EFFICACY OF HYDROXYCHLOROQUINE IN SYSTEMIC LUPUS ERYTHEMATOSUS WITH HEMATOLOGICAL INVOLVEMENT.

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Abstract

Introduction: Systemic Lupus Erythematosus is an autoimmune disease with systemic multiorgan involvement that requires continuous follow-up to control the clinical course of the disease. Based on the current problems in our country, this paper aims to highlight the role of Hydroxychloroquine as a highly effective immunosuppressive therapy in the treatment of SLE and the hematological complications that are caused.

Objectives: The aim of this study is to evaluate the effectiveness of Hydroxychloroquine in the treatment of patients with Hematological involvement. Determination of the treatment protocol based on clinical signs and current evidence according to the Eular system. Evaluation of comorbidities from Hydroxychloroquine therapy and combination therapy with Immunosuppressants such as Methotrexate, Azitropine, Mycophenolate and Corticosteroids.

Materials and methods: For the realization of this work, real data obtained from a contigent (group) of 120 cases (patients) hospitalized at the Rheumatology ward at the "Mother Teresa" University Hospital in Tirana. At the same time, cases presented at the Consultation Center at the QSUT in Tirana during the time period April 2021-April 2024 were also used. The data were processed according to the SPSS statistical program.

Study results: From the data of our study it results that in 89% of cases the patients are female, the average age of the patients is 45.2±10.2 years of patients with SLE. Based on the study of the laboratory characteristics of SLE patients with Hematological involvement we have the presence of Anemia, Chronic Anemia has appeared in 72% of the patients, that from Fe deficiency in 46.6% of the patients who have developed anemia and AIHA in 7% of them. PRCA resulted positive in 7 clinical cases, 19 patients have developed leukopenia and 50 patients developed thrombocytopenia. Description of the results of the study regarding to the effectiveness of therapy in patients with SLE resulted that the use of hydroxychloroquine as a single and combined therapy reduces the activity of the disease in 78% of cases by inhibiting clinical signs and improving the course of the disease.

Conclusions: Based on the results of our study, the importance of monitoring the clinical course of patients in time is highlighted, enabling the combination of therapy in the initial phase of disease treatment and maintenance therapy.Hydroxychloroquines resulted in effective therapy both alone and in combination in the treatment of SLE patients with hematological involvement.

Keywords: Systemic Lupus Erythematosus, Hematological involvement, Hydroxychloroquines, Effectiveness.

EFIKASITETI I HYDROXYCHLOROQUINES NË LUPUS ERITEMATOZ SISTEMIK ME PREKJE HEMATOLOGJIKE.

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Abstrakt

Hyrje: Lupusi Eritematoz Sistemik është një sëmundje autoimune me prekje sistemike multiorganore i cili kërkon një ndjekje të vazhdueshme për të mbajtur në kontroll dekursin klinik të sëmundjes.

Bazuar në problematikën aktuale në vëndin tonë ky punim synon të evidentojë rolin e Hydroksiklorikinës si terapi imunosupresore me efektshmëri të lartë në trajtimin e LES dhe komplikacioneve me natyrë Hematolgjike që shkaktohen.

Objektiva: Qëllimi i këtij studimi është vlerësimi i efektshmërisë së Hydroxychloroquinës në trajtimin e pacientëve me prekje Hematologjike. Përcaktimi i protokollit të trajtimit bazuar në shenjat klinike dhe evidencat aktuale sipas sistemit të Eularit. Vlerësimi i komobirditeteve nga terapia me Hidroksiklorikinë dhe terapia e kombinuar me Imunosupresorë si Metotrexate, Azitriopinë, Mycofenolate dhe Kortikosteroidë.

Metodologji: Për realizimin e këtij punimi u përdorën të dhëna reale të marra nga një kontigjent (grup) prej 120 rastesh (pacientësh) të shtruar pranë pavionit të Reumatologjisë në Spitalin Universitar "Nënë Tereza" në Tiranë. Në të njëjtën kohë, u shfrytëzuan edhe rastet e paraqitura në Qëndrën e Konsultave në QSUT në Tiranë gjatë periudhës kohore në periudhën Prill 2021-Prill 2024.Të dhënat u përpunuan sipas programit statistikor SPSS.

Rezultatet e studimit: Nga të dhënat e studimit tonë rezulton se në 89% të rasteve pacientët janë femra, mosha mesatare e pacientëve është 45.2±10.2 vjec të pacientëve me LES. Në bazë të studimit të karakteristikave laboratorike të pacientëve LES me prekje Hematologjike kemi prani të Anemisë, Anemia kronike është shfaqur në 72% të pacientëve, ajo nga mungesa e Fe në 46.6% të pacientëve që kanë zhvilluar anemi dhe AIHA në 7% të tyre. PRCA rezultoi pozitive në 7 raste klinike, 19 pacientë kanë zhvilluar leukopeni dhe 50 pacientë zhvilluan trombocitopeni. Përshkrimi i rezultateve të studimit lidhur me efektshmërinë e terapisë në pacientët me LE rezultoi që përdorimi i hidroksiklorikinës si terapi e vetme dhe e kombinuar ul aktivitetin e sëmundjes në 78% të rasteve duke frenuar shenjat klinike dhe duke përmirësuar ecurinë e sëmundjes.

Konkluzione: Në bazë të rezultateve të studimit tonë evidentohet rëndësia e ndiekjes së dekursit klinik të pacientëve në kohë duke mundësuar kombinimin e terapisë në fazën fillestare të trajtimit të sëmundjes dhe terapisë mbajtëse. Plaquenili rezultoi terapi e efektshme qoftë e vetme dhe e kombinuar në trajtimin e pacientëve LES me prekje hematologjike.

Fjalë kyce: Lupus Eritematoz Sistemik, prekje Hematologjike, Hydroxychloroquines, Efektshmëri.

Introduction

Hydroxychloroquine (HCQ) is an antimalarial drug originally used for the treatment of Plasmodium parasitic infection, from which the drug class derives its name. (1,6,8)

Beyond its initial indication as an antimalarial, HCQ has been used in autoimmune and infectious diseases, as well as in metabolic or neoplastic disorders. Based on recent studies, clear benefits were reported mainly in Systemic Lupus Erythematosus (SLE). Our article focuses on the value of

the drug in SLE patients with hematological involvement.

Objectives

The aim of this study is to evaluate the effectiveness of Hydroxychloroquine in the treatment of patients with Hematological involvement. Determination of the treatment protocol based on clinical signs and current evidence according to the Eular system. Evaluation of comorbidities from Hydroxychloroquine therapy and combination therapy with Immunosuppressants such as Methotrexate, Azitropine, Mycophenolate and Corticosteroids.

Materials and methods

Real data obtained from a contigent (group) of 120 cases (patients) admitted near the Rheumatology ward at the "Mother Teresa" University Hospital in Tirana were used for the realization of this paper. At the same time, the cases presented at the Consultation Center at the QSUT in Tirana during the period April 2021-April 2024 were used. The data were processed according to the SPSS 2022 statistical program. Based on the clinical evidence, it was possible to evaluate the clinical signs of the patients according to the SLEDAI model.

SLEDAI Assessment (5)

The SLEDAI assessment was performed for each patient to enable the generalization of as much real data as possible regarding the course of the disease, its management and the combination of therapy based on clinical and laboratory data. (Below is the type card, the data of which were used to carry out the statistical processing of the paper.)

Table nr 1 The SLEDAI type card that was used in our study.

Elements	Description	Points
Convulsions	Immediate onset, without metabolic, infectious or drug-related causes	**8**
Psychosis	Inability to reason and perceive the real surrounding environment; including hallucinations, associative disorders, illogical thinking, and catatonic or strange behavior, certainly in the absence of uremia or medications.	**8**
Organic brain damage syndrome	Alteration of mental function characterized by poor memory, clouding of consciousness accompanied by loss of ability to concentrate and react to the surrounding environment plus at least two of the following elements: loss of continuity of thought, incoherent speech, insomnia at night or being sleepy during the day, and increased or decreased psychomotor activity, in the absence of infectious, metabolic, or drug causes	**8**
Visual	Retinal changes due to LES deposits accompanied by retinal hemorrhage, serous or hemorrhagic choroid exudate, otic neuritis (in the absence of infectious, drug-related, or HTN causes)	**8**
Cranial nerve	Sudden onset of a sensory or motor neuropathy	**8**

	involving the cranial nerves	
Headache	Headache in lupus is persistent, severe; may be migraine-like in nature and does not respond to analgesics.	**8**
AVC	Immediate onset; rule out atherosclerosis	**8**
Vaskulitis	Ulcerations, gangrene, soft nodules on fingers, periungual infarctions, subungual hemorrhage, vasculitis confirmed by biopsy or angiogram	**8**
Arthritis	Affection of more than two joints with inflammatory pain accompanied by swelling	**4**
Myositis	Muscle pain associated with weakness of the extremities and increased levels of aldolase/creatine phosphokinase; electromyographic changes on EMG; myositis on biopsy	**4**
Crust	Containing blood, granules, or erythrocytes	**4**
Haematuria	> 5 erythrocytes per field in complete urine (exclude causes of kidney stones)	**4**
Proteinuria	> 0.5 g in 24-hour urine	**4**
Pyuria	> 5 leukocytes per field (exclude infectious causes)	**4**
Molar rash	Sudden onset of a rash of an inflammatory nature	**4**
Alopecia	Abnormal diffuse hair loss	**4**
Mukosis of nose/mouth	Appearance of ulcerative phenomena in the mouth or nose	**4**
Pleuritis	Chest pain accompanied by pleural effusion and pleural thickening	**4**
Pericarditis	Chest pain accompanied by pericardial effusion, confirmed by ultrasound and ECG	**4**
Hipokomplementemia	Decreased levels of C3 or C4	**2**
Increase DNA binding capacity	> 25% evidenced in laboratory techniques	**2**
Temperature	> 38 ˚C in the absence of infectious causes	**1**
Thrombocitopeny	< 100,000 platelets	**1**
Leukopeny	**< 3000/mm 3 (exclude drug causes)**	**1**

Study results

Of the 120 patients included in this study, 107 (89%) individuals were female versus 13 (11%) male subjects. Overall, the mean age of the patients included in the study was 45.2 years and there was a significant difference in the mean age value according to the gender of the patients (in males, the mean age was: 56.2 years, while in females the mean age was: 39.5 years).

The mean age of male patients was 63.7±11.2 years, while the mean age of female patients was 45.3±14.5 years.

There was evidence of a statistically significant difference in the mean age value by gender: thus, the mean age value was significantly higher in males compared to females (Student's T-test: P<0.001; a similar result was obtained by the Mann-Whitney test: P<0.001).

Table nr 2. Age distribution among patients in the study

Ages		**Number**	**Percentage**
Valid	<=17	1	1.2
	18-25	18	15
	26-35	34	28.3
	36-45	13	10.8
	46-55	37	30.8
	56-65	15	12.5
	66-75	2	2.4
Total		120	100.0

As can be seen from the results of the study, the highest frequency of cases belongs to the age group 46-55 years, 30.8%, followed by 26-35 with 28.3% patients. In a clinical surveillance based on the factors that trigger the outbreak of SLE, these age groups have the highest incidence of cases.

The average age in women is lower than in male patients and this is also due to the greater prevalence of autoimmune diseases affecting the female gender. (2)
Compared to current studies, LES appears in female patients more than males. Even in our study, the largest number of cases is in female patients 89% females. (3)
The clinical signs of the patients included in the study are presented in the table below.

Table 3. Clinical manifestation:

Clinical manifestation	Raste në %	Clinical manifestation	Raste në %
Joint pain	**72%**	**Temperature**	**15%**
Leukopenia	**48%**	**LE cutaneous**	**11%**
Butterfly rash	**43%**	**Renal disfunction**	**10%**
Alopecia	**36%**	**'Le Diskoid' lesions**	**8%**
Oral ulcerations	**27%**	**Seizuritis**	**5%**
Lupus nephritis	**22%**	**Phericarditis**	**5%**
Pleural effusion /perikardial	**16%**	**Autoimun hemolysis**	**4%**
Thrombocytopenia	**36%**	**Psychosis**	**2%**

The clinic of LES begins with fatigue, body weakness, temperature, fever of an unknown nature,

then the clinical signs become more evident and correlate with the diagnosis. (1,2)Thus, in our study, the most pronounced and general clinical manifestations are joint pain, leukopenia, butterfly rush, oral ulcerations, nephritis etc. As can be seen from the percentage of cases, the patients' clinic is diverse, with a combination of one or more clinical signs.This will be more explained in the material discussion.
SLE presents a diverse clinical course where clinical manifestations can orient from the beginning towards the diagnosis and on the other hand some independent clinics develop as an early sign of SLE. Based on contemporary literature (2) but also the results of the study we have treated the number of cases for each symptom that our patients have referred, which are presented below:
Systemic lupus erythematosus as a multiorgan disease exhibits extensive clinical symptomatology even in the cases taken into the study. Below are presented the secondary clinical signs that were identified in our work, not with a high frequency but are in line with the studies conducted for this diagnosis.

Table nr 4 presents cases of the appearance of clinical symptoms in a broader spectrum of the disease and extended over time.

The system where clinical signs developed	Symptoms	Nr of cases	Cumulative %
Gastrointestinal	Dysfagia	9	7.5
Oral	Ulcerations of oral mucosa	13	10.8
Respirator	Dyspnea	15	12.5
Neurologic	Numbness of the hands	22	18.3
Haematologic	Pale face, fatigue	35	29
Digities	Puffy finger	13	10.8

Hematological manifestations in systemic lupus erythematosus
They are frequently encountered in the clinic and range from mild to severe. Therefore, treatment approaches are needed; biologic drug therapy has shown good results in improving hematological parameters but further studies are needed on the management modalities with Hydroxychloroquine. (3,4,6)
The most prominent hematological manifestations of SLE in our study population are anemia, leukopenia, thrombocytopenia. The bone marrow (BM) is also considered a target organ in SLE and features such as myelofibrosis, aplastic anemia, and pure red cell aplasia. Thus, we will briefly review the pathogenesis and management of specific hematological manifestations in the patients studied. (4)

Anemia Anemia is common, affecting more than 50% of patients throughout the clinical course. Anemia is defined as a hemoglobin level of less than 12 g/dl in women and 13.5 g/dl in men. In patients with SLE, it may be immunological or non-immunological.

Chronic anemia is the most common type of anemia in SLE patients studied, present in 2/3 of cases or 72%. It usually presents as normocytic and normochromic anemia, with normal or elevated serum ferritin values and a normal BM. The etiology of chronic anemia in Systemic Lupus Erythematosus is not yet fully understood, but it appears to be related to alterations in iron homeostasis, inadequate erythropoietin response or activity, and impaired erythropoiesis.

Iron deficiency anemia, in our study population, low blood Fe levels are common in patients with SLE, affecting about g78 patients with anemia or 46.6% of SLE patients. Based on the clinical history of the patients and the questionnaire developed for the clinical course over time, iron deficiency anemia is associated with chronic gastrointestinal bleeding as a complication in those patients who have been treated with nonsteroidal anti-inflammatory drugs and glucocorticoids.

Autoimmune hemolytic anemia (AIHA) Hemolytic anemia with reticulocytosis is included in both the ACR and SLICC. Autoimmune hemolytic anemia (AIHA) is caused by antibodies that damage red blood cells (RBCs) in a complement-dependent or complement-independent manner. AIHA may be the first manifestation of SLE and may occur several years before the diagnosis of SLE is made. Also in our case, in 7 patients out of 12 cases of SLE-related AIHA, anemia had begun before the patient was diagnosed with SLE. Its prevalence varies, probably due to the different diagnostic criteria for AIHA. Patients who presented with anemia before the diagnosis of SLE had severe hemolytic anemia (defined by hemoglobin <8.0 g/dl, in the presence of a positive direct antiglobulin test (DAT), an increased reticulocyte count, and a decrease in hemoglobin by 3.0 g/dl within a 1-week period (2 patients who confirmed it through hospitalization medical records, increased conjugated bilirubin and reticulocyte count >5%) was identified in 4 (%) patients.

Pure red cell aplasia (PRCA) Characterized by normocytic normochromic anemia and reticulocytopenia, with severe aplasia or hypoplasia of the red cell lineage, while the leukocyte and megakaryocyte lineages in the BM remain normal. In most cases, PRCA is diagnosed simultaneously with or shortly after the diagnosis of SLE. The pathogenesis of PRCA is diverse and includes genetic defects affecting the erythropoietic lineage, viral infections (such as parvovirus B19), and autoimmune factors. Aplastic anemia is characterized by pancytopenia with a low reticulocyte count. It is rare in SLE, with only 10 cases reported.

Leukopenia In the study population, it turns out that we have 19 cases with leukopenia, with values at levels <4000/mm3 and lymphopenia at levels <1500/mm3 in at least 12 cases. Similarly, in the SLICC classification criteria, leukopenia (<4000/mm3 in at least 5 cases) and lymphopenia (<1000/mm3 at least 2 times) are also part of the classification criteria for SLE with hematological involvement.

Immune thrombocytopenia in SLE Immune thrombocytopenia is an immune-mediated disorder that presents as primary (P-ITP) characterized by isolated thrombocytopenia. Immune thrombocytopenia in SLE is a common clinical manifestation, defined by a platelet count <100x109/mm3 with no other identifiable cause. In our study, 50 of 120 patients had thrombocytopenia. Of these 50 patients, 54% had platelet counts between 50 and 100 x 109/mm3, 18% had counts between 20 and 50 x 109/mm3, and 28% had platelet counts less than 20x109/mm3.
Antiplatelet autoantibodies are present in up to 60% of patients with SLE, the majority of which are IgG (60%) (23% are IgM). In P-ITP, the antigens for antiplatelet antibodies are glycoprotein IIb/IIIa (GpIIb/IIIa) and membrane glycoprotein (αIIaβ3integrin), and they can also be seen in patients with SLE. SLE patients with thrombocytopenia are more often positive for lupus anticoagulant, and higher levels of IgM ACA have been associated with a possible role of aPL in its pathogenesis.

Table nr 5. Thrombocytopenia in SLE patients

	Nr of cases	**Nr of cases in %**
Positive thrombocytopenia	50	41.6
Negative thrombocytopenia	70	58.4
Total	120	100%

Nr of thrombocytes	**Nr of cases in %**	**Nr of cases**
50 to 100 x 109 /mm3,	54	27
20 to 50 x 109 /mm3	18	9
Less than 20x109 /mm3	28	14
Total	100%	50

Imunological Examinations

The patients performed a series of laboratory examinations such as complete blood, leukocyte formula, PCR, FR, etc., in which the findings were identified, but because they are not the focus of our study, we did not stop to analyze and interpret them. Valuable examinations in the diagnosis of SLE are immunological analyzes ANA, Anti ds DNA, CD3, CD4, ENA. (16)

They are the most valuable diagnostic mediators to determine the aggressiveness and course of the disease from diagnosis, to follow-up and provide an indication regarding the benefits of drug therapy. In the patients studied, the reference examinations on which we are based are ANA, Anti ds DNA, CD3, CD4, ENA. (17)

Thus, according to clinical evidence, except the medical records, laboratory examinations ANA were performed as an examination from 120 patients, from which it resulted positive in 98 patients, negative in 22 patients.

Anti ds DNA, the DNA antibody, is the second immunological parameter taken in the study. As an examination, it has value in following the progress of SLE, but Anti ds DNA does not always provide information on the activity of the disease, so a negative Anti ds DNA does not exclude Lupus.(17)

Based on the data of our examination, 110 patients underwent the examination, from which 86 patients resulted positive and 24 patients negative. There is a correlation between contemporary literature and the scientific evidence of the study.

The ENA assessment was performed in 109 patients in total out of 120 patients included in the study, from which it resulted positive in 78 cases and 31 cases ENA resulted negative according to the data of the patient cards included in the study. The lack of assessment of this parameter in 100% of the population included in the study is multifactorial and is open to discussion.

The assessment of monoclonal antibodies CD3, CD4 in the patients included in the study resulted in a positive result in 72% of cases 86 patients, where C3 is presented with increased values in 22 patients, C4 It is important to evaluate the antibodies as it helps in the scientific evidence on the correlation of the positive results of the immunological examinations and the progress of the disease. is presented with increased values in 18 patients.

Treatment and complications in midterm and long term usage of medications

In patients included in the study, the treatment protocols were applied according to the latest EULAR guidelines. The focus of the study is the use of hydroxychloroquine and its effectiveness in inhibiting the clinical course of SLE. A careful assessment has been made for each patient and

special treatment protocols have been drawn up. It is understood that difficulties have been encountered in the periodic follow-up of patients as a result of not appearing in the hospital, not performing specific examinations which hinder to some extent the accurate interpretation of the data.(7,8)
Medical therapy applied in SLE patients with Hydroxychloroquine as a single therapy and its combination with Immunosuppressants such as Methotrexate, Mycophenolate, Azathioprine and Corticosteroids Prednisone and Medrol. (3,7)

Table nr 6. Description of therapy

Therapy	Patients number
Plaquenil 200 mg	12
Plaquenil 200 mg + Prednisone 5 mg	30
Plaquenil 200 mg + Mycophenolate 500 mg+ Medrol 4 mg	12
Plaquenil 200 mg+ Medrol 4 mg	21
Plaquenil 200 mg + Azatiopinë 50mg+ Prednisone 5 mg	23
Plaquenil 200 mg+ Azatiopinë 50 mg + Medrol 4 mg	14
Prednisone 5 mg / Medrol 4 mg	8

The combination therapy was adapted based on the clinical and laboratory evidence of the patients, the international treatment protocols according to Eular and the assessment of disease activity using the SLEDAI index. In general, during the period under study, the treatment was started in low doses and remained under control; in patients who have shown a lack of response to therapy, the dose of the drug has been increased or we have combined medications with the aim of activating the inhibition mechanisms.
In addition, the treatment was carried out under medical surveillance through laboratory examinations (complete blood) in cases where we encountered thrombocytopenia, leukopenia or unjustified forms of anemia.Table nr 7 summarizes the causative mechanisms that have induced hematological abnormalities affecting RBC in the patients studied.

Table nr 7. Anemia in LES

RBC ALTERATIONS IN SLE PATIENTS
Causes of anemia

• **Chronic anemia**
• **Low blood iron levels**
  ○ **Blood loss (GI, menorrhagia)**
  ○ **Decreased absorption of Fe in the intestines**
• **Autoimmune hemolytic anemia**
• **Microangiopathic hemolytic anemia**
• **Red blood cell aplasia**
• **Shkaqe të tjera të anemisë**
  ○ **Nutritional deficiencies (Vitamin B12, Folate)**
  ○ **Other immune blood disorders (Pernicious anemia)**
  ○ **Iatrogenic ASA,CYC**
  ○ **Anemia in pancytopenia associated with disorders: Myelofibrosis, Thrombotic thrombocytopenic purpura**

In this spectrum of hematological changes affecting the Leukocyte formula, the treatment protocol

implemented in patients is presented in

Table 8:

Treatment of Anaemia		
Treatment	Indications	Discussion
Glucocorticosteroids	First-line therapy Dose: 1mg/kg/day	□ After 3 weeks of treatment □ Prednisone > 15 mg/day □ >0.1mg/kg/day prednisone equivalent to maintenance therapy
AZAs	To promote the remission phase	We have no evidence in AIHA.
CSAs	To induce remission in refractory cases. Discontinuation may be difficult.	Evidence in refractory AIHA, Immune thrombocytopenia and Evans syndrome.
CYC	Për të nxitur remisionin në rastet refraktare	In patients who underwent high-dose CYC treatment in AIHA: □ All became transfusion independent. □ 2/3 of patients went into complete remission (5P-AIHA and 1 S-AIHA).
CNIs	Possible adjunctive treatment when other drugs are considered with pronounced toxicity.	Immediate benefit in 1/3 of patients with AIHA. Regarding the response: □ Hepatomegaly. □ Low pre-treatment Hb (6-7g/dl).
Hydrpchlorciquine	Sporadic adjunctive use as first line of treatment	17 patients (10 with antibody positive AIHA, 5 who responded well to prednisone and 2 with refractory AIHA): □ Better responses. □ Successful as maintenance therapy.
Plasma transfusion	Pre-transfusion use of RBCs without benefit.	19 patients underwent a total of 38 plasma transfusion sessions: □ There was no significant increase in Hb in patients who received plasma before red blood cell transfusion
Mycophenolate	Induces the remission phase	□ 13 patients had >1.5 g/dL increase in Hb and >50% reduction in reticulocyte count. Leukocyte cell changes in patients with systemic lupus erythematosus. □ 2 patients who did not respond had AIHA with positive IgG autoantibodies.

Table nr 9 summarizes the changes in leukocytes in SLE patients with hematological involvement.

Changes in leukocyte formula in SLE patients
Factors that cause leukopenia ▪ Neutropenia **Immune mediators** **Infections** **Iatrogenic (AZA, CYC)** ▪ Lymphopenia **Immune mediators** **Viral infections** **Iatrogenic**
Factors that cause leukocytosis ▪ **Infections** ▪ **Disease activity** ▪ **Iatrogenic (Use of IG)**

Table nr 10 presents the treatment for cases with thrombocytopenia in the setting of SLE.

Treatment	Indications	Discussions
GC	First line therapy	□ Response to treatment begins within 1-8 weeks. □ No efficacy in long-term use High-dose dexamethasone, per os (40 mg/day for 4 days x 4-8 cycles at 2-4 week intervals). Prednisone (starting at 0.5- 1 mg/kg/day) may be used, Dexamethasone responds better as long-term maintenance therapy. Methylprednisolone presents an increased risk of avascular necrosis. No benefit compared with high-dose oral GCs.
HCQ	Combined with GCs when the effectiveness of first-line treatment is reduced	Variable dosage depending on the progress. 16 patients: • Initially treated with 200 mg/day and then the dose was increased by 200 mg every four weeks. • All patients had a good response within the first two months. • At a mean follow-up of 18.2 months, the medication was reduced to 200 mg/day without relapse.

		6 patients intolerant to GCs were successfully treated with: • High initial dose (800 mg/day for 8 weeks). • Lower dose as maintenance therapy (ranging from 200 to 600 mg/day). Hydrochlorothiazide cannot be discontinued without relapse. Hydrochlorothiazide is safe and well tolerated. • Can be used during pregnancy
HCQ		Increased and sustained response rate.
CYC	Relapsed immune thrombocytopenia	10-15 mg/kg CYC intravenously, every month for at least 4 months: □ Platelet count increases within 2-18 weeks. □ High response rate to therapy. □ Long-term therapy rarely applied Concerns about adverse effects led to the proposal of a new regimen: □ Administered dose 500 mg, every two weeks for 3 months. □ Followed by MMF or AZA, improves drug tolerability without loss of efficacy.
MCI	Relapsed immune thrombocytopenia.	Limits steroid use Use as maintenance therapy
AZA	Limits the use of steroids	Përdorim si terapi mbajtëse
CSA	Chronic immune thrombocytopenia. Limits steroid use	Risk of nephrotoxicity □ Administration at lower doses has been used successfully. □ Serious side effects: neuropathy and bone pain.
IVIg	Preferred if a rapid increase in platelet count is needed due to: • Active bleeding. • Emergency surgery.	Initial dose: 400 mg/kg per day for 5 consecutive days. Maintenance: 400 mg/kg per month Intermittent or continuous. There was insufficient evidence to analyze long-term response
Biologics preparates	Chronic thrombocytopenia.	Significantly reduces antiplatelet antibodies, especially the IgG isotype. Preferred over splenectomy because it is beneficial for other manifestations of SLE.
IL-11	life-threatening chronic thrombocytopenia	Case report of a patient with intrabronchial hemorrhage refractory to IVig, high-dose GCS,

		CYC and plasma exchange. Response to IL-11 during a 5-day administration, reaching a platelet count of 50x109 /mm3

Based on the treatment scheme according to the categories of clinical manifestation of SLE with hematological involvement in a 3-month follow-up plan, improvements in laboratory blood values, inhibition of the progression of the disease, and successful treatment of cases identified in the initial stages of the disease were seen in the patients included in the treatment.

Material discussion

Of the 120 patients included in this study, 107 (89%) individuals were female versus 13 (11%) male subjects. Overall, the mean age of the patients included in the study was 45.2 years and there was a significant difference in the mean age value according to the gender of the patients (in males, the mean age was: 56.2 years, while in females the mean age was: 39.5 years). Referring to contemporary literature, there is a statistical significance between gender and autoimmune diseases such as SLE, which is most in females it is more developed in women as a result of genetic predisposition, lifestyle, stress, exposure to factors that promote se, autoimmune disorders.(3)

The clinic of LES begins with fatigue, body weakness, temperature, fever of an unknown nature, then the clinical signs become more evident and correlate with the diagnosis. (13,14,15) Thus, in our study, the most pronounced and general clinical manifestations are joint pain, leukopenia, butterfly rush, oral ulcerations, nephritis etc. SLE makes a combination of clinical signs, being a systemic disease, so patients have seen more than a few characteristic elements of the SLE clinic.As can be seen from the percentage of cases, the patients' clinic is diverse, with multiorgan effects that require a combination of objective and imaging examinations for their evidence.

The most prominent hematological manifestations of SLE in our study population are anemia, leukopenia, thrombocytopenia. The bone marrow (BM) is also considered a target organ in SLE and features such as myelofibrosis, aplastic anemia, and pure red cell aplasia. Thus, we will briefly review the pathogenesis and management of specific hematological manifestations in the patients studied. (4)

Anemia	**Chronic Anemia** **Iron deficiency anemia** **Autoimmune hemolytic anemia AHA**	**72%** **46.6%** **12%**
Pure red cell aplasia PRCA		10%
Leukopenia	Lymphopenia	19%
Immune thrombocytopenia in SLE		41.6%

Treatement and complications. Here are listened principles and 13 recommendations, concerning the use of hydroxychloroquine (HCQ), glucocorticoids (GC), immunosuppressive drugs (ISDs) (including methotrexate, mycophenolate, azathioprine, cyclophosphamide (CYC)), calcineurin inhibitors (CNIs), cyclosporine, tacrolimus, voclosporin) and biologics (belimumab, anifrolumab, rituximab).

Advice is also provided on treatment strategies and targets of therapy, assessment of response, combination and sequential therapies, and tapering of therapy.

HCQ is recommended for all patients with lupus at a target dose of 5 mg/kg real body weight/day,

considering the individual's risk for flares and retinal toxicity. GC are used as 'bridging therapy' during periods of disease activity; for maintenance treatment, they should be minimized to equal or less than 5 mg/day (prednisone equivalent) and, when possible, withdrawn. (6,11)
Prompt initiation of ISDs (methotrexate, azathioprine, mycophenolate) and/or biological agents (anifrolumab, belimumab) should be considered to control the disease and facilitate GC tapering/discontinuation. (9,12)
CYC and rituximab should be considered in organ-threatening and refractory disease, respectively. For active lupus nephritis, GC, mycophenolate or low-dose intravenous CYC are recommended as anchor drugs, and add-on therapy with belimumab or CNIs (voclosporin or tacrolimus) should be considered. Updated specific recommendations are also provided for cutaneous, neuropsychiatric and hematological disease, SLE-associated antiphospholipid syndrome, kidney protection, as well as preventive measures for infections, osteoporosis, cardiovascular disease. (1,18,20)

Conclusion

The updated recommendations provide consensus guidance on the management of SLE, combining evidence and expert opinion.
Follow-up of patients and combination of maintenance therapy depending on the clinical course.
Evidence of the effectiveness of Hydroxychloroquine in the treatment of patients with SLE, especially those with hematological involvement.
Creation of an accurate database for chronic patients with SLE to enable a real assessment of the patient's health situation. Increased cooperation between the primary, secondary and tertiary health systems.
Development of diagnostic and therapeutic protocols according to the needs and clinical presentation of the patient.

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