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RESEARCH ARTICLE

Clinical Pharmacological Management Status of Systemic Lupus Erythematous Population: Situational Analysis

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that has various manifestations among different populations. This study aims to provide an overview of medical pharmacological management that SLE population received immediately at time of diagnosis.

Method: This is a retrospective analysis using patients' registry medical information system. All patients diagnosed with SLE were reviewed by accessing their medical records including pharmacy prescription and dispersions at the Royal hospital from 2006 to 2014. The following comorbidities were analyzed: diabetes mellitus (DM), hypertension (HTN), hyperlipidemia, lung disease, cardiovascular disease (CVD), cerebrovascular accident (CVA), chronic kidney disease (CKD), end-stage kidney disease (ESKD), infections, thyroid disease, malignancy, and miscarriages.

Results: There were 966 patients diagnosed with SLE during the period from 2006 to 2014. The Mean (SD) of age at presentation was 35.5 (11.5) years. Most patients were female (88.7%) with mean age of 27.6 (1.4) years. Unsurprisingly anti-malarial drug, hydroxychloroquine was used in 95% of SLE patients and steroid therapy was used in 93% in which 60.95% received Methylprednisolone pulse. The immunosuppressive agent of choice was Cyclophosphamide in 25.04%. Mycophenolic acid (MPA) medication in 39.85% and azathioprine in 37.06% of patients. Anti CD20 monoclonal antibodies, rituximab, was used in 20.91%. Calcineurin inhibitors were used in total of 11% of patients (cyclosporin a in 6.72% and tacrolimus in 4.35%).

Conclusion: The complexity of SLE presentation have led to diverse pharmacotherapeutic strategies based on the organ systems involved. Management is individualized and depends on presenting symptoms and reducing the likelihood of permanent damage to organs and tissues. Strengthen health system at primary level and education of public and health work force is the main challenge to further improve the management. The overall aim of management was to determine the extent of disease and prevent extensive organ involvement and deal with various traditional and non-traditional CVD risk factors. The involvement of clinical pharmacist is very important to further strengthen the pharmacological management of lupus patients.

Keywords

Systemic lupus erythematosus, Chronic kidney disease, End stage kidney disease, Co-comorbidities, RRT, Diabetes, Hypertension, Dyslipidemia, Oman, Middle East

List of Abbreviations

SLE: Systemic Lupus Erythematosus; DM: Diabetes Mellitus; HTN: Hypertension Hyperlipidemia; LD: Lung Disease; CVD: Cardiovascular Disease; CVA: Cerebrovascular Accident; CKD: Chronic Kidney Disease; ESKD: End-Stage Kidney Disease

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a highly variable course and prognosis with a main pathological central defect of several autoantibodies production against a diversity of self-antigens [1]. B cells show a fundamental part in SLE pathology and treatment directed towards the B-cell compartment is the new trend in the current therapies [2-4].

SLE is a prototypical autoimmune disease characterized by alternating periods of disease activity and quiescence [5]. The main aim of treatment is to control

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inflammatory disease activity and prevent lupus flares [6,7]. The mortality and morbidity associated with SLE have improved significantly over the past few decades with the introduction of treatments such as corticosteroids, antimalarial agents (AMs), immunosuppressive drugs and most recently, biological agents [8-11]. These modalities of treatment help in management of disease activity during flares, but all patients should be maintained on the minimum long-term treatment necessary to keep the disease under satisfactory control [9,12,13].

In our setting, where majority of patients are women of childbearing age, the use of biologics was observed in clinical practice to be of great value compared to the conventional immunosuppressive treatment which has significant side effect profile such as infertility that's is no easily accepted by large number of patients Despite that the management of the disease is still a clinical challenge for the treating physicians as many aspects regarding the disease pathogenesis, clinical picture and outcomes remain to be elucidated. Moreover, SLE patients have many traditional risk factors for cardiovascular diseases but even more worrying they tend to have an alarming risk of non-traditional risk factors such us disease activity and chronic inflammation [14,15]. All these risk factors need to be managed appropriately to further reduce mortality and morbidity. Patients centered management approach among such a young fertile population incorporating patients concerns and preference should be one of the main drives of final decisions regarding further therapy.

This study aims to provide an overview of medical management that SLE population received immediately at time of diagnosis.

Methods

This is a retrospective analysis using patients' registry medical information system (Alshifa system). All patients diagnosed with Systemic SLE based on the American College of Rheumatology classification criteria (ACR97) were included.

All patients diagnosed with SLE were reviewed, records of medications were evaluated including: Specific medications like, hydroxychloroquine, steroid, cyclophosphamide or rituximab and antimetabolites including mycophenolic acid (MPA) or Azathioprine (AZA) and calcineurin (Cyclosporine and Tacrolimus). And non-specific medications like antihypertensive medications (calcium channel blocker (CCB) angiotensin converting enzyme inhibitors (ACEI), angiotensin receptors blocker (ARBs), Beta blockers and diuretics), statins, anti-diabetic medications either insulin or oral hypoglycemic, antiplatelets (Aspirin or Clopidogrel), anticoagulants (Heparin or warfarin) and other supportive treatment like, antibiotics, H2 blockers (Ranitidine),Proton pump inhibitors (PPI), oral iron and Calcium with vitamin D.

The process of data entry and analyses was always rechecked by two researchers and a clinical pharmacist. An epidemiologist was involved throughout the study. This started from the first meeting and conception of the research idea till the end of the study. Quality control data was done as per our institute research guidelines. Statistical analysis was completed using Stata software, Chicago, Ill. USA.

Results

There were 966 patients diagnosed with SLE during the period from 2006 to 2014. Their mean (SD) of age

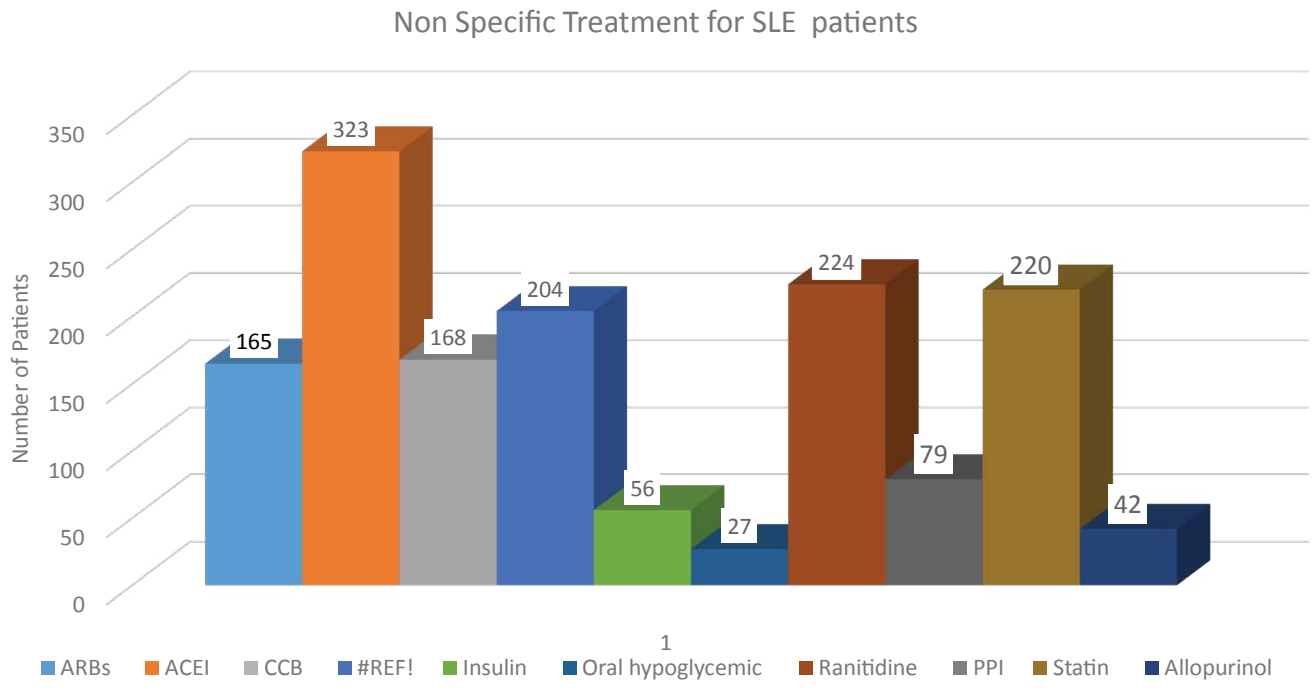

Figure 1: Non-Specific Treatment for SLE patients.

was 35.5 (11.5) years. Female represent 88% of the studied SLE population, with mean age 27.6 (1.4) years.

Nonspecific treatment for proteinuria and comorbid disease in the form of: Renin Aldosterone System blockage medications was used in 50.0% where ACEI used in 33.4%, and ARBs in 17.08%, as shown in Figure 1.

Calcium channels blockers were used in 17.39% whereas Beta blockers used in 14.9%. In addition, diuretics was used by 21.1%, as shown in Figure 1 and Figure 2.

Anti-diabetic medications were used in 9% where insulin utilized by 6% and oral hypoglycemia by 3.0%, as shown in Figure 1.

Anti-platelets medications were not uncommonly used, Acetylsalicylic acid utilized by 21.42% and clopidogrel by 3.0%, while anticoagulants were used in 19.9%, Heparin was most commonly used in 13.14% while warfarin was prescribed in 5.38%, as shown in Figure 2.

Lipid lowering agents (statins) were used by 22.79% of patients, as shown in Figure 1.

Ranitidine was prescribed in 23.18% while proton pump inhibitor used in 8.17% of patients, as shown in Figure 1. Calcium and vitamin D supplements were given to 60.04% of SLE patients, as shown in Figure 2. Ferrous

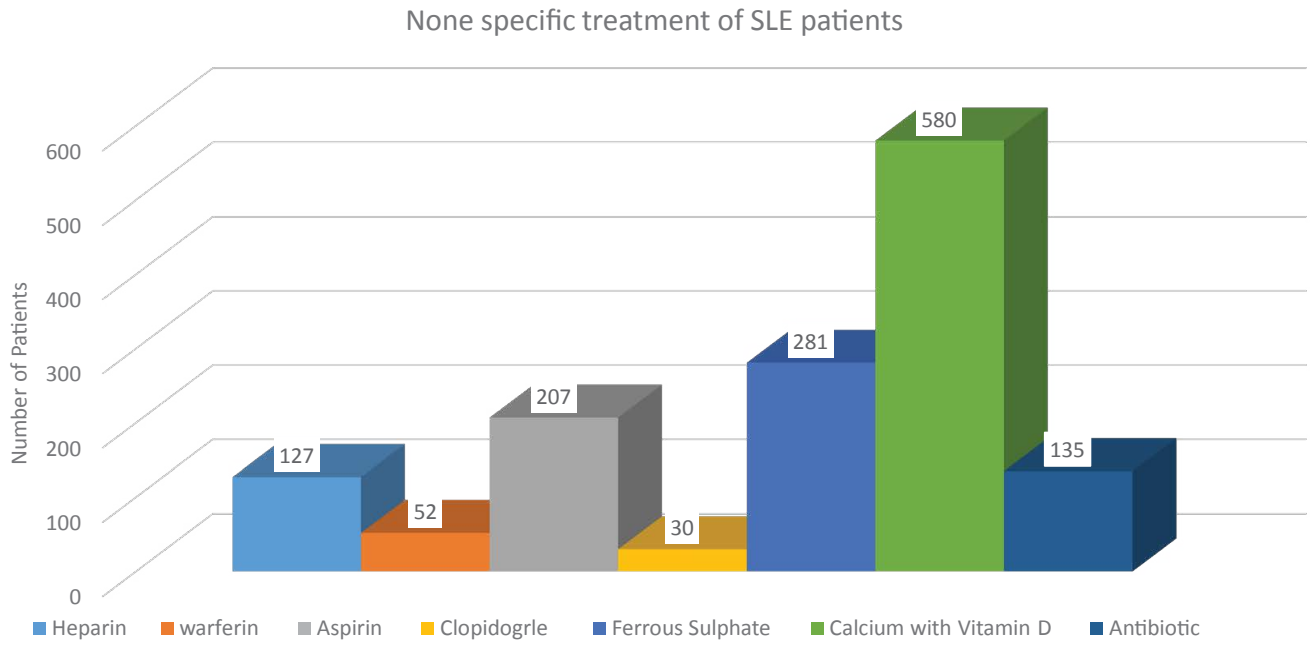

Figure 2: None specific treatment of SLE patients.

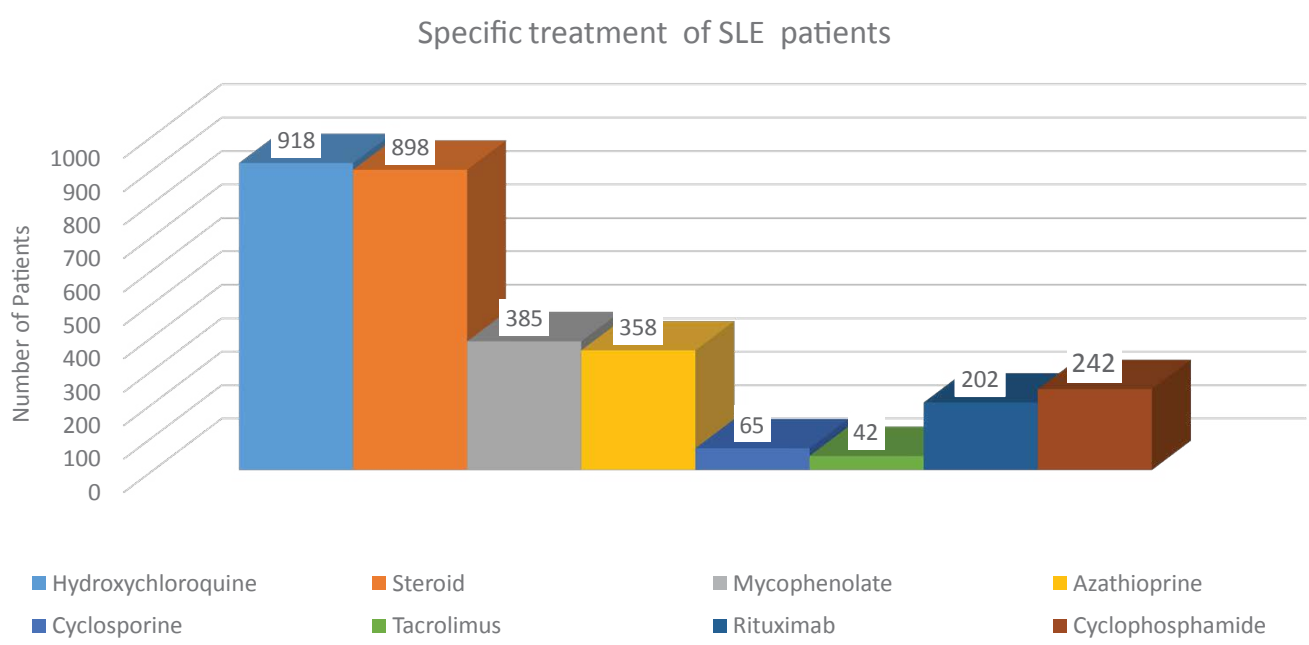

Figure 3: Specific treatment of SLE patients.

sulphate was used in 29.09% of patients whereas Allopurinol and antibiotics were rarely used (4.34% and 14%, respectively), as shown in Figure 1 and Figure 2.

Specific treatment for SLE disease including anti-malarial drug, Hydroxychloroquine was used unsurprisingly in 95% of SLE patients and Methyl prednisolone pulse was used in about 60.95% (all patients received Cyclophosphamide & Rituximab 20.91% and 15% of patient who received Mycophenolic acid (MPA) medication) while maintenance oral steroid used in 93% s shown in Figure 3.

The immunosuppressive agent of choice was Cyclophosphamide in 25.04%. MPA medication in 39.85% and azathioprine in 37.06% of patients, as shown in Figure 3.

Anti CD20 monoclonal antibodies, rituximab, was used in 20.91%, as shown in Figure 3. Calcineurin inhibitors were used in total of 11% of patients (cyclosporin a in 6.72% and tacrolimus in 4.35%), as shown Figure 3.

Discussion

This study reviews the current state of clinical practice in the management of SLE population where almost 90% were female of young fertile age. The number of effective treatments for SLE has been utilized very well among our population with traditional drugs, and new therapies have been utilized off label to better deal with SLE manifestations. The complexity of SLE presentation have led to diverse pharmacotherapeutic strategies based on the organ systems involved. Management is individualized and depends on presenting symptoms and reducing the likelihood of permanent damage to organs and tissues.

Soon after the diagnosis of SLE, this study showed that 25% were managed with cyclophosphamide, while rituximab was used in 21%, MPA in 40%, azathioprine in 37% and calcineurin in 11%. In addition, other medical management on case specific presentation were prescribed as shown in Table 1.

The role of anti-malarial (AMs) in the treatment of SLE is well-known and mounting attention has emerged in the last few decades toward these drugs. Hydroxychloroquine (HCQ) is an effective treatment in SLE, especially for arthritis and cutaneous manifestations. Furthermore, it is well tolerated and has a protective effect in reducing damage accrual in the long term and confers a survival benefit in SLE patients. A Danish registry-based cohort reported an

Table 1: Age of patients at presentation.

Age group	Number	%
0-17 years	45	4.7
18-45 years	786	81.4
46-60 years	109	11.2
More than 60 years	26	2.7

increased and an earlier use of AMs after SLE diagnosis is made resulting in prevention of damage and possibly reduction in mortality [16,17]. This is consistent with our findings were 95% of the studied population were treated with HCQ. The current guidelines recommend using long-term AMs in all patients with SLE unless contraindicated [16,18,19]. Saudi studies reported a similar finding where almost 100% of their SLE patients treated with HCQ [20,21]. Finnish nationwide register data reported that almost 73% of their patients were on HCQ [22]. AMs are also increasingly recognized as having beneficial effects beyond disease control and damage prevention, In particular it has a protective effect against thrombosis and loss of bone mass, It also improves lipid profiles and maternal outcomes during pregnancy [1,23-25]. HCQ should be considered an anchor drug in SLE because of the multiple beneficial effects of this agent. Thus, physicians may choose to continue long-term AMs for reasons beyond disease control [16,18,26].

Corticosteroid usage for SLE management started during twentieth century with good clinical responses in very ill lupus patients with major organ involvement including myocarditis and cerebritis. In the present study, corticosteroid was used in 93% of cases to decrease inflammation swiftly and allow time to introduce other treatments. Likewise, a Saudi study reported steroid utilization in 96-100% of their SLE patient [20,21,27]. However, this practice is linked with both short- and long-term adverse events with increasing of dosage and duration of steroid use [28]. Longstanding usage may prime life-limiting side effects and events and have an undesirable bearing on quality of life [29,30]. Clinicians are well trained into these adverse events and majority tend to reduce steroid dose and stop it as soon as disease control is achieved. However, a substantial percentage (almost 30%) of physician continue to keep their patient on “small” dose of steroid regardless of clinical remission especially in cases of end organ damage [26,28,31]. In fact, failure to reduce/withdraw steroids beyond prespecified endpoints can be deemed as ‘treatment failure’ in clinical trials, that are conducted across large geographical regions.

Azathioprine (AZA) is a commonly used drug for the management of various rheumatologic disorders [32]. It was introduced in mid 1950s and used for SLE management in 1960s and as a steroid sparing drug and provided a better renal outcome compared to steroid therapy [32-34]. Due to individual variation of the metabolism of AZA, serious toxic effects can result if inappropriate dose is administered [31-33]. AZA dosing according to patients thiopurine methyl transferase (TPMT) status can reduce drug-induced morbidity and can be cost effective [32]. AZA remains an important part of the SLE pharmacopeia, and it is especially useful for its safety during pregnancy, however, AZA was shown to be less effective than MMF in maintenance of

LN remission [7,25,32-34]. In the present study, it was used in the treatment of almost 37% of SLE patients .The Saudi study reported comparable findings where third of patients received AZA [27], whereas it was used in very small number of Iraqi patients [35]. A European Finnish nationwide register data reported that 15% of their patients used AZA [22], whereas AZA is often preferred in Asia due to economic constraints and because of its safety in pregnancy [7].

Cyclophosphamide (CYC) treatment in SLE was first reported in the 1960s [26,36], and the National Institutes of Health (NIH) studies subsequently confirmed efficacy especially in the treatment of lupus nephritis, leading to widespread use of the monthly i.e. treatment protocol [7,26,36]. The original NIH protocol that is characterized by high doses of CYC is widely replaced by the Euro-Lupus protocol that utilizes low-dose CYC. Researchers found that patients who are treated according to the Euro-Lupus protocol may experience a higher health-related quality of life than patients who receive the NIH treatment [5,37]. Furthermore, the low-dose protocol was associated with fewer infections and lower risk of premature gonadal failure [5,37]. After 10 years, generally good clinical responses were maintained in the low-dose group, although a decrease in the incidence of malignancies was not shown. Saudi studies reported that 34-72% of their patients were treated with CYC [20,27]. Iraqi and Egyptian studies reported that almost one third of their SLE patients received CYC [35,38]. In the present study, 25% of SLE patients were treated with CYC.

Researchers have found that MPA is an efficacious alternative to CYC for both induction and maintenance phases of SLE of non-renal and renal disease [39-46]. In the present study, MPA was utilized by almost 40% of SLE patients. An Iraqi study reported that 26% of their SLE patients were treated with MMF [35]. An Egyptian study found that IV cyclophosphamide superseded as induction treatment, while MPA was the best maintenance treatment [47]. However, other studies found that these two medications are equivalent for the treatment of renal and non-renal SLE [40-46]. As majority of our SLE patients are young fertile female, serious discussion about pregnancy must be advised, with CYC and oral CYC regimen is more toxic and should be reserved for high-risk patients [48]. Teratogenicity is significant, and counseling about pregnancy avoidance is mandatory [49].

Rituximab is a monoclonal antibody, chimeric antibody directed against CD20 on B lymphocytes, which is expressed on pre-B cells, immature, mature naïve and mature B cells but not plasma cells [4,19]. Rituximab leads to apoptosis (cell death) of all the CD20-positive B cells [19,50]. Rituximab is becoming an alternative therapy to the possibly serious toxicities of immunosuppressive agents currently in use [19,51,52]. Trials found that rituximab may improve several symptoms and signs of SLE [19,50-52]. In the present study, rituximab was utilized by almost 21% of SLE population. This off-label medicine was used in view of patient request to avoid CYC in view of fertility concerns. Clinical trials have found a promising part for rituximab in the treatment of SLE [4,50,53]. A combination of rituximab with a short-term intensive steroid treatment and low doses of intravenous cyclophosphamide may be of use as an effective therapeutic strategy to reduce the adverse events related to long-term immunosuppression [7,19,50,51,54]. However, controlled trials especially for long-term outcome studies are awaited to further define its clinical application and to improve the care of patients. Rituximab might be more efficient in Caucasians. Recent Japanese and Chinese studies have indicated a potential benefit of tacrolimus as a substitute for or in addition to CYC or MPA (dual or triple immunosuppression) [7].

The calcineurin inhibitors (CNIs) are immunosuppressive agents that block T-cell activation through the suppression of the calcium/calcimodulin-dependent phosphatase calcineurin. Agents such as cyclosporine A (CSA) and tacrolimus (TAC) are being used in organ transplantation and immunological disorders including SLE. In the present study, CSA was used by nearly 7% whereas TAC was used by almost 3% of SLE population. Similarly, Saudi SLE patients utilizes CNIs in less than 10% [20,54,55]. TAC is preferred to CSA in SLE because of the lower frequency of cosmetic, hypertensive and dyslipidemia adverse effects. Recent randomized controlled trials have demonstrated noninferiority of TAC to MPA or CYC for induction therapy of lupus nephritis. Low-dose combination of TAC and MPA has also been shown to outperform CYC pulses in inducing remission of lupus nephritis in Chinese patients. TAC does not affect fertility and is relatively safe in pregnancy that generally a good alternative option in our young SLE population, particularly in those who are intolerant or refractory to conventional immunosuppressive, or when contraindications to other immunosuppressive agents exist.

Tacrolimus may be more effective at reducing proteinuria, having potential implications for long-term outcome. A multidrug therapy including CsA and Tac may be an attractive option for young patients with SLE and lupus nephritis. Tacrolimus was found to be more effective and safer than IV CYC as an induction therapy for Chinese LN patients. Researchers suggest that low-dose CyA treatment could ameliorate the severe clinical SLE disease activity as well as improve proteinuria in Japanese patients with diffuse proliferative lupus nephritis. This treatment would be safe and useful for SLE patients with satisfactory kidney function. Combined low-dose MPA and TAC is an option for lupus nephritis that fails to respond adequately to standard regimens, with two-thirds of patients improving after 12 months.

In the present study, heparin was used in 13% and warfarin in 5% of our population. Anticoagulation therapy is well-known for its usage in life threatening preventable medical condition involving sudden occlusion of arteries [1,56]. SLE predisposes patients to both arterial and/or venous thrombosis and may occur in almost 20% of patients [57]. Thrombosis occurred as a result of the hypercoagulable state accompanying the presence of anticardiolipin antibodies [58]. Pulmonary hypertension in association with SLE may be primary or secondary to TE events and antiphospholipid syndrome, its often severe and progressive even in association with minimal disease activity and requires long-term anticoagulation therapy [59]. Anti-phospholipids condition improves with anticoagulants, corticosteroid therapy and the addition of hydroxychloroquine [1,56,60,61]. Combination of SLE and thromboembolism has a more negative influence on reported health related quality of life, compared to having SLE or APS alone [62]. Patients with APS should receive anticoagulation +/- low-dose aspirin [1,56,60,61] however in patients with APL there are conflicting data and variation in clinical practice in treatment worldwide and there are many factors to be considered . In the present study, aspirin was utilized by 21%, comparable to the findings reported in European literature [57]. Premature coronary heart disease (CHD) is a major cause of morbidity and mortality in patients with SLE where aspirin may be used [9,10]. Platelet aggregation is another problem among SLE population that leads to various cardiovascular complications throughout the human body [63-65]. Clopidogrel reduces the incidence of cardiovascular events and improved all measures of disease and overall survival [63,64], and it was used in about 3% of our patients.

SLE have a higher prevalence of clinical and subclinical atherosclerosis compared with age- and sex-matched controls. SLE patients have a higher prevalence of subclinical atherosclerosis compared with controls, with approximately 30% having evidence of subclinical involvement., and 5-6-fold increased risk of CHD, which is a major cause of morbidity and mortality [8,66,67]. Traditional cardiovascular (CVD) risk factors, including hypertension, diabetes mellitus or dyslipidemia, are more prevalent in SLE patients than in the general population, but they cannot fully account for accelerated atherosclerosis in SLE [68-70]. In fact, a number of nontraditional risk factors have been identified, including disease activity, damage and various treatments [71-73]. Preventive strategies for CHD are mandatory in SLE patients and should include giving up smoking; performing regular physical activity; managing metabolic abnormalities such as dyslipidemia, insulin resistance, and diabetes; treating persistent disease activity; and minimizing chronic exposure to corticosteroids [10]. Low-dose aspirin, ACE inhibitors/ARBs, vitamin D supplementation, and, when indicated, should also be considered. In the present study, all these factors being considered and found that the following percentages of these medication were used in SLE population, 33% for ACEI, 17% ARBs 17% for CCB, 15% B blockers, 21% for diuretics, 9% for anti-diabetic, 60% for calcium with vitamin D and 23% for antihyperlipidemic therapies.

Our study has a number of limitations. Although data were entered electronically prospectively at time of patients visit, we collected it and analyzed retrospectively. Single center study, some of the patients are managed outside the country at initial presentation so missed to include them in our analysis.

Conclusion

This is the first study to state the management in details of SLE population soon after their diagnosis. It showed that there is a good adherence to recommended guidelines for various management strategies, however, there is an off-label use of medication when clinical decision and patient centered care taken into consideration with the support of health system for such expenditure. The overall aim of management was to determine the extent of disease and prevent extensive organ involvement and deal with various traditional and non-traditional CVD risk factors. The involvement of clinical pharmacist is very important to further strengthen the pharmacological management of lupus patients.

Ethics Approval and Consent to Participate

Authors confirm compliance with animal/human ethics guidelines. The ethical clearance for the study was approved by the Medical Ethics and Scientific Research Committee at the Royal Hospital.

Consent for Publication

Not applicable.

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Authors' Contributions

All authors contributed equally to this manuscript. All authors read and approved the final manuscript.

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Competing Interests

Authors confirm compliance with animal/human ethics guidelines. The ethical clearance for the study was approved by the Medical Ethics and Scientific Research Committee at the Royal Hospital.

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