INTRODUCTION

Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disease that can affect almost all organs of the body ***(Macejová et al., 2013).*** Symptoms range from rather mild manifestations such as rash or arthritis to life-threatening end-organ manifestations ***(Postal et al., 2012).***

SLE has a relapsing-remitting course, with patients experiencing disease activity flares over time. Aiming at flare reduction, Hydroxychloroquine is the standard treatment for most SLE patients during the entire disease course and conventional immunosuppressors are given to those with severe organ involvement ***(Inês et al., 2014).***

Hydroxychloroquine is an antimalarial agent which traditionally has been used to treat muco-cutaneous, musculoskeletal, serosal and constitutional manifestations of SLE. Previous studies have shown that hydroxychloroquine usage is associated with a reduced risk of damage accrual ***(Fessler et al., 2005)*** and improved survival ***(Alarcon et al., 2007).***

Fifteen percent of patients with systemic lupus erythematosus had complete non adherence to hydroxy-chloroquine therapy, while a larger percentage of patients had only partial adherence, according to research presented at the American College of Rheumatology annual meeting ***(Petri, 2013).***

A study held in the University of California San Francisco confirmed the positive effects of HCQ on measures of disease activity and organ damage suggesting that SLE patients should be using this drug in the absence of adverse effects. HCQ's potential effects on cardiovascular risk factors including lipids, diabetes, and thrombosis and its low cost also argue that it should be a staple of SLE care ***(Schmajuk et al., 2010).***

French patients with active SLE had a lower mean blood HCQ concentration than patients with inactive SLE and, as expected, also had a lower mean C3 level and were more frequently positive for antibodies to double-stranded DNA ***(Costedoat-Chalumeau et al., 2006).***

Data from the Amsterdam Lupus Cohort showed that non-use of Anti-malarials was associated with longer disease duration, higher damage accrual and history of lupus nephritis. Despite increased awareness of the importance of antimalarial treatment in SLE, there is still room for improvement, especially in patients with lupus nephritis and/or long-standing disease ***(Tsang-A-Sjoe et al., 2013).***

Based on the previous data, and the scarce studies available regarding HCQ treatment and its relation to SLE disease activity in Egyptian patients and the middle easterns, we believe that proving the positive correlation between the

blood level of the drug, disease activity and end organ damage can encourage more physicians and rheumatologists to re-evaluate the mandatory role of hydroxychloroquine, and help raise the patients' awareness and compliance, hopefully leading to less morbidity and mortality.

AIM OF THDE STUDY

To measure blood levels of Hydroxychloroquine in a cohort of systemic lupus erythematosus patients, assess their adherence to the drug intake, and its relation to disease activity and end organ damage.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a fairly heterogeneous autoimmune disease of unknown etiology that mainly affects women in the childbearing age. SLE is a prototype type III hypersensitivity reaction in which immune complex depositions cause inflammation and tissue damage in multiple organs ***(Pieterse and van der Vlag, 2014).*** In SLE, the skin, the musculoskeletal system, the kidneys, the cardiovascular and central nervous systems can be involved ***(Kuhn et al., 2011).***

In terms of ethnicity, there is a greater incidence of SLE in the African-American, Hispanic and Asian populations ***(Bertsias et al., 2012).*** These observations lend further support that both genetic and environmental factors play a role in this disease. In view of the female to male ratio of 9:1, it is considered that the pathophysiology of SLE is influenced by hormonal factors ***(Nelson et al., 2014).***

The clinical course of SLE is characterized by periods of both active disease and remission, with manifestations ranging from mild dermatological and joint symptoms to life threatening internal organ failure and cytopenias. The diagnosis is based on clinical and laboratory findings. Lupus has no cure, up to 90% of patients require corticosteroids for

disease control and more than half of patients with lupus have permanent organ damage ***(Petri and Brodsky, 2006).***

Diagnosis of SLE

i. Clinical picture:

The common pattern is a mixture of constitutional complaints with skin, musculoskeletal, mild hematologic and serologic involvement. However, some patients have predominately hematologic, renal, or central nervous system manifestations. The pattern that dominates during the first few years of illness tends to prevail subsequently ***(Schur and Hahn, 2014).***

Constitutional manifestations

Fatigue, the most common constitutional symptom associated with SLE, can be due to active SLE, medications, lifestyle habits, concomitant fibromyalgia or affective disorders. Fatigue due to active SLE generally occurs in concert with other clinical and laboratory markers ***(Zhou and Yang, 2009).***

Fever, another common yet nonspecific symptom of SLE, may also result from many causes, the most common of which include active SLE, infection, and drug fever. Careful history taking may help to differentiate these ***(Cojocaru et al., 2011).*** Episodic fever is suggestive of active

SLE or infection; in comparison, sustained fever may reflect CNS involvement or an adverse effect to a drug ***(Zhou and Yang, 2009).***

These symptoms can mimic other autoimmune diseases, infectious diseases, endocrine abnormalities, chronic fatigue, and fibromyalgia ***(Greco et al., 2003).***

Musculoskeletal manifestations

Arthritis and arthralgia have been noted in up to 95% of patients with SLE. Involvement is usually symmetrical and polyarticular with a predilection for the knees, carpal joints, and joints of the fingers, especially the proximal interphalangeal (PIP) joints. The ankles, elbows, shoulders, hips, sacroiliac joints, and cervical spine are less frequently involved. Monoarticular arthritis is unusual and suggests an alternative cause such as infection**.** Morning stiffness is usually measured in minutes, not prolonged as in rheumatoid arthritis (RA). The degree of pain often exceeds objective physical findings. Although the arthritis of SLE is generally considered to be non deforming, flexion deformities, ulnar deviation, soft tissue laxity, and swan neck deformities-as seen in RA-have been noted in 15 to 50% of patients with SLE ***(Ostendorf, 2003).***

Tenosynovitis is a relatively common musculoskeletal manifestation ***(Grossman, 2009).***

Myalgias, muscle tenderness and muscle weakness occur in up to 70% of patients with SLE, and may be the reason that the patient initially seeks medical attention ***(Greco et al., 2003).***

Mucocutaneous manifestations

Skin involvement in SLE is seen in 75-85% of patients, which can be presented in an acute fashion such as the malar rash or other photosensitive rash, or chronic fashion such as discoid lupus ***(Arai and Katsuoka, 2009).***

Acute Cutaneous Lupus Erythromatosus (ACLE) is characterized by erythema over the malar eminences of the face and bridge of the nose (butterfly rash). The nasolabial folds are typically spared. The clinical activity of ACLE typically cycles in parallel with the activity of the underlying SLE ***(Werth, 2005).***

Subacute Cutaneous Lupus Erythromatosus (SCLE) is defined as erythematous, symmetrical, non scarring, non indurated lesion on the upper trunk, extensor forearm, and dorsal surfaces of the hands ***(Schur and Moschella, 2014).***

Chronic cutaneous Lupus Erythromatosus (CCLE) may be in the form of :

- Discoid lupus erythematosus which presents as one or more photodistributed scaling erythematous papules and/or

plaques surrounded by an adherent scale extending into patulous follicular orifices. Typically involvement is confined to head and neck with a predilection for periorbital areas and ears ***(Crowson and Magro, 2009).***

- Hypertrophic lupus erythematosus which are hypertrophic lesions or wart like lesions, or other rare subtypes like palmer-planter lupus erythematosus ***(Arai and Katsuoka, 2009).***

Less frequent SLE skin lesions include urticaria, bullae, erythema multiform, lichen planus-like lesions, and panniculitis (lupus profundus) ***(Ramos-Casals et al., 2006).***

Photosensitivity: More than 50% of SLE patients demonstrate photosenstivity. The lesions of LE-specific or LE-non-specific skin disease may be induced or exacerbated by UVR. In addition to the skin reaction, patients may develop exacerbations of their systemic disease also when exposed to UVR ***(Vasudevan and Ginzler, 2010).***

Mucosal Ulcerations: Small and painless ulcers on the oral or nasal mucosa are common in SLE; the lesions resemble aphthous ulcers ***(Hahn, 2010).*** They may be painful if there is secondary infection ***(Patel and Werth, 2002).***

Alopecia: Hair loss occurs in a majority of patients with SLE at some time during their illness. In some cases,

it can precede other manifestations of lupus. Lupus alopecia may involve the scalp, eyebrows, eyelashes, beard, and/or body hair ***(Schur and Moschella, 2014).***

Raynaud's phenomenon is a frequent problem in SLE that is characterized by color changes in the fingers in response to cold ***(Cervera et al., 2003).***

Livedo reticularis is common in SLE patients during activity. It occurs more commonly in association with anticardiolipin antibodies and is thought to be due to vasospasm of the dermal ascending vessels leading to reddish cyanotic reticular rash on lower and upper limbs ***(Edworthy, 2005).***

Renal manifestations

Lupus nephritis (LN) is one of the most serious manifestations, and contributes significantly to mortality. It occurs in 30-50% of SLE patients during their disease course ***(Ortega et al., 2010).*** LN presents as proteinuria (or an otherwise abnormal urine analysis), hypertension, or a rising serum creatinine level, all of variable degree. In its early stage lupus nephritis is painless and asymptomatic. In more advanced stages, edema, anemia, symptomatic hypertension, and symptomatic uremia occur. Patients with inflammatory forms of nephritis are usually hypocomplementemic; most have high levels of anti-DNA or anti-Sm antibody ***(Weening et al., 2004).***

However, persistent proteinuria may not necessarily indicate ongoing inflammation in the kidneys and may be due to pre-existing chronic lesions. Renal biopsy is the gold standard for providing information on the histological classes of lupus nephritis and the relative degree of activity and chronicity in the glomeruli ***(Mok, 2010).***

Histological patterns of LN have been classified by the World Health Organization and more recently by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) **(Table 1)**. These histological patterns are predictive of prognosis and provide a basis for treatment guidelines to prevent end-organ damage and improve mortality and morbidity ***(Toong et al., 2011).***

Table (1): ISN/RPS 2003 classification of lupus nephritis.

Class I	Normal glomeruli by light microscopy, but mesangial immune deposits by Immuno-fluorescence
Class II	**Mesangial proliferative lupus nephritis** Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits. May be a few isolated subepithelial or subendothelial deposits visible by immuno-fluorescence or electron microscopy, but not by light microscopy.
Class III	**Focal lupus nephritis** Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	**Diffuse lupus nephritis** Active or inactive diffuse, segmental or global endo- or extracapillary glomerulo-nephritis involving≥50 % of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental(IV-S) lupus nephritis when≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis

Table (1): Continued

Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
Class IV-G (A/C)	Active and chronic lesions: diffuse global proliferative and sclerosing nephritis.
Class IV-S (C)	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V	**Membranous lupus nephritis** Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed. Class V lupus nephritis show advanced sclerosis
Class VI	**Advanced sclerosis lupus nephritis** ≥90% of glomeruli globally sclerosed without residual activity

(Adapted from Weening et al., 2004)

Haematologic manifestations

Anemia is observed in half of all SLE cases and could be due to multiple causes such as chronic disease, iron deficiency, chronic renal impairment, drug-induced myelotoxicity, and also autoimmune hemolytic anemia. This latter condition is described in 5-10% of SLE cases ***(Domiciano and Shinjo, 2010).***

Leukopenia is common in SLE and may reflect disease activity. Leukopenia is such a regular feature of SLE that its absence should raise the suspicion that the diagnosis is incorrect. Usually lymphocyte counts show greater reductions than do granulocyte counts ***(Mackay et al., 2004).*** Functional defects of neutrophils have also been noted ***(Schur and Berliner, 2014).***

Thrombocytopenia; About, 20% to 25% of patients with SLE have platelet counts less than 100 x 10^9/L. It is rarely severe, with less than 10% with platelet counts of less than 30 x 10^9/L ***(Arkfeld and Weitz, 2009).***

Serosal manifestations

Pleuritic pain occurs in most patients with lupus. It is often distressing and may be prolonged, occasionally necessitating pleurectomy. Although many patients present with painless pleural effusions, frequent findings include fever, pleural rub and tachycardia ***(Bouros and Vassilakis, 2008).***

Pericardial involvement is the most common echocardiographic lesion in SLE, and is the most frequent cause of symptomatic cardiac disease ***(Doria et al., 2005).***

One autopsy study found that 60%-70% of SLE patients had evidence of peritonitis, whereas only around 10% of them were recognized clinically ***(Takeno and Ishigatsubo, 2006).***

Cardiac manifestations

Clinical cardiac involvement is relatively common in SLE, developing in 50% of patients during the course of illness ***(Goodson and Solomon, 2006).*** The reason why patients with SLE have a higher cardiovascular mortality and morbidity seems to be related to the presence of an accelerated atherosclerotic process, which seems to be due to a complex interplay of traditional and lupus-specific risk factors ***(Croca and Rahman, 2012).***

Verrucous (libman-sacks) endocarditis is usually clinically silent in SLE, but can produce valvular insufficiency and serve as a source of emboli ***(DeLeeuw et al., 2006).*** Lesions occur primarily on the mitral valve but also occur on aortic valve, and rarely on the pulmonary or tricuspid valves. Symptomatic valve disease may be more common in patients with antiphospholipid antibodies ***(Roman et al., 2003).***

Myocarditis is an uncommon, often asymptomatic manifestation of SLE with a prevalence of 8 to 25% in different studies. Global hypokinesis may be an echocardiographic indication of myocarditis and is present in approximately 6% of patients with SLE ***(Schur and Costenbader, 2014).***

Pulmonary manifestations

Pulmonary manifestations may be the presenting symptoms in 5% of patients and lungs are involved in