. In 2012 United States and European guidelines for the treatment of LN emphasize the importance of repeated renal biopsies. The guidelines recommend repeating renal biopsy when immunosuppressants or biological do not reduce ≥50% of proteinuria, when proteinuria persist for > 1 year, when GFR deteriorates, and when the disease relapses. Its purpose is to clarify histological changes or progression, to provide prognostic information and to identify other pathological changes, which may cause nephropathy, such as infections and drug toxicity. One of the options for treatment is calcineurin inhibitor. The data show that the total remission rate was 22% after the combination of cyclosporin or tacrolimus in patients with the combination of hormones and CPA [38,39]. It should be noted that these drugs could act directly on the glomerular podocyte and rapidly reduce urinary protein. Therefore, urinary protein quantification is not an accurate indicator of the effect of abnormal immune system in LN patients [40]. Another option is a biological agent, especially the rituximab, which is a high-expected drug for the treatment of such LN. However, there are many related studies and cases, and the overall results suggest that rituximab may be potentially useful in the treatment of refractory LN. However a randomized controlled trial of rituximab in the treatment of LN has not reached the anticipated end point [18]. Different studies show different definition of refractory LN and different use of rituximab [41–43].

6. Prevention of cardiovascular complications in SLE

Cardiovascular complications have replaced LN and neuropsychiatric lupus as the main cause of death in SLE patients, with the improvement of SLE level and prolongation of patients' survival time. Studies show that the risk of myocardial infarction in SLE is 50 times that of the normal population. Cardiovascular risk factors do not fully explain the rapid progression of atherosclerosis in lupus patients. Vasculitis and chronic kidney disease are all risk factors for their occurrence. Therefore, preventing and reversing the atherosclerotic process in SLE patients is important to improve the prognosis, especially in children and adolescents. The European guidelines for the treatment of SLE in 2008 emphasizes the importance of cardiovascular risk, but it is not clear how to monitor and treat it. Researchers once have great expectations for statins. However, the LAPS study is published in 2011 fails to confirm its efficacy. There was no significant difference in coronary calcification score, carotid artery intima thickness or carotid plaque score between atorvastatin treatment group and control group [44]. Consensus of high-risk factors in clinical practice should be strengthened in patients with lupus blood pressure, blood lipid and blood glucose monitoring, a high degree of vigilance may indicate cardiovascular events therefore symptoms should be evaluated as soon as possible, the development of long-term application of hydroxychloroquine may help to delay the development of atherosclerosis.

In patients with lupus nephritis, mycophenolate mofetil and intravenous pulses of cyclophosphamide have recently shown comparable efficacy with regard to total non-renal disease activity [45,46].

7. Conclusion

SLE is characterized by various clinical manifestations, complicated course of disease and many other disciplines involving such as the kidney, blood, nerves etc. There are still many problems that are not covered in the study, such as lupus complicated with pregnancy, opportunistic infections with lupus, and tumors. In addition, relatively rare organ involvement is also attracting more and more attention such as, lupus combined with pseudo intestinal obstruction, albumin enteropathy and pulmonary hypertension associated with lupus. Due to the difficulty of conducting evidence-based medicine research, there is still a lack of relevant treatment methods with high quality evidence-based medicine. It is believed that with the accumulation of clinical data in large cohorts and the translational medical research from the pathogenesis to the development of therapeutic drugs, it is believed that further understanding and treatment of SLE will be improved and the prognosis of patients will be improved.

Author contributions

Ali Mohamed and Yongjian Chen wrote the manuscript; Haijing Wu and Jieyue Liao edited the manuscript; and Qianjin Lu and Bo Cheng revised the manuscript.

Acknowledgement

This work was supported by the National Natural Science Foundation of China (No. 81522038, No. 81602767, No. 81430074, No. 81502734), the Programs of Science-Technology Commission of Hunan Province (2013F J4202), the Natural Science Foundation of Hunan Province (2017JJ3453, 2017SK2042) and the Natural Key Clinical Specialty Construction Project of National Health and Family Planning Commission of the People's Republic of China.

Conflict of interest

The authors declare no conflicts of interest.

References

[1] D. Novak, Handout on Health: Systemic Lupus Erythematosus, (2000).
[2] Doria, A., et al., Long-term prognosis and causes of death in systemic lupus

erythematosus. Am. J. Med., 2006. 119(8): p. 700–706.
[3] Lopez, R., et al., Lupus disease activity and the risk of subsequent organ damage and mortality in a large lupus cohort. Rheumatology, 2011. 51(3): p. 491–498.
[4] Via, C.S., et al., T cell-antigen-presenting cell interactions in human systemic lupus erythematosus. Evidence for heterogeneous expression of multiple defects. J. Immunol., 1993. 151(7): p. 3914–3922.
[5] Okudaira, K., et al., Detection of antilymphocyte antibody with two-color method in systemic lupus erythematosus and its heterogeneous specificities against human T-cell subsets. J. Clin. Invest., 1979. 64(5): p. 1213–20.
[6] Jung, J.-H., et al., Thrombocytopenia in systemic lupus erythematosus: clinical manifestations, treatment, and prognosis in 230 patients. Medicine, 2016. 95(6).
[7] M.C. Hochberg, Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus, Arthritis Rheum. 40 (9) (1997) 1725.
[8] Petri, M., et al., Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum., 2012. 64(8): p. 2677–2686.
[9] Uramoto, K.M., et al., Trends in the incidence and mortality of systemic lupus erythematosus, 1950–1992. Arthritis Rheum., 1999. 42(1): p. 46–50.
[10] Arden, N., et al., Safety of hormone replacement therapy (HRT) in systemic lupus erythematosus (SLE). Lupus, 1994. 3(1): p. 11–13.
[11] H. Jonsson, O. Nived, G. Sturfelt, Outcome in systemic lupus erythematosus: a prospective study of patients from a defined population, Medicine 68 (3) (1989) 141–150.
[12] Toloza, S.M., et al., Systemic lupus erythematosus in a multiethnic US cohort (LUMINA): XXIII. Baseline predictors of vascular events. Arthritis Rheum., 2004. 50(12): p. 3947–3957.
[13] Gordon, C., et al., The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. Rheumatology, 2017. 57(1): p. e1-e45.
[14] Fischer-Betz, R., et al., Renal outcome in patients with lupus nephritis using a steroid-free regimen of monthly intravenous cyclophosphamide: a prospective observational study. J. Rheumatol., 2012: p. jrheum. 120537.
[15] Pepper, R., et al., Rituximab is an effective treatment for lupus nephritis and allows a reduction in maintenance steroids. Nephrol. Dial. Transplant., 2009. 24(12): p. 3717–3723.
[16] P.K. Chugh, Lupus: novel therapies in clinical development, Eur. J. Intern. Med. 23 (3) (2012) 212–218.
[17] Ramos-Casals, M., et al., Rituximab in systemic lupus erythematosusA systematic review of off-label use in 188 cases. Lupus, 2009. 18(9): p. 767–776.
[18] Rovin, B.H., et al., Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the lupus nephritis assessment with rituximab study. Arthritis Rheum., 2012. 64(4): p. 1215–1226.
[19] Furie, R., et al., A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum., 2011. 63(12): p. 3918–3930.
[20] Furie, R., et al., Anifrolumab, an anti-interferon-α receptor monoclonal antibody, in moderate-to-severe systemic lupus erythematosus. Arthritis Rheum., 2017. 69(2): p. 376–386.
[21] Clowse, M.E., et al., Efficacy and safety of epratuzumab in moderately to severely active systemic lupus erythematosus: results from two phase III randomized, double-blind, placebo-controlled trials. Arthritis Rheum., 2017. 69(2): p. 362–375.
[22] E.I. Lichtman, S.M. Helfgott, M.A. Kriegel, Emerging therapies for systemic lupus erythematosus—focus on targeting interferon-alpha, Clin. Immunol. 143 (3) (2012) 210–221.
[23] Shah, K., et al., Dysregulated balance of Th17 and Th1 cells in systemic lupus erythematosus. Arthritis Res. Ther., 2010. 12(2): p. R53.
[24] Yang, J., et al., Recovery of the immune balance between Th17 and regulatory T cells as a treatment for systemic lupus erythematosus. Rheumatology, 2011. 50(8): p. 1366–1372.
[25] He, J., et al., Low-dose interleukin-2 treatment selectively modulates CD4+ T cell subsets in patients with systemic lupus erythematosus. Nat. Med., 2016. 22(9): p. 991.
[26] Liu, X., et al., OP0043 the Number of Circulating Regulatory T Cells Is Reduced and Low-Dose Il-2 Selectively Stimulates its Proliferation in Patients with Systemic Lupus Erythematosus. 2017, BMJ Publishing Group Ltd.
[27] Kiyokawa, T., et al., SAT0259 high plasma concentration of mycophenolate acid in early phase of induction therapy predicts good renal outcome in lupus nephritis class iii or iv. Ann. Rheum. Dis., 2017. 76: p. 872.
[28] Humrich, J.Y., et al., 06.08 Low-Dose Il-2 Therapy in Refractory SLE: Results from a Single Centre Phase I/IIa Clinical Trial. 2017, BMJ Publishing Group Ltd.
[29] Jing, X., et al., SAT0261 Refractory Systemic Lupus Erythematosus Is Mainly Associated with the Decreased Number of Regulatory T Cells and Low-Dose Il-2 Combined with Rapamycin Can Efficiently Recovery the Balance of Th17/Regulatory T Cells. 2017, BMJ Publishing Group Ltd.
[30] Costedoat-Chalumeau, N., et al., Very low blood hydroxychloroquine concentration as an objective marker of poor adherence to treatment of systemic lupus erythematosus. Ann. Rheum. Dis., 2007. 66(6): p. 821–824.
[31] Petri, M.A., et al., Effects of prasterone on corticosteroid requirements of women with systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum., 2002. 46(7): p. 1820–1829.
[32] Petri, M.A., et al., Effects of prasterone on disease activity and symptoms in women with active systemic lupus erythematosus: results of a multicenter randomized, double-blind, placebo-controlled trial. Arthritis Rheum., 2004. 50(9): p. 2858–2868.
[33] Steiman, A.J., et al., Outcomes in patients with systemic lupus erythematosus with and without a prolonged serologically active clinically quiescent period. Arthritis Care Res., 2012. 64(4): p. 511–518.
[34] Hahn, B.H., et al., American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res., 2012. 64(6): p. 797–808.
[35] Touma, Z., et al., Mycophenolate mofetil for induction treatment of lupus nephritis: a systematic review and metaanalysis. J. Rheumatol., 2011. 38(1): p. 69–78.
[36] Dooley, M.A., et al., Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N. Engl. J. Med., 2011. 365(20): p. 1886–1895.
[37] Mitwalli, A.H., et al., Comparison of high and low dose of cyclophosphamide in lupus nephritis patients: a long-term randomized controlled trial. Saudi J. Kidney Dis. Transpl., 2011. 22(5): p. 935.
[38] Ogawa, H., et al., Prospective study of low-dose cyclosporine A in patients with refractory lupus nephritis. Mod. Rheumatol., 2007. 17(2): p. 92–97.
[39] Lee, T., et al., Tacrolimus is an alternative therapeutic option for the treatment of refractory lupus nephritis. Lupus, 2010. 19(8): p. 974–980.
[40] Wang, L., et al., Calcineurin (CN) activation promotes apoptosis of glomerular podocytes both in vitro and in vivo. Mol. Endocrinol., 2011. 25(8): p. 1376–1386.
[41] Díaz-Lagares, C., et al., Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. Autoimmun. Rev., 2012. 11(5): p. 357–364.
[42] Gunnarsson, I., et al., Histopathologic and clinical outcome of rituximab treatment in patients with cyclophosphamide-resistant proliferative lupus nephritis. Arthritis Rheum., 2007. 56(4): p. 1263–1272.
[43] Catapano, F., et al., Long-term efficacy and safety of rituximab in refractory and relapsing systemic lupus erythematosus. Nephrol. Dial. Transplant., 2010. 25(11): p. 3586–3592.
[44] Petri, M.A., et al., Lupus atherosclerosis prevention study (LAPS). Ann. Rheum. Dis., 2011. 70(5): p. 760–765.
[45] Ginzler, E.M., et al., Nonrenal disease activity following mycophenolate mofetil or intravenous cyclophosphamide as induction treatment for lupus nephritis: findings in a multicenter, prospective, randomized, open-label, parallel-group clinical trial. Arthritis & Rheumatism, 2010. 62(1): p. 211–221.
[46] M. Aringer, R. Fischer-Betz, F. Hiepe, Stellungnahme zum Einsatz von Mycophenolat-Mofetil beim systemischen Lupus erythematodes (Statement on the use of mycophenolate mofetil for systemic lupus erythematosus), Z. Rheumatol. 72 (6) (2013) 575–580.