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CLINICAL APPROACH TO DIAGNOSIS & UPDATE ON CURRENT TARGETED THERAPIES: SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

Systemic lupus erythematosus (SLE) is a worldwide chronic autoimmune disease which may affect every organ and tissue. Genetic predisposition, environmental triggers and hormonal milieu, interplay in disease development and activity. Clinical manifestations and the pattern of organ involvement are widely heterogeneous, reflecting the complex mosaic of disrupted molecular pathways converging into the SLE clinical phenotype. The SLE complex pathogenesis involves multiple cellular components of the innate and immune system, presence of auto antibodies and immune-complex, engagement of the complement system, dysregulation of several cytokines including type I interferons, and disruption of the clearance of nucleic acids after cell death. Use of immunomodulators and immunosuppre the natural course of SLE. In addition, morbidity and mortality in SLE not only derive from direct immune mediated tissue damage but also from SLE and treatment associated complications such as accelerated coronary artery disease and increased infection risk.

KEYWORDS: *Systemic lupus erythematosus, Epidemology, Diagnosis, Management.*

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, autoimmune connective tissue disorder complicated and challenging disease to diagnose and to treat. The etiology of SLE is unknown, but certain risk factors have been identified that lead to immune system dysfunction with antibody formation and immune complex deposition. This immune system dysregulation causes organ injury, contributing to the variable manifestations and relapsing-remitting course of the disease. Criteria were created to aide in the diagnosis, focusing on

clinical manifestations and antibody profiles specific to SLE. Treatment options are limited to a few medications to control the inflammation and decrease organ damage. Continuing investigations into the pathogenesis of SLE has led to new discoveries, making more medications available to treat this difficult disease. Disease severity is wide ranging, with most suffering milder forms; however, it is potentially fatal depending on organ involvement. The disorder was recognized as early as the middle ages, within the 12th century physician Rogerius being the first to apply the term lupus to the classic malar rash, and in 1872, Moric Kaposi first recognized the systemic nature of the disease.[1]

2. EPIDEMOLOGY

Systemic lupus erythematosus (SLE) is seen worldwide, with incidence and prevalence rates differing geographically. Studies have shown that the incidence rate of SLE around the world is about 1 to 10 per 100,000 person-years, while the prevalence rates range from 20–70 per 100,000 person-years. In the United States (US), the all race incidence was found to be 5.1 per 100,000 person-years and the prevalence was estimated to be over 300,000 person. SLE predominantly affects women, with a reported peak female-to-male ratio of 12:1 during the childbearing years. The disease can also be seen in children and the elderly with a narrower gender distribution. Studies have shown racial/ethnic variations, with SLE being more common in non-Caucasian person, occurring three to four times more often in African-Americans. In addition to African-Americans, Hispanics and Asians develop SLE more frequently than Caucasians. In these populations, SLE tends to be more active and severe, with a higher risk of relapses and organ system involvement or damage. Even with advances in diagnosis and treatment of the disease, the mortality risk in patients with SLE is higher than that of the general population. For newly diagnosed patients, the 5-year survival rate is over 90% and the 15 to 20 year survival rate is about 80%.[2] Worse outcomes and higher mortality risk correlated with this ethnic disparity, which may be influenced by a lower socio-economic status as well. The disease often begins in puberty; if SLE is diagnosed in patients under the age of 5 years, a rare monogenic form may be present. The survival rate has risen significantly in recent decades (1955 Vs. 2003; 5-year survival rate 5% Vs. 95%; 10-year survival rate 0% Vs. 92%), mainly due to earlier diagnosis and improved management. During the a first years after the onset of SLE, mortality is increased mainly due to disease activity and bacterial infection as a result of high glucocorticoid dosage, while cardiovascular complications predominate in the period beginning 5 years after initial diagnosis.[3]

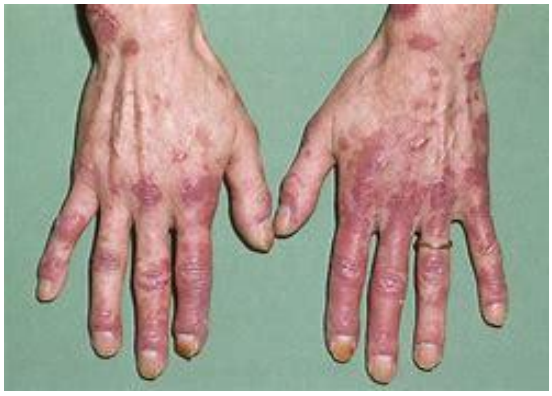

Fig 1. SLE in hands

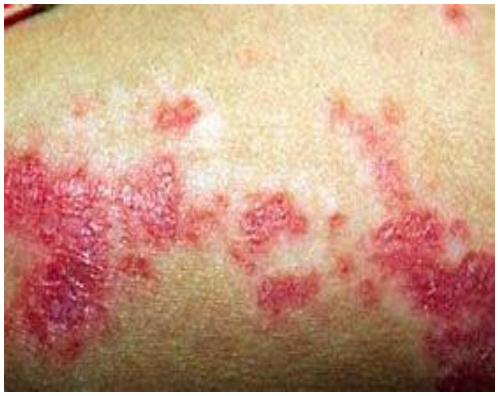

Fig 2. Subcutaneous SLE

3. PATHOGENISIS

The pathogenesis of SLE is complex and appears linked to autoimmunity against various native cellular components. Multiple genetic susceptibility loci have been identified in genomic studies, and specific major histocompatibility complex are also linked to lupus.[4] It is possible that these major histocompatibility complex bind antigens in such a way that they increase the likelihood of T-cells mounting an immune response to self-antigens. Implicated susceptibility genes include IRF 5, STAT4, ITGAM, and several deficiencies in complement components C1q, C4, and C2. Damage subsequently results from autoimmunity-induced inflammation or tissue deposition of immune complex.

Other factors have been implicated in the pathogenesis of SLE, but conclusive evidence is lacking. Factors implicated include current smoking[5], exposure to crystalline silica[6], Epstein–Barr virus seropositivity[7], and hormones, with an association between early menarche and SLE[8] and a protective effect of breastfeeding.[9] Socio-economic factors have been associated with poorer outcomes and higher disease activity, although it remains unclear whether it plays a role in disease susceptibility or subsequent progression.[10]

Exposure to certain drugs may induce a lupus-like illness or exacerbate SLE. There are no standardized diagnostic criteria for drug-induced lupus erythematous, but in such cases there must have been continuous exposure to a pharmacological trigger for at least a month, with resolution after discontinuation of the drug. The clinical manifestations of drug-induced lupus erythematous are generally milder with arthralgia's and serositis being the predominant symptoms, and major organ involvement is usually absent.[11]

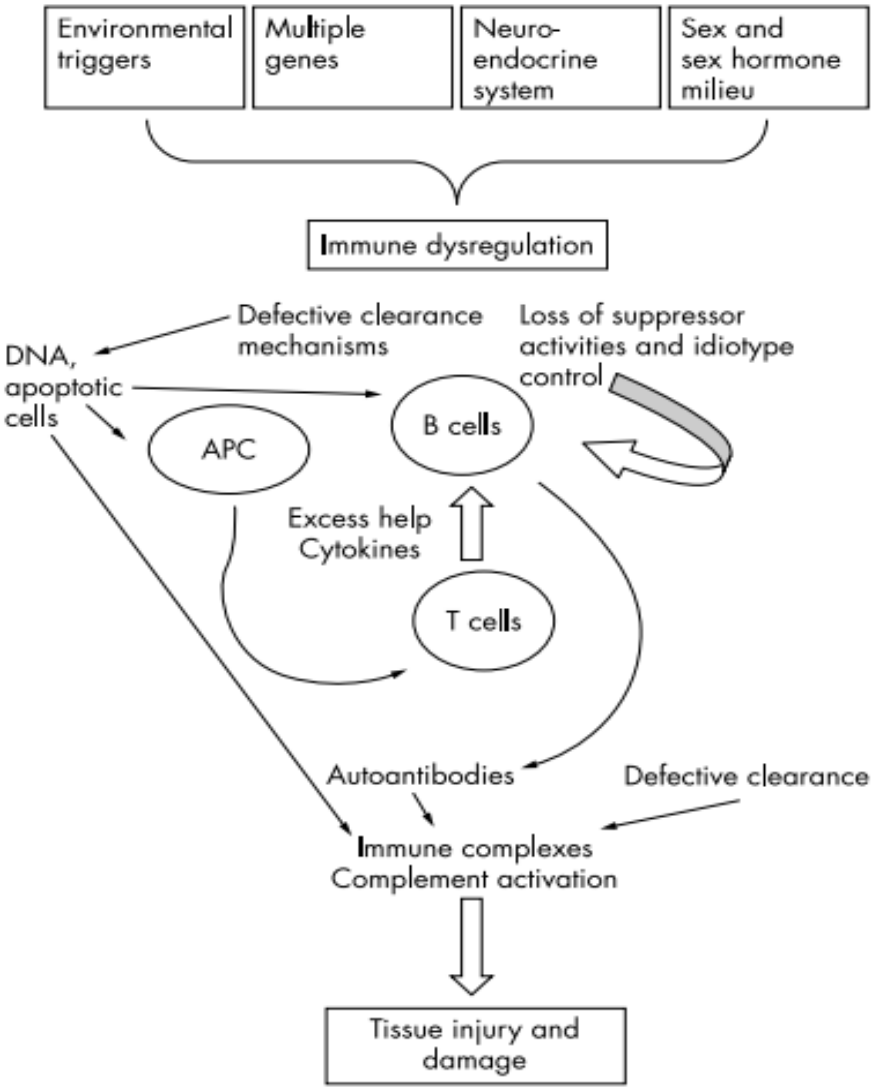

Fig. 3: The pathogenesis of Systemic lupus erythematosus. APC (Antigen presenting cell).

4. DIAGNOSIS

Consensus guidelines provided by the American College of Rheumatology (ACR) provide the basis for accurate and standardized diagnosis of SLE. The original recommendations published in 1982 were updated in 1997 and contain 11 diagnostic categories. The presence of any 4 of these criteria, either concurrently or consecutively, confirms the diagnosis of SLE. The major change in the 1997 revision was the inclusion of newer immunological tests, namely, anti-phospholipid (aPL) antibodies, anti-cardiolipin (aCL) antibodies, and lupus anti-coagulant (LAC), and the removal of redundant histological preparations.

Serological biomarkers hold a significant potential in diagnosis and monitoring of SLE given that the pathogenesis is most likely the result of immune dysregulation. Anti-double -stranded DNA (anti-dsDNA) is highly specific for lupus, with 70% of SLE patients being positive in comparison with only 0.5% of the healthy population or those with other autoimmune diseases.[12] In contrast, anti-nuclear antibody is highly sensitive, being positive in 99% of SLE patients at some point in their illness, but is also found in 32% of the general population at a 1:40 dilution and in 5% at a 1:160 dilution.[13] The search for biomarkers with higher sensitivity and specificity continues with flow cytometric analysis of erythrocyte-bound complement activation product C4d and complement receptor 1 giving promising results.[14] Despite advances it must be recognized that there is no definitive laboratory test for the diagnosis or monitoring of SLE and that all results must be viewed in the context of each individual patient's clinical course.

5. MANAGEMENT

In routine clinical care[15], assessment and monitoring of the SLE patient includes the following: disease status (activity, end-organ dysfunction and damage); co-morbid conditions (e.g. screening for cardiovascular risk factors such as hyperlipidaemia, diabetes mellitus, osteoporosis and malignancy); medication safety (e.g. immunosuppressive drug adverse reactions, HCQ eye screening); preventive health (e.g. annual immunization); reproductive health (adults and adolescents); and child/adolescent health (e.g. transition of care to adult services). These have been developed into clinical quality indicators by the ACR[16] and EULAR[17] for routine care, reproductive health[18] and child health.[19] Although several clinical practice guidelines for monitoring and treatment of SLE exist, the methodological quality, scope and recommendation vary.[20]

The goals of treatment in lupus are 1) maintain lowest degree of activity using immunomodulators, immunosuppression as appropriate and avoiding known triggers, 2) prevent organ damage from active lupus, 3) reduce comorbidities secondary to lupus and its treatment, especially accelerated atherosclerosis, the major cause of death, and 4) address fatigue and pain, which often are not associated with active lupus. Early initiation of treatment as well as partnership with the patient towards these shared goals is essential. This translates into avoidance of known triggers of flares, the need for sun protection, maximization of immunomodulators (Hydroxychloroquine and Vitamin D, including monitoring for adherence), avoidance of maintenance prednisone >6mg daily, and control of

active disease with immunosuppression or biologics when required. Here, we review the rationale for current and future treatments.

5.1 Immunomodulators

Immunomodulators can favourably regulate the immune system in SLE without increasing the risk of infection or malignancy.

5.1.1 Hydroxychloroquine

Hydroxychloroquine pleiotropically modulates the immune response by inhibition of B cell receptor and TLR signaling as well as intracellular TLR-3 and-7 activation, fundamental in nucleic acid sensing.[21] It increases the lysosomal pH interfering with MHC-antigen binding, thus processing of autoantigens, as well as secretions of cytokines. Hydroxychloroquine exerts an anti-type 1 interferon effect by interfering with the STING pathway.[22]

Hydroxychloroquine is the cornerstone of medical therapy in lupus. It should be used in every patient unless there is a clear contraindication. It is the only medication shown to increase survival in lupus patients. It has been shown to reduce lupus flares, prevent organ damage including cardiovascular events, triple mycophenolate response in lupus nephritis, prevent seizures and reduces the risk of developing neuropsychiatric lupus. Hydroxychloroquine improves skin manifestations and arthritis. Hydroxychloroquine has a favorable effect on lipids, reduces insulin resistance and the risk of thrombosis and has a favorable effect on bone density.

Hydroxychloroquine is non immunosuppressive and does not increase the risk of infection or malignancy. Retinal toxicity is a rare complication increasing after 20 years duration of treatment. Retinal screening occurs at baseline, at 5 years, and then yearly. Optical coherence tomography is the preferred screening test. Hyperpigmentation can occur. Very rare complications include cardiomegaly and myopathy.

5.1.2 Vitamin D

Vitamin D should be supplemented in all SLE patients with insufficiency or deficiency, for its immunomodulatory and anti-fibrotic effects. Vitamin D immunomodulatory properties are mediated by the vitamin D3 receptor (VDR) in multiple immune cells lineages including monocytes, dendritic cells, and activated T cells as well as in the skin, vasculature and other tissues.[23] *In-vitro*, Vitamin D exerts an anti-inflammatory and anti-proliferative effect by

promoting Th1 (TNF-α, IL-2, IFN-γ) to Th2 (IL-4, IL-5, IL-10, GATA3) polarization as well as Th17 (IL12, IL23, IL-6, 17) to Treg (IL-10, TGF-β, FoxP3, CTLA4) state. It affects the development and function of NKT cells.

In addition, Vitamin D may act as an anti-fibrotic agent. Vitamin D deficiency is associated with increased risk of multi-organ fibrosis including, among others, the kidneys and the lungs. Importantly, Patients with lupus nephritis refractory to mycophenolate have increased expression of profibrotic pathways in the affected kidneys suggesting that renal tissue could be rescued by targeting such pathways.[24] Vitamin D supplementation prevented fibrosis in animal models and inhibits pro-fibrotic pathways mediated by TGF-beta and RAS.

Vitamin D deficiency is common in patients with SLE. Some VDR polymorphisms are associated with lower serum Vitamin D levels and have been associated with SLE.[25] In patients with lupus, Vitamin D deficiency correlates with increased disease activity and fatigue as well as an increased risk for thrombosis, including from anti-phospholipid antibodies. Importantly, supplementation of Vitamin D is associated with reduction of proteinuria, higher complement levels, and improvement in global disease activity in SLE as demonstrated in an observational cohort and in a randomized controlled study. Supplementation should be aimed to a 25(OH) Vitamin D level of 40 mg/ml. Vitamin D supplementation is safe and should be continued indefinitely. Vitamin D levels should be monitored periodically to assess adequate absorption and dosing and adherence.

5.1.3 Dehydroeipandrosterone (DHEA)

DHEA is an adrenal hormone regulated by ACTH. It is an important precursor of both estrogens and androgens via peripheral conversion. Women with lupus tend to have lower levels of androgens, higher estradiol, lower DHEA and DHEA-S (its metabolite), independently of corticosteroid use. In addition, DHEA supplementation has been associated with regulation of proinflammatory cytokines (IL-2, IL-1, IL-6, TNF-a) and may reduce antibody production in mice.

Many of the several randomized clinical trials in women with SLE showed a modest improvement in disease activity along with improvement in cytokine profile and bone density. DHEA should not be used in postmenopausal women since it may increase the risk of hormone sensitive malignancies. There is no evidence to support DHEA use in men.[26]

5.2 Corticosteroids

Corticosteroids affect all components of the immune system. High dose or "pulsed" corticosteroids are important to rapidly ablate the autoimmune response in life or organ threatening manifestations such as some cases of nephritis, vasculitis, central nervous system lupus, myocarditis, or alveolitis, among others. In lupus nephritis for example, pulsed therapy (250–1000 mg IV daily for 3 days) was previously recommended along with cyclophosphamide or mycophenolate for induction, but there is no consensus on an oral maintenance regimen. The "Rituxilup" protocol showed that lupus nephritis remission can be induced without any oral corticosteroids using rituximab and mycophenolate suggesting that corticosteroids might not be necessary to control even severe lupus manifestations. In the recent voclosporin phase 2 clinical trial, only 25 mg of prednisone was used. Importantly, any of the studied immunosuppressants agents (cyclophosphamide, azathioprine, mycophenolate, tacrolimus) is better than corticosteroids alone to prevent end stage renal disease.

Oral corticosteroids should be avoided as much as possible. In lupus patients, 80% of organ damage after diagnosis is directly or indirectly attributable to prednisone. Doses of even 10 to 20 mg daily increase the risk of cardiovascular events and any dose above 6 mg increases later organ damage by 50%. Even low doses, over time, increase cataracts, osteoporosis, fractures and coronary artery disease.

Intramuscular triamcinolone, or a brief 1-week methylprednisolone dose pack, is effective for management of most mild to moderate flares. Results from the FLOAT trial showed that a single intramuscular triamcinolone 100 mg injection is a faster acting and effective alternative to oral maintenance corticosteroids.[27] As it is released slowly, its effect lasts for about 1 month and has equipotency of approximately 2 mg of prednisone daily.

5.3 CYTOTOXIC-IMMUNOSUPPRESSANTS

5.3.1 Cyclophosphamide

Cyclophosphamide is a highly toxic alkylating agent that depletes T and B cells and suppresses antibody production. It was more widely used in the past for the induction and maintenance of lupus nephritis and other severe lupus manifestations such as central nervous system lupus. However, it has now been largely replaced by less toxic immunosuppressive medications such as mycophenolate, calcineurin inhibitors, and azathioprine for nephritis and rituximab for severe central nervous system lupus. Cyclophosphamide is associated with

premature ovarian failure, hemorrhagic cystitis, increased risk of bladder and other malignancies, and leukopenia along with an increased risk of infections.[28]

5.3.2 Azathioprine

Azathioprine is a purine analogue. It is converted *in vivo* to 6-mercaptopurine followed by thioinosinic acid and 6-thioguanine which are incorporated into DNA and RNA, inhibiting their synthesis. Besides its antimetabolite role, azathioprine may have a tolerogenic effect by inhibiting CD28-mediated signal 2 in T cells.

Azathioprine has been commonly used in renal and extrarenal lupus since the late 1960s. In two small randomized studies, azathioprine compared to corticosteroids alone was shown to reduce mortality, rate of flares and corticosteroid use, including patients with severe renal or central nervous system disease. In the following decades, its use in induction in lupus nephritis waned given its inferiority to cyclophosphamide. Azathioprine was inferior to mycophenolate in the ALMS trials and equal in the MAINTAIN trial.

In extrarenal lupus, azathioprine is widely used as a corticosteroid sparing agent. However, a recent non-blinded randomized controlled study showed that mycophenolate was superior to azathioprine to control disease activity and prevent flares (renal and extrarenal) while maintaining a similar side effect profile.

Azathioprine remains an excellent choice to control renal and extrarenal disease during pregnancy as the metabolite 6-MMP is not generated in the fetus.[29]

5.3.4 Methotrexate

Methotrexate is an anti-metabolite interferes with DNA synthesis, repair, and replication by irreversibly binding to dihydrofolate reductase, thus reducing purine synthesis. However, the mechanism of its anti-inflammatory effects goes beyond arresting the cell cycle by folate depletion and is not completely understood. For instance, co-administration of folate does not impair its efficacy, while mitigating side effects. Low-dose methotrexate has pleiotropic effects involving increased anti-inflammatory adenosine signalling, apoptosis of activated lymphocytes, reduction of circulating pro-inflammatory T-cells, reduction of adhesion molecules on endothelial and synovial cells, reactive oxygen species, and others.

In lupus, methotrexate has been used since the 1960s. Combined evidence from 3 small randomized trials and several observational studies showed that methotrexate reduced disease

activity, was corticosteroid sparing, had efficacy for joint and skin disease, and ameliorated anti-ds DNA and complement levels. Methotrexate showed a modest steroid sparing activity in a randomized controlled trial.[30]

5.3.5 Mycophenolate

Mycophenolate preferentially depletes guanoside nucleotides in T and B cells inhibiting proliferation. It suppresses lymphocyte and monocyte recruitment to inflamed tissue. It inhibits inducible nitric oxide synthase which may curtail nitric oxide oxidative tissue damage mediated by macrophages.

Mycophenolate is effective for induction and maintenance of lupus nephritis. The ALMS trial (n=140) showed that 22.5% of patients treated with mycophenolate achieved complete renal remission at 24 weeks compared to 5.8% in the cyclophosphamide group. The larger ALMS lupus nephritis induction trial showed similar efficacy of mycophenolate compared to cyclophosphamide. Mycophenolate had a better safety profile. This was confirmed by a recent Cochrane systematic review, although with low certainty evidence. This review also confirmed that mycophenolate is superior to azathioprine in preventing nephritis relapses. Mycophenolate is also effective in extrarenal lupus in all the analyzed domains in multiple case series and in a post-hoc analysis of the ALMS trial.[31]

5.3.6 Calcineurin inhibitors

Calcineurin inhibitors target T cells by blocking the inhibition of calcineurin. This prevents translocation of transcription factors such as nuclear factor of activated T-cells (NFAT) resulting in T cells inhibition with reduction of IL-1b, IFN-γ, IL-6 and IL-10. B cell activation is also impaired along with class switching and immunoglobulin production. Furthermore, calcineurin inhibitors affect the kidneys directly by stabilizing podocytes, reducing mesangial proliferation, and improving proteinuria.

Calcineurin inhibitors are commonly used to prevent transplant rejection. In lupus, tacrolimus has been used, alone or in combination with mycophenolate, more extensively than cyclosporine given its better side effects profile. However, both have significant variability in plasma concentration and require monitoring.

Multiple small RCTs showed that lupus nephritis induction with calcineurin inhibitors (cyclosporine or tacrolimus) is as effective as cyclophosphamide or mycophenolate. A recent

metanalysis suggested a possible superiority of tacrolimus over cyclophosphamide. A larger trial comparing mycophenolate Vs. tacrolimus in 150 Chinese patients with active class III/IV showed similar complete response rates at 6 months (59% Vs. 62%, respectively) and side effects.

Combination of calcineurin inhibitors and mycophenolate is used to prevent graft rejection and is also effective in refractory lupus nephritis in Caucasian and African American patients. In a large RCT, 368 Chinese patients with class III/IV/V lupus nephritis were randomized to receive a combination of tacrolimus (4 mg/day) and low dose mycophenolate (1 g/day) ("multitarget") or monthly IV cyclophosphamide (0.5–1 g/m2). After 6 months, complete remission was achieved in 45.9% Vs. 25.6%, and overall response in 83.5% Vs. 63% in the multitarget and cyclophosphamide, respectively. More patients withdrew from the multitarget arm, mostly due to pneumonias and zoster reactivation.

Calcineurin inhibitors have also been proven effective for maintenance therapy of lupus nephritis, as well as for pure membranous lupus nephritis with a significant antiproteinuric effect. They are recommended by EULAR.

Voclosporin is a new calcineurin inhibitor. It has greater pharmacological potency, faster elimination and less variability in blood concentration. It is non-inferior to tacrolimus in preventing kidney transplant rejection. The AURA phase IIb study randomized 265 patients with active lupus nephritis to receive voclosporin or placebo in addition to mycophenolate and corticosteroids. Both voclosporin doses showed higher complete remission rate than mycophenolate alone at 24 and 48 weeks (48 weeks complete remission 40%, 49%, and 24% in the high dose, low dose, and mycophenolate alone arm, respectively). Glomerular filtration rate decreased with voclosporin. There was an imbalance of death in the low dose voclosporin arm. A phase III trial (AURORA) is ongoing.

5.4 BIOLOGICS AND SMALL MOLECULES

5.4.1 Rituximab

Autoantibodies and immune complex formation are an immunological hallmark of lupus. B cells have been targeted in SLE for years with immunosuppressants such as cyclophosphamide and mycophenolate. Targeted therapies toward B cells that avoid broad immunosuppression are the goal.

Rituximab is an anti-CD20 monoclonal antibody that leads to peripheral B cell depletion. Several observational studies showed benefit in renal and non-renal lupus. Two large randomized placebo-controlled trials in renal and non-renal lupus failed to meet their primary outcomes. In the EXPLORER non renal trial, the primary (proportion of patients achieving complete or partial remission based on BILAG score) and secondary endpoints were not met. B-cell depletion was obtained in about 90% of treated patients. Rituximab did reduce anti-dsDNA titers and improved C3 and C4 levels.

In the LUNAR renal trial, 144 patients with class III or IV lupus nephritis were randomized to receive rituximab (1,000 mg on day 1, 15, 168, and 182) or placebo in addition to mycophenolate and corticosteroids. The rituximab group failed to achieve the primary outcome defined as better overall (complete and partial) renal response compared to mycophenolate alone at 52 weeks (57% Vs. 46%, p = 0.18). Further analysis showed that rituximab did reduce proteinuria better than mycophenolate alone at 18 months and reduced the need for rescue cyclophosphamide (8/72 in the placebo group Vs. 0/72 for rituximab).

The disappointing results led to the consideration of the issue of reconstitution of B cells after rituximab. The surge of BAFF upon depletion of B cells with rituximab may contribute to the lack of sustained response to rituximab. This provided the rationale for SynBioSe, a proof of concept phase 2A trial of rituximab followed by belimumab in patients with refractory severe lupus nephritis. Eleven out of 16 patients showed a renal response, 5 with complete response. The renal response was paralleled by amelioration of immune-complex mediated NETs formation. In the CALIBRATE trial, patients with refractory lupus nephritis were treated with rituximab, cyclophosphamide and corticosteroids followed by either belimumab or placebo. This did not show a benefit of belimumab, with 24 week renal responses of 24% Vs. 23%.[32]

Evidence for the efficacy of rituximab comes from “Rituxilup”, an oral corticosteroid-avoidance protocol to treat lupus nephritis with mycophenolate and rituximab. In this prospective observational single-center cohort study, partial or complete remission was achieved in 45 of 50 patients by a median time of 37 weeks.

5.4.2 Belimumab

B cells maturation, Ig-class switching, and antibody production are most potently driven by antigen specific T cells. Since T cells tolerance is much more strictly regulated, such T cell

dependence should ensure that autoreactive naïve B cells that escaped central tolerance will be eliminated by lack of stimulation. However, T cell-independent pathways such as B cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL) may bypass T cells in the selection of autoreactive B cells. BAFF exists in a soluble and membrane bound form and is produced by antigen presenting cells (dendritic cells, B-cells, monocyte/macrophages, plasmacytoid dendritic cells), neutrophils, activated T cells and endothelial cells. BAFF provides essential activation and survival signals via NFkB and MAP-K pathways to B cells as mediated by 3 receptors: BAFFR, TACI and BCMA. BAFFR ligation provides the strongest signal while TACI and BCMA also bind to APRIL. Importantly, patients with lupus have higher circulating BAFF and APRIL levels and the BAFF level is predictive of flares. BAFF-transgenic mice have a lupus-like phenotype independent of T cells.

Two large phase 3 RCT, BLISS-52 and BLISS-76, assessed the SLE responder index at 52 weeks in patients with non-renal lupus. In both trials, there was a higher response rate with the higher dose of belimumab (10 mg/kg) compared to standard of care (BLISS-52: n=867, 58% vs 44%, p=0.006; BLISS-76: n=819, 43.2% vs 33.5%, p=0.017). Belimumab also significantly reduced the number of flares. In addition, belimumab normalized anti-dsDNA in up to 17–25% (placebo 6–8%) and normalized C3 in 34–44% (vs 14–21%) and C4 in 43–46% (vs 17–19%). Belimumab decreased circulating B cells and CD20+/CD27^{bright} short lived plasma cells were decreased by >50% and up to 43%, respectively. Pooled data analysis of both trials showed that combined hypocomplementemia and anti-dsDNA positivity was the best predictor of response to belimumab. Based on these results, belimumab became the first new drug in the last five decades to be approved by the EMA and FDA (and later by NICE) for the treatment of active non-renal lupus despite standard therapy.

5.6 Currently studied

5.6.1 Anifrolumab

Type 1 interferon signalling is mediated by the type I IFN-α/β/ω receptor (IFNAR). Anifrolumab is a monoclonal antibody blocking IFNAR. In a phase 2b trial, 305 lupus patients were randomized to receive placebo or one of two dosages of anifrolumab. At 24 weeks, 34% and 29% of patients receiving anifrolumab (300mg and 1000mg every 4 weeks, respectively), while only 17.6% in the placebo group, achieved the primary outcome of SRI-4 response with sustained reduction of oral corticosteroids. The effect was greater in patients with the interferon signature at baseline. Both skin and joint disease showed a favorable

response. In addition, anifrolumab was associated with decreased anti-dsDNA titers and higher C3 levels. There was a mild increased risk of viral infections, including influenza and herpes zoster. However, the first phase III trial (TULIP 1) did not reach its primary end point of decreasing the SRI-4.[33] TULIP 2 is currently under way.

5.6.2 Ustekinumab

There is increased Th17 activity in lupus. Serum IL-17 and IL-23 levels are higher in SLE and correlate with disease activity. IL-17-producing cells are present in biopsies from lupus nephritis. Double negative T cells are also a source of IL-17. STAT3, which is downstream to IL-23 stimulation, is upregulated in lupus, and promotes IL-17 production as well as differentiation toward Th17 and Tfh. Tfh are expanded in SLE and have been implicated in the overstimulation of B cells. IL-23 promotes the development of double negative T cells and impairs the production of IL-2 suggesting a possible indirect effect on the production of Tregs.

The IL-23/Th17 axis can be disrupted by Ustekinumab, a monoclonal antibody blocking IL12 and IL-23 currently approved to treat psoriasis, psoriatic arthritis and inflammatory bowel disease. In a phase 2 trial, 102 patients with SLE were randomized (3:2) to Ustekinumab vs placebo. At 24 weeks, 60% of Ustekinumab-treated patients achieved the primary endpoint, SLE responder index-4 (SRI-4) compared to 31% in the standard of care group (p=0.0046). Subgroup analysis showed significant improvement in skin and joint scores. Ustekinumab improved C3 and reduced anti-dsDNA levels.[34]

5.6.3 Baricitinib

The Janus kinases (JAKs) are a family of tyrosine kinases mediating intracellular signaling of several cytokines via the JAK-STAT pathway. Inhibition of a single JAK may lead to blocking the downstream effect of several cytokines at the time. However, this is a redundant system in which a group of cytokines may signal through different JAKs and different JAKs mediate signaling from different groups. At present, Baricitinib and Tofacitinib are FDA approved for the treatment of rheumatoid arthritis. Baricitinib is a reversible inhibitor of JAK1 and JAK 2. These mediate signaling for type 1 interferons, IFN-γ, IL-6, IL-12, and IL-23 among others. An international, multicenter, double-blind, placebo-controlled phase 2 trial assessed the efficacy of Baricitinib in patients with SLE. The primary outcome was the proportion of patients achieving resolution of rash or arthritis at 24 weeks, defined by SLEDAI-2K. Three-hundred and fourteen patients with inadequate control despite standard

of care were included. The primary outcome was achieved in a statistically significant higher proportion of patients treated with Baricitinib 4 mg daily, but not 2 mg daily, as compared to placebo (67% Vs. 58% Vs. 53%, respectively). Most of the results were driven by the Baricitinib effect on arthritis as no significant difference was noted on skin scores. The frequency of flares was also lower in the 4 mg group compared to placebo (33% Vs. 51%). There were more serious infections in the 4 mg arm (6%) compared to the 2 mg (2%) and placebo (1%). There was 1 deep venous thrombosis (1%) detected in the 4 mg arm.

5.6.4 Atacicept

Atacicept is a TACI-Ig fusion protein that inhibits B cells by dual inhibition of APRIL and BLyS. In a phase 1b trial, atacicept showed a dose dependent reduction in circulating B cells and immunoglobulins. In the ADDRESS II, a phase 2b trial, 306 patients were randomized to receive weekly subcutaneous atacicept (75mg or 150mg) or placebo. Atacicept was associated with a trend toward better SRI-4 response at 4 weeks compared to placebo, especially in individuals with high disease activity, serologically active disease, or both. For example, in the serologically active group, 62% of patients treated with atacicept achieved SRI-4 at 24 weeks compared to 24% in the placebo arm.[35]

5.7 Lifestyle

Some of lupus management is non-pharmacological. Patients should avoid sun exposure using protective garments and sunscreen of at least SPF 50 (as demonstrated in a randomized clinical trial).

Fibromyalgia and “fibromyalgia-ness” (tendency to respond to illness and psychosocial stress with fatigue, general increase in symptoms, and widespread pain) is increased in SLE. Regular exercise, stretching and can help to improve fatigue, cognitive dysfunction, and pain from fibromyalgia.[36]

5.8 Prevention of comorbidities

Lupus confers a 2.4-fold increase in all-cause mortality. The number one cause of death in lupus is cardiovascular events, followed by infections, and finally by renal and respiratory complications of lupus.

The risk of cardiovascular events is increased 2.66 fold. Therefore, aggressive management of traditional (smoking, obesity, diabetes mellitus, hypertension, dyslipidemia) and lupus

(lupus activity, anti-phospholipid antibodies, homocysteinemia, excessive corticosteroid use) modifiable cardiovascular risk factors is paramount to prevent early death.

Homocysteinemia is present in 15% of patients and has an independent association with cardiovascular risk, renal injury and fibrosis, and is associated with higher prevalence of myocardial infarction and thrombosis in patients with anti-phospholipid antibodies. Hyperhomocysteinemia is an independent risk factor for cardiovascular disease in patients with lupus.

Infections are common in lupus, particularly from encapsulated bacteria. Typical organisms are the most common causal agents but opportunistic bacterial, mycobacterial, protozoal, fungal and viral infection are also increased Pneumonia, especially from Streptococcus pneumonia, is common in lupus and is associated with excess mortality. In addition to the local immunization schedule, pneumococcal and influenza vaccination should be followed.

Osteoporosis and fragility fractures are higher in lupus. Notably, fracture risk calculators may underestimate in lupus. Optimal bone health should be pursued recommending smoking cessation, optimal vitamin D levels, adequate dietary calcium intake (rather than supplementation), weight bearing exercise, avoidance of corticosteroids, bone density screening according to risk and treatment with DHEA (never in men) and bisphosphonate as appropriate.[37]

5.9 Future prospective and personalized medicine

The more granular understanding of the molecular basis of lupus pathogenesis has led to several new promising treatments that are undergoing late phase clinical testing. These recent phase 2 trials underlined how targeting a specific pathway may elicit dramatically different responses in patient subgroups. Precise characterization of disease phenotypes based on molecular and clinical features is crucial to design personalized treatment. The Accelerated Medicine Partnership (AMP), for example, is an ongoing effort to identify the molecular pathways, at the single cell level, involved in lupus nephritis.[38] This may help to redefine the way we classify SLE and lupus nephritis and identify precise predictors of treatment response. We expect that the understanding of the heterogeneity of autoimmunity in lupus will lead to more effective and less toxic regimens in the future.[39]

6. CONCLUSION

SLE is a multisystem autoimmune disorder with a complex pattern of disease manifestations and damage accrual. Prognosis has steadily improved, with longer survival resulting in more patients presenting for surgery; this results in a need for anaesthesiologists to understand the potential complications that they may encounter when caring for a SLE patient. Given the heterogeneity of this disease and its ability to affect any organ in the body, anaesthetic and perioperative management remains dependent on clinical acumen and understanding of the medical issues at play in patients.

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8. CONFLICTS OF INTEREST

Nil.

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