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Updating medications and treatment strategy for systemic lupus erythematosus: A narrative review

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Systemic lupus erythematosus (SLE) is one of the most heterogeneous systemic autoimmune diseases physicians manage. Despite therapeutic advances, the morbidity of SLE has remained considerable. All hopes for the future in this regard are pinned on targeting the interferon pathways, drugs that block B-cell function or T-cell function, Janus kinase inhibitors, also known as JAK inhibitors, and approaches involving stem cells or mesenchymal cells. New treatment recommendations clarifying anti-inflammatory and immuno-modulatory drugs emphasized the treat-to-target medical strategy, which combines low disease activity and low glucocorticoid (GC) exposure. Researchers support GCs at the lowest dose. The SLE patients need to take hydroxychloroquine. Biological medicines, including belimumab and anifrolumab, are prescribed based on disease stage and severity. To proceed with personalized therapy choices, we need a deeper understanding of biological pathways and specific disease-perpetuating components. New information from ongoing therapeutic studies and real-world data will assist in further clarifying the underlying multidimensional interrelations, bringing in a new era of precision medicine in lupus erythematosus that will benefit both patients and physicians. In order to determine the most effective therapy plan for lupus nephritis, rheumatologists and nephrologists should engage in close interdisciplinary communication. This review study will examine the most recent steps to deal with and treat this disease and future plans to help SLE patients.

Keyword: Systemic lupus erythematosus; JAK inhibitors; Treat-to-target; Interferon-α blockers; Anifrolumab

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune condition that may cause damage to multiple organs simultaneously or asynchronously [1, 2]. It is a multisystem autoimmune disease with a high morbidity and mortality rate brought on by the accumulation of irreparable end-organ damage [3]. Autoantibodies or immune-complex depositions induce tissue damage in the kidneys, cardiovascular system, arteries, central nervous system, skin, lungs, muscles, and joints, significantly increasing morbidity and mortality [4]. The SLE is distinguished serologically by the presence of autoreactive B cells, resulting in the overproduction of autoantibodies against several cytoplasmic and nuclear antigens. This, in consequence, leads to irreparable organ damage [5].

One of the main acute phase proteins, C-reactive

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protein (CRP), also rises under inflammatory situations. It is still debatable how CRP functions as an inflammatory marker in systemic lupus erythematosus (SLE). CRP levels were tested in specific investigations using more accurate techniques, such as high-sensitive CRP (hs-CRP) and anti-CRP during SLE [6-9]. In 2011, a study examined the relationship between hs-CRP blood concentrations and lupus disease activity. Data revealed that while hs-CRP levels in the serum grow in lupus patients, they are not a reliable indicator of disease activity or organ involvement [10]. Continuous disease activity decreases the long-term prognosis in prototypic organ-dedicated or multi-systemic autoimmune rheumatic conditions [11, 12]. According to estimates, there are 30-50 cases of SLE per 100,000 people, or about 500,000 cases in Europe and 250,000 cases in the USA. Ancestry, race, and ethnicity have a significant impact on the symptoms and severity of SLE, according to evidence from studies [13]. Black, Asian, and Hispanic people have a higher incidence and prevalence of SLE compared to white patients. These patients also tend to acquire lupus earlier and experience a more severe active disease with long-term damage and a higher mortality rate [14, 15].

Over the past 60 years, the survival of SLE patients has increased, with a five-year survival rate rising from around 50% in the 1950s to over 95% in the 2000s [16]. Higher mortality rates are correlated with older and younger ages at diagnosis, lower socioeconomic status and level of education, as well as more serious medical conditions, including damage. Nonetheless, it is worth noting that the standardized mortality ratio (SMR) for SLE is 2.6-3.0 times greater than in the general population. This is likely due to increased frequencies of infections (SMR = 5.0), renal disease (SMR = 4.7), and cardiovascular disease (SMR = 2.3), all of which are associated with SLE [17, 18]. Since the middle of the 1970s, a bimodal pattern of mortality has been observed in SLE, with patients passing away earlier in the course of the disease as a result of active conditions and/or both infections and patients dying later in the course of the disease as a result of cardiovascular conditions, often with the inactive disease at the stage of their death [19].
In terms of disease-related factors, increased mortality has been linked to higher levels of disease activity at diagnosis and throughout time, as well as the existence of damage, particularly kidney damage. An increased risk of mortality has been linked to the presence of hematologic disorders (such as thrombocytopenia and hemolytic anemia), neurological, psychiatric, pulmonary, and renal dysfunction, the anti-phospholipid syndrome, and multiple conditions, such as coronary artery disease and the hemo-phagocytic syndrome. Apart from the potential reflection of disease severity, lupus management therapies are known to exert a marked impact on mortality. Among these therapies, we can refer to high dosages of glucocorticoids (GCs) and immune-suppressive medications, such as cyclo-phosphamide (CYC). Nevertheless, it has been demonstrated that antimalarials increase survival, most likely in a time-dependent manner [20].

The management of chronic diseases, such as hypertension, diabetes, and rheumatoid arthritis, has greatly benefited from treat-to-target strategies, and it has been demonstrated that the achievement of treatment endpoints that can be measured in single-organ systems is associated with better outcomes [21, 22]. Nevertheless, in SLE, the development of treatment endpoints necessary for the development and ultimate acceptance of treat-to-target methods has been complicated by intrinsic clinical difficulty and heterogeneity of SLE [23]. Great efforts have been made to put treat-to-target (treat-to-target is a treatment technique that aims to treat patients towards a goal capable of enhancing desired outcomes[11, 23, 24]. Furthermore, alkylating agents (CYC), inhibitors of inosine mono-phosphate dehydrogenase (IMPDH), myco-phenolic acid (MMF), selective inhibitors of purine and/or both pyrimidine synthesis (azathioprine and methotrexate) and calcineurin inhibitors including, cyclosporine and tacrolimus (TAC) [25] are the conventional immune-suppressive drugs used to treat SLE. Although these medications non-selectively inhibit different cellular processes without targeting any particular

molecules, the drugs, such as IMPDH inhibitors, is lymphocytes (excluding plasma cells) since lymphocytes are highly proliferative and preferentially use metabolic pathways that are targeted by these drugs [26]. As illustrated in studies, combination therapy has a more significant therapeutic effect than the total of the solo pharmaceuticals in SLE, indicating synergy. For instance, it is noteworthy that combination therapy is effective in treating SLE and lupus nephritis (for instance, combining inhibition of calcineurin with MMF as the initial or maintenance therapy). The combination of TAC and MMF in lupus nephritis was more effective than intravenous CYC in inducing renal remission in six months (46% vs. 26%) [27]. In another study, the patients who attained renal relief with either treatment in the initial stage were observed for 18 months [28]. In the maintenance stage, those who had taken MMF and TAC proceeded with this therapy, while those who had got intravenous CYC were shifted to azathioprine. Our research team showed in previous studies that combining steroids and CYC can effectively suppress the immune system in treating lupus nephritis by reducing the side effects [29].

As previously reported [30], both groups had the same renal recurrence rates by follow-up. Combination therapy reduced side effects, including leukopenia and liver dysfunction, compared to azathioprine alone [28]. The induction trial revealed that the patients undergoing the combination therapy had a higher rate of severe infections and varicella zoster reactivation, raising issues about its safety. The noticeable variations between the two investigations can be attributable to the higher doses needed for the initial stage compared to the maintenance stage. Nevertheless, since TAC has higher inter-individual variability in pharmacokinetics, its plasma levels should be closely monitored and typically kept at or below 4-6 ng/ml in SLE [31].

Antimalarial drug

Antimalarial medications, most frequently hydroxychloroquine (HCQ), play various roles in the management of SLE. It has a long history of usage as a successful treatment for less severe symptoms of SLE, particularly arthritis. According to current treatment guidelines, HCQ should be administered to all SLE patients, unless contraindicated. Some cohort research projects have demonstrated its preventive efficacy in lowering flares and long-term damage accumulation and providing a survival benefit for SLE patients [32]. Despite a significant risk of side effects, other antimalarials, such as quinacrine and chloroquine, are used in some areas due to access problems. The immune-modulatory properties of HCQ on various immune cells, including dendritic cells, macrophages, and lymphocytes, facilitate its anti-inflammatory effects. Since HCQ is a weak base pharmacologically, it lowers lysosomal protease activity and raises lysosomal PH. Both autophagy and the presentation of the autoantigen to the class II major histocompatibility complex may be affected.

The activity of toll-like receptors 7 and 9 is inhibited by HCQ in vitro [33], affecting the production of type 1 IFN and other cytokines [34]. The inhibition of platelet aggregation is one of the extra antithrombotic actions of HCQ [35]. Studies conducted in vitro have demonstrated that HCQ can reinstate the annexin A5 shield in human endothelial cells and syncytiotrophoblasts; moreover, it can reverse the binding of anti-phospholipid antibodies (APL) to beta 2 glycoprotein 1. Therefore, people with anti-phospholipid syndrome (APLS) may experience additional advantages. Some risk groups, such as those applying doses greater than 5 mg/kg/d or those with renal impairment, tamoxifen usage, or previous macular disease, are candidates for an early review [32].

However, researchers hypothesized that prospectively monitoring HCQ levels might assist in preventing medication toxicity based on research that is currently accessible. The long-term toxicity of HCQ can be prevented by monitoring levels, which can allow for adequate monitoring and drug dosage reduction, especially following 5–10 years of treatment [36].

Belimumab

The TNF superfamily of cytokines includes the B-lymphocyte stimulator (BLyS), often called the B-

cell activating factor (BAFF), and other cytokines. Transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI), B-cell maturation antigen (BCMA), and BLyS receptor 3 (BR3) are the three receptors that BLyS binds to [37]. The inhibition of BLyS binding prevents B cells from differentiating and surviving while promoting apoptosis [38]. In other words, by binding to BLyS and inhibiting the binding of soluble BLyS to B-cell receptors, Belimumab inhibits the survival of B-cells. It reduces Ig-producing plasma cell differentiation [39]. BLyS is a potentially significant therapeutic target in SLE because it overexpresses SLE patients [40].

The medication Benlysta (belimumab) received global marketing authorization in 2011 as an intravenous formulation and in 2017 as a subcutaneous self-injection. The mechanism of action of this drug is to reduce the number of autoreactive B cells (BLyS) and, as a result, lower the creation of damaging autoantibodies that attack healthy tissue, causing inflammation and organ damage. It does this by focusing on a cytokine called a B-lymphocyte stimulator. Nonetheless, only a tiny percentage of individuals benefit from Benlysta due to the complexity of the disease. This medicine has been introduced in response to the needs of patients in the treatment of lupus disease in the last 60 years; however, the medical need for new treatments is still critical [3]. It was demonstrated that Benlysta (belimumab) inhibits B-lymphocyte stimulator, also known as B-cell activating factor [3].

Some signaling pathways and mechanisms of anti-lupus treatments

Due to some problems, the science of creating SLE medications has rapidly advanced over the science of evaluating their efficacy. Since there is no accepted method for defining response to therapy or a reliable gold standard to assess disease activity in SLE, most clinical trials define their primary endpoint as the proportion of patients who reach a predetermined benchmark in a given period of treatment, putting researchers at risk of discarding drugs that work. The interferon pathway, T-cell signaling, and B-cell signaling have all been modulated in studies in various ways. For instance, the mechanism of anifrolumab targets the human monoclonal antibody interferon-α receptor 1; Lupuzor (rigerimod) provokes the elimination of autoreactive lymphocytes, Olumiant (baricitinib) is an inhibitor of Janus kinase 1 and 2; Stelara (Ustekinumab) is a human monoclonal antibody directed against interleukin-12 and interleukin-23; RTX, chimeric anti-human CD20, is approved for the treatment of SLE. Abatacept is a soluble fusion protein that links the extracellular domain of human cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) to the modified Fc region of the immunoglobulin IgG, and voclosporinis, an analog of cyclosporine with enhanced activity against calcineurin for lupus nephritis [3].

New medications and interesting mechanisms

Late-stage drug development focuses on dys-regulated intracellular signaling pathways and targets T- and B-cell activities [41]. Signorini et al. summarized the essential scientific contributions to SLE and its pathophysiology, clinical symptoms and comorbidities, biomarkers, and therapeutic strategies published in 2019. Key findings in SLE pathophysiology affirmed the importance of interferon (IFN) and activated neutrophils in disease-driving pathways. There is an intensive expression of IFN-I-induced gene transcripts in SLE blood and tissues. This genomic signature appears accountable for various immunologic and pathologic aspects of the recurrent self-directed immune reaction [42]. Researchers identify the endosomal Toll-like receptors (TLRs), specifically TLR7, and the cytosolic sensors of DNA or RNA that engage the adaptor STING (stimulator of interferon genes) as potential cellular pathways that might trigger type I IFN response in SLE [43].

Kim et al. looked at how mitochondrial stress affected the production of IFN-I using a mouse model of SLE. The most prevalent protein in the mitochondrial outer membrane, the voltage-dependent anion channel (VDAC), was the subject of their study. Ca2+ influx, metabolite entrance and departure, and finally, cell death are all regulated by VDAC. They discovered that moderate stress conditions brought on by the host

or the environment (such as microbial infections) caused mitochondrial DNA damage and fragmentation. Mitochondrial DNA fragments could penetrate the cytosol and activate the sensor cGAMP synthase, resulting in a STING-mediated type I IFN inflammation since the interaction of these fragments with VDAC caused its oligomerization and pore creation [44].

Interferon-α blocking medications

Type I interferons frequently protect against viral infections. The production of BAFF and APRIL, as well as the upregulation of T cells and the deactivation of T-regulatory cells, are all the outcomes reported for interferon-α's promotion of the growth of diverse immune cells, notably plasma cells and myeloid dendritic cells. The interferon pathway has been studied as a potential therapeutic target in SLE as a result of the discovery of interferonopathies (rare mendelian disorders associated with type 1 interferon overproduction) and the long-standing recognition of an interferon gene signature in many SLE patients the magnitude of which is correlated with disease activity. The most significant difference from placebo was found in SLE patients with a strong IFN gene signature, according to a previous study of collected TULIP data [45]. A anifrolumab therapy was linked in a different trial to previously more prevalent, longer-lasting, and maintained lupus low disease activity state (LLDAS) [46]. Patients with strong baseline interferon gene profiles were more affected by this variation than other groups of patients. Phase 3 research is still going on [41]. Morand et al. published the results of a second phase 3 trial of anifrolumab in active SLE (Treatment of Uncontrolled Lupus via the Interferon Pathway (TULIP-2)), using the based Composite Lupus Assessment (BICLA) secondary end point from the first phase 3 trial as its primary endpoint. This study was carried out at 119 sites in 16 countries. Contrary to the results of patients in a similar phase 3 trial patient groups with SLE, monthly intake of anifrolumab resulted in a larger response (as measured by a composite endpoint) at week 52 than placebo [47].

Additional B-cell Aims and Treatments

Atacicept, a dual APRIL/BLyS inhibitor that failed early phase tests due to hypogammaglobulinemia and infection, has shown promise. A phase 2B trial [48] randomly assigned patients with active, autoantibody-positive illness (n = 306) receiving standard therapy to atacicept (75 mg or 150 mg) or placebo for 24 weeks. Atacicept 75 mg showed the most marked improvement in the SLE responder index-4 score at week 24; nonetheless, this trial did not fulfill its primary goal. In high-disease active patients, 75 mg and 150 mg reduced flares. High-baseline BAFF and APRIL amounts significantly reduced flare in the post-hoc analysis [49]. Combination B-cell treatments are also gaining acceptance. In the Synbiose research, a phase 2 demonstration of concept study, severe refractory patients were treated with RTX and belimumab. This treatment reduced serological abnormalities and neutrophil extracellular traps and produced a remarkable clinical response [50].

T-cell immunotherapy

Since SLE patients have abnormalities in T-cell pathways [51], T-cell treatment interests researchers, although most study results have been disappointing thus far. Ustekinumab is an IL-12 and IL-23 monoclonal antibody. A phase 2 trial revealed that 60% of patients in the ustekinumab group responded better than the placebo group. As a result, researchers anticipated that this treatment would be used in the future [52]. Several medicines are now being developed to minimize the impact of cytotoxic T cells or boost regulatory T cells' anti-inflammatory qualities [53]. Amiselimod (MT-1303) is a sphingosine 1-phosphate (S1P) receptor 1 functioning antagonist tolerated well in a multicenter, open-label, phase Ib clinical trial for patients with SLE. The S1P plays a role in T cell egress from secondary lymphoid organs to sites of inflammation [54]. Patients who completed the 24-week study period observed a decrease in skin symptoms, according to the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K); however, no further information was provided. The CD40 ligand is another possible target; antagonistic medicines may interfere with antigen presentation to T cells. A randomized, placebo-controlled phase II study of dapirolizumab pegol in individuals with mild to severe active SLE was conducted. Although the

main target was not accomplished, marked improvements were reported in numerous clinical indicators, such as the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), compared to placebo [55]. Fexalimab (SAR441344) is another CD40 ligand antagonist. Clinical trials for SLE and elementary Sjögren's syndrome currently recruit participants; nevertheless, no results are available. Another T-cell-directed method is the selective growth of regulatory T cells, with efavaleukinalfa (AMG 592) as a substance of attention. The outcomes of a phase Ib research involving 35 cases with SLE have been published, demonstrating a favorable safety profile. Phase II research will look into clinical efficacy [56].

Inhibitors of Bruton tyrosine kinase and Janus kinase (JAK)

Bruton tyrosine kinase (BTK) inhibitors are highly elevated in lupus nephritis patients [57]. The kinase activates intracellular signaling in B cells and monocyte and macrophage activation. Experiments in mice models of SLE revealed that BTK inhibition demonstrated potential. Janus kinases (JAKs) play a role in numerous inflammatory pathways linked with SLE. The JAK 1 and 2 inhibitor baricitinib has demonstrated promising outcomes, particularly at 4 mg/day dose. Tofacitinib, which inhibits JAK 1 and JAK 3, has been tested in mice models [58], and human trials are currently underway.

Proteasome repression

Bortezomib, a proteasome inhibitor, is commonly used to treat multiple myeloma by targeting plasma cells and inhibiting the activation of the anti-apoptotic nuclear factor kappa B. This medicine was demonstrated to diminish disease activity, notably serologic abnormalities, in a small number of individuals with refractory SLE, with a considerable reduction in type 1 interferon activity [41].

Treatment utilizing stem cells

Autologous (self), haploidentical (partial HLA match and frequently from a sibling), or allogeneic (donor, HLA-matched, related or unrelated) stem cell transplantation provides a chance for a cure without treatment. Different regimens have been recorded using these, primarily CYC therapy. Traynor et al. reported myeloablative autologous stem cell transplantation in seven patients, all of whom had their serologic abnormalities and disease activity resolved [59]. In a European study, high-dose CYC was followed by autologous peripheral stem cell transplantation in 53 cases. At six months, 66% of patients were in remission; nonetheless, one-third of patients relapsed, and 12 cases died during the procedure [60]. A nonmyeloablative autologous hematopoietic stem cell transplant regimen employing lower CYC dosages was tested in 48 individuals. With two deaths, 5-year survival was 84%, with a 50% chance of disease-free survival [61]. Mesenchymal stem cell (i.e., pluripotent stromal cell) treatments have been studied with and without CYC, improving disease severity and serologic abnormalities. Although promising, these SLE therapies have not been examined in randomized controlled trials, and all reported methods vary significantly [41].

Our research team recently studied whether Mesenchymal stem cells (MSC) engraftment helps prevent or ameliorate the clinical course of SLE in an animal model of generated lupus by Pristane (as an adjuvant used in humanized vaccinations). Allogenic MSC transplantation demonstrated the ability to restore the healthy balance of Th17/Treg and Th1/Th2 and reestablish the plasma cytokine network in a disease-dependent pattern. In other words, MSC-based immunotherapy delayed the progression of acquired SLE illness in a treatment-stage-dependent way while avoiding immune-suppressive drug-related cytotoxicity. The differences in outcomes between early and advanced therapy indicate that MSCs may have varying effects based on the moment they are delivered and their activation level [62].

Treat-to-target in SLE

Treat-to-target (T2T) is a therapeutic method in which treatment modifications are made at predetermined intervals to reach a well-defined, clinically relevant target. In rheumatology, the goal of therapy is usually to achieve the simultaneous normality of various factors

represented in a mixed score. Therefore, implementing T2T for rheumatic conditions is considerably more complicated since the target is a score combining various clinical and laboratory alterations that ultimately serve as replacements for disease activities. The 2019 update of the EULAR suggestions for managing the symptoms of SLE supports the use of T2T. It states specifically that the ultimate objective of treatment is supposed to be the achievement of relief without the symptoms of disease activity, thereby reducing comorbidities and toxic effects of drugs, making longevity, avoiding damage accumulation, and improving health-related quality of life (HR-QoL) [20].

Implementation of T2T in SLE, unlike other diseases such as cardiovascular diseases, requires a different approach to targeting with close monitoring (every 3–6 months) of disease activity, response to medical care, and deterioration (both disease- and drug-related), in conjunction with therapeutic changes and optimization. Cohort studies have pinpointed that failure to reach LLDAS at six months following therapy commencement is an independent predictor for initial damage, notwithstanding the lack of information or agreement regarding the period in which a target should or must be accomplished; therefore, researchers suggested a six months interval for the evaluation of clinical status in the general T2T treatment for SLE. Controlling the clinical symptoms of SLE, as in a large percentage of systemic autoimmune disorders, usually depends on the use of GCs that could contribute to damage accrual over time, which may explain the decision to include optimal treatment doses in the definition of targets [63].

Lupus slow disease activity state concept

Although prolonged total remission is rare and difficult to attain in controlling SLE in practice, attempts are made to define a suitable treatment target as part of the overall consideration of treatment goals [64]. The idea of a lupus low disease activity state (LLDAS), first described as a condition of tolerable disease activity with minimal therapeutic impact based on an expert consensus procedure among Asia Pacific lupus specialists, has been advanced as a therapy goal. LLDAS requires a global physical evaluation of 1 or less on a three-point scale, no new or significant organ involvement, and a disease activity threshold of 4 or less on the SLEDAI-2K. It permits concurrent treatment of immune-suppressants, antimalarials, and prednisolone [65]. Moreover, the Definition of Remission in SLE (DORIS) task force defines remission as the ultimate goal of treatment. It was described based on such conditions as no clinical SLE disease activity index (CSLEDAI), physician's global activity with a score of < 0.5, as well as the consumption of antimalarial, low-dose GCs, and/or both stable immunosuppressive medicines, including biologics [63]. Due to its association with protection from flare and damage accumulation, LLDAS has now been prospectively verified as a critical therapeutic target in SLE [65, 66]. It has been tested in several sizable lupus cohorts and demonstrated to be linked to positive long-term results, such as increased survival and quality of life [32].

Guidelines, therapeutic goals, and suggestions

European League Against Rheumatism (EULAR) published its management recommendations in 2008, and in 2019, they were revised in light of new information [67, 68]. Notably, they are just suggestions and not requirements [69, 70]. Survival in the long term, protection of vital organs, and improvement of health-related quality of life are all treatment targets. Remission or minimal disease activity and flare prevention should be treatment goals. A dose of HCQ not exceeding 5 mg/kg of actual body weight should be administered to all lupus patients [71]. The recent publication of a major study compared the outcomes of SLE patients taking HCQ with those of SLE patients who discontinued HCQ. The termination of HCQs was linked with an increased risk for flares in this retrospective research on over 500 individuals with SLE. This was notably true for patients who ceased treatment after less than a year and for those with articular and hematological involvement. Pregnant women are also encouraged to use HCQ since it is safe and has been linked to improved birth outcomes [72]. A recent retrospective cohort study pointed out

that the incidence of preeclampsia was considerably reduced in the HCQ therapy group than in the HCQ non-treatment group, with a total of 151 pregnancies in 122 SLE patients [73].

GCs must be kept to a minimum during chronic maintenance therapy—less than 7.5 mg/day (prednisone equivalent)—and removed whenever feasible [71].In addition, patients with SLE have long been treated with a combination of GC and HCQ plus an immunosuppressant by rheumatologists if this is well tolerated and disease activity can be controlled. Patients who do not respond well to original treatments may benefit from testing some available combination therapies [32]. The results of more recent studies, such as the research by Atisha-Fregoso et al., examined the combination of RTX with CYM, followed by belimumab in lupus nephritis, and demonstrated the acceptable safety of this approach. The clinical efficacy endpoint in this study did not improve; nevertheless, the study did indicate a decreased amount of naive B cells and an increased negative selection of autoreactive B cells[74]. On the contrary, preliminary results from an open-label study called Synergetic B-cell modulation in SLE (SynBioSe) have recently been presented. These results look promising regarding the general effect assessed via LLDAS and renal response (Kraaij et al., published in abstract format only) [32].

Furthermore, the T2T in the SLE task group recommends eliminating GCs and increasing immunosuppressive and biological therapies [63]. Immune suppressive substances, such as alkylating medications, specific blockers of purine and/or both pyrimidine synthesis, inosine monophosphate dehydrogenase inhibitors (IMPDH), calcineurin inhibitors [67, 75], and Vitamin D supplements should be included in the treatment strategy to avoid osteoporosis during sun protection and GC use [76]. Although GCs remain an important part of SLE treatment today, it is best to reduce and eventually stop taking them if possible. After achieving and maintaining long-term remission or LLDAS, patients with SLE can safely reduce or stop using GCs altogether, according to a trial conducted on 148 patients in Italy [77]. The tapering/discontinuation of GCs can be accelerated by starting immunomodulatory medications (such as methotrexate, azathioprine, and mycophenolate) at the right time.

RTX or CYC may be looked at in organ-threatening, resistant diseases, and add-on belimumab should be considered in constantly active or flare disease. The most recent revision included cutaneous, neuropsychiatric, hematological, and renal disease suggestions. Preventive measures should be modified by the results of the assessment of the aPL antibody status and the risk profile for infections and cardiovascular diseases in patients with SLE [71]. Patients with lupus nephritis (LN) have been recommended a variety of treatment approaches. The effectiveness and safety of four distinct treatment protocols—low-dose CYC (total dosage = 3 g), high-dose CYC (mean total dose = 5.1 g), mycophenolate (MMF), and RTX—were compared in a study on 222 Indian SLE patients with biopsy-proven active lupus nephritis. High-dose CY and RTX were more clinically effective in this cohort, with 90.3% and 90.9% renal responses, respectively. Rezayizdi et al. reported that mycophenolate (2 gr/day) maintenance treatment for SLE proliferative function showed significant efficacy and safety after intensive induction therapy with short-term IV monthly, CYC pulse, and recovery and renal recurrence, in addition to mentioning that it also reduced the toxicity of CYC [78].

RTX was similarly successful in treating relapsing illness [79]. In the induction therapy of proliferative LN, investigations indicated that low-dose leflunomide combined with prednisone had roughly the same efficiency and safety as CYC plus prednisone [80]. In comparison with the group receiving only intravenous CYC treatment, the rate of total response and complete remission at 24 weeks was greater in the group receiving CYC, HCQ, and an oral immune-suppressant drug (MMF, azathioprine, or leflunomide) [81]. In addition, the response to combination therapy (MMF and TAC) in patients with lupus nephritis who had failed monotherapy with either MMF or TAC indicated greater long-term safety without sacrificing efficacy [82].

Another study reported that after three months of treatment with a combination of MMF and TAC, there was an early response (a decrease in proteinuria and the lupus disease activity score).

At six months and one-year, complete remission was attained in 22.6% and 36.4% of patients, respectively. With a benign adverse-event profile, the total response rate was 56.5% after six months and 69.1% after one year [83]. Moreover, a comprehensive review of the efficacy and safety of current medications and prospective novel drugs for patients with SLE has been published by Ruiz-Irastorza et al. Their findings highlighted the importance of administering methylprednisolone pulses for moderate to severe flares, followed by low to moderate oral prednisone doses with rapid tapering to maintenance doses of 5 mg/day, and, in the case of severe disease, the immediate institution of immunosuppressive medications, which can serve both as steroid-sparing agents and to control the immune system. In addition, they referred to biological medications, such as belimumab and RTX, for the treatment of refractory or life-threatening diseases. In conclusion, some individuals who do not repond to the gold standard of care may get relief using existing or planned biologic medicines [2].

Conclusion

There is still no cure for SLE; nonetheless, treatments have come a long way in managing symptoms and reducing disease progression. The focus has shifted towards a treat-to-target medical strategy combining low disease activity and low GC exposure, according to new treatment recommendations that clarify the use of existing anti-inflammatory and immunomodulatory medications. Biological medications, such as belimumab and anifrolumab, are also advised depending on the stage and severity of the disease. Studies focusing on specific structural remarks of SLE and randomized controlled trials of potential treatment strategies, are still required to provide data supporting suggestions. Furthermore, enormous effort must be made to understand the best approach to assessing a patient's response and develop more effective treatment protocols for patients in general.

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Conflict of Interests

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