A New Treatment Approach in Systemic Lupus Erythematosus Associated with Sepsis and Activation of Disease: A Preliminary Study

SEPSiS VE HASTALIK AKTİVASYONUNUN BİRLİKTE OLDUĞU SİSTEMİK LUPUS ERİTEMATOZUSLU HASTALARDA YENİ BİR TEDAVİ YAKLAŞIMI: BİR ÖNÇALIŞMA

Mustafa GÜLLÜLÜ*, Alpaslan ERSOY**, İsmail ASLANHAN**, Mahmut YAVUZ*, Yusuf KARABULUT***, Ediz DALKILIÇ***, Kamil DİLEK*, Mustafa YURTKURAN*

* Dept. of Nephrology and Rheumatology, Medical School of Uludağ University,
** Dept. of Nephrology, Medical School of Uludağ University,
*** Dept. of Rheumatology, Medical School of Uludağ University, Bursa, TURKEY

Summary

Purpose: In systemic lupus erythematosus (SLE) patients with serious infection complications like sepsis, it is highly difficult to choose the appropriate treatment modality. Herein we reported the results of a new therapeutic approach in 5 patients with active SLE and sepsis.

Materials and Methods: Five patients with SLE who admitted to Nephrology-Rheumatology department of Medical Faculty in Uludağ University because of sepsis, while receiving immunosuppressive therapy during active SLE between 1996 and 1999 were included in the study. Their immunosuppressive drug doses were reduced and the appropriate antibiotic treatments were applied. Because of the unresponsiveness to this therapy, 5 sessions of immunoadsorbance treatment and later on 0.4 gr/kg/day human immunoglobulin for 5 days following every session were administered to all patients. Clinical and laboratory findings were followed.

Results: The remission of the primary disease was obtained in 3 patients and their infections were treated with this protocole and appropriate antibiotic regimens. Immunologic and serologic parameters of these patients were improved. In all patients while serum levels of C3c and C4 were increasing (from 84 ± 62 mg/dl to 98 ± 45 mg/dl and from 32 ± 33 mg/dl to 39 ± 26 mg/dl, respectively), ANA and anti-dsDNA titers decreased (from 1/176 ± 1/87 to 1/132 ± 1/116 and from 1/50 ± 1/30 to 1/30 ± 1/28, respectively). Remaining two patients died because of multiple organ failure.

Conclusion: We obtained positive results with this new treatment approach in 3 of 5 patients with both sepsis and active SLE. However, this approach should be tested in a larger series of patients for definitive results.

Key Words: Lupus erythematosus, Immunoadsorption, Immunoglobulin, Sepsis

T Klin J Med Res 2001, 19:63-68

Received: Aug. 14,2000

Correspondence: Mustafa GÜLLÜLÜ
Department of Nephrology
Uludağ University Medical School
16059 Gorukle, Bursa, TURKEY

Özet

Amaç: Sepsis gibi ağır enfeksiyonlu aktif sistemik lupus eritematozuslu (SLE) olgularda yüksek mortalité nedeniyle uygun tedavi modalitesini seçmek zordur. Burada aktif SLE'li ve sepsisli 5 hastada yeni bir tedavi yaklaşımının sonuçlarını değerlendirdik.

Materyal-metod: 1996-1999 yıllan arasında aktif hastalık döneminde immunosupresif tedavi altında iken sepsis sebebi ile Uludağ Üniversitesi Tıp Fakültesi Nefroloji-Romatoloji kliniğine yatırılan 5 SLE'lu hasta çalışmaya dahil edildi. İmmunosupresif ilaç dozları azaltıldı ve uygun antibiyotik tedavileri başlandı. Uygulanan tedaviye cevap alınmaması nedeniyle tüm hastalara 5 seans immunoadsorbsiyon ve sonra her seansı takiben 5 gün süreyle 0.4 gr/kg/gün human immunoglobulin tedavisi uygulandı. Klinik ve laboratuvar bulguları takip edildi.

Bulgular: Bu protokol ve uygun antibiyotik rejimi ile, 3 hastada remisyon elde edildi ve infeksiyonlan tedavi edildi. Hastaların immünolojik ve serolojik laboratuvar parametrelerinde belirgin düzelme gözlemlendi. Tüm hastalarda ortalama C3c ve C4 düzeyleri yükselirken (sırasıyla, 84 ± 62 mg/dl'den 98 ± 45 mg/dl'ye ve 32 ± 33 mg/dl'den 39 ± 26 mg/dl'ye), ANA ve anti-dsDNA titreleri azaldı (sırasıyla, 1/176 ± 1/87'den 1/132 ± 1/116'ya ve 1/50 ± 1/30'den 1/36 ± 1/28'e). Diğer 2 hasta multiorgan yetmezliği ile kaybedildi.

Sonuç: Sonuç olarak, bu tedaviyle aktif SLE'li ve sepsisli 5 hastanın 3'ünde olumlu sonuçlar elde ettik. Ancak bu yaklaşımın etkinliği hakkında kesin sonuçlara varmak için daha büyük hasta gruplarında başka araştırmaların yapılması gerekmektedir.

Anahtar Kelimeler: Lupus eritematozus, İmmunoadsorbsiyon, immunoglobulin, Sepsis

T Klin Araştırma 2001, 19:63-68

Systemic lupus erythematosus (SLE) is a disease of unknown etiology, which at onset may involve only one organ system or be multisystemic. Recently, the treatment options such as cyclosporin, mycophenolate mofetil, dehydroepiandrosterone, intravenous immunglobulin (IV Ig) and plasmapheresis have been commonly applied (1,2).

Infections are one of the major causes of morbidity and mortality during the course of SLE (3). As with all infections, but particularly in immunocompromised patients, the early initiation of appropriate antimicrobial therapy is essential and often life-saving (4). In all studies which serious infections like sepsis accompanied SLE in its active status, mortality was found to be over 50% (5,6). In these conditions physician should have to choose a treatment modality which would both control the infection and decrease the activation of disease. Herein, we reported the results of combined immunoadsorption and IV Ig treatments in 5 patients with active SLE and sepsis.

Materials and Methods

This study was performed in 5 patients with SLE who were hospitalized due to sepsis during the activation of the disease while they were receiving maintenance doses of immunosuppressive treatments [prednisolone or combinations of prednisolone and cyclophosphamide (CYC) or azothioprine].

Case 1; Thirty years old female patient attended to our clinic because of alopecia, fatigue, nausea and vomiting and pain in her joints which she has been suffering for about 4 months. On her exam; there was alopecia, malar rush, arthritis signs in her hand, ankle and foot. Laboratory tests was determined as follows: Hb: 8.6 g/dl, leukocyte: 3400 /mm^3, erythrocyte sedimentation rate (ESR): 114 mm/hour, proteinuria: 1.2 gr/day, the positivites of anti-nuclear antibody (ANA) (in 1/320 titer), anti-doublestrain DNA (anti-dsDNA) (in 1/80 titer) and lupus cell and a decreased C3c and C4 levels (15 mg/dl and 40 mg/dl, respectively), high IgG and IgM levels (3050 mg/dl and 312 mg/dl, respectively). The renal biopsy of the patient was consistent with diffuse proliferative lupus nephritis (Type IV). The diagnosis was SLE. Oral prednisolone therapy of 60 mg per day was initiated. The patient who had remission of the disease with this therapy was followed with maintenance doses. She was also treated for hypertension. The patient did not come to the follow-up visits. One year later, she again admitted to our emergency department with the complaints of fatigue and fever, pain and swelling in her right knee and swelling and hyperemia of righl lower limb. She had hypertension, edema, anemia, leukopenia, a high ESR, a proteinuria of 4 g/day, azothemia, hypocomplementemia, the positivities of ANA, anti-dsDNA and CRR She was admitted to our clinic because of having active SLE. Salmonella plus pseudomonas cultured from blood as well as synovial fluid (sepsis and septic arthritis).

Case 2; Thirty seven years old, female patient attended to our clinic in March 1996 because of having fever, pain in the joints, alopecia, fatigue, photosensitivity and rash in the face and the cheeks lasting for about one month. A physical examination revealed alopecia, malar rash, arthritis in the joints of hands and feet. Her laboratory tests were as follows: Hb: 8.6 g/dl, leukocyte: 8100 /mm3, ESR: 36 mm/h, proteinuria: 15.2 gr/day, ANA positivity in a dilution of 1/640, and lower C3c and C4 levels (22 and 5 mg/dl, respectively). The renal biopsy was consistent with diffuse proliferative lupus nephritis (Type IV) and a diagnosis of SLE was made. After a pulse therapy of 500 mg intravenous (IV) methylprednisolone for 3 days oral prednisolone with a dosage of 60 mg/day and pulse IV CYC therapy was initiated. After remission of the disease with this therapy the patient was followed with the maintenance dosages. After 6 months she again attended to our clinic with fever, rash in upper and lower extremities and pain in the joints. Pyodermia and activation of SLE was noticed. She had edema, anemia, proteinuria, the positivities of ANA, anti-dsDNA and CRP and hypocomplementemia. She was admitted to our clinic because of having active SLE. Staphilococcus aureus cultured from blood.

Case 3; Forty five years old female patient visited our clinic because of fatigue, abdominal pain, oral ulcers and photosensitivity which lasted for about 6 months. In her physical examination malar rash, arthritis in joints of hands and feet and edema

were found. Laboratory findings included anemia, trombocytopenia, high ESR, a proteinuria of 2.2 g/day, ANA and anti-dsDNA positivities and hypocomplementemia. Due to diagnosis of SLE, a pulse dose of 3 gram of methylprednisolone was given intravenously and oral prednisolone and IV pulse CYC were given for maintenance therapy. The patient had the remission of the disease and was followed up by our department. In August 1998, she again visited us with the complaints of fever, malaise, edema, oral ulcers, arthralgia and myalgia. She had anemia, high ESR, proteinuria, azothemia, the positivities of CRP, ANA and anti-dsDNA. Acinetobacter baumanii cultured from blood (sepsis). Primary foci was not determined.

Case 4; Twenty years old female patient attended to our clinic with the complaints of fever, fatigue, cough, pain and swelling in hand wrist. In her physical examination fever, alopecia, oral ulcers, malar rash, arthritis in joints of hands and feet and hepatomegaly were found. Laboratory findings included a haemoglobin concentration of 8.1 g/dl, 3900 /mm3 leukocyte, 52 mm/h of ESR, a proteinuria of 1.8 g/day, positivity of ANA in 1/1280 dilution, positivity of anti-dsDNA in 1/80 dilution, hypocomplementemia and polyclonal gammopathy. The renal biopsy of the patient was consistent with diffuse proliferative lupus nephritis (Type IV). After administration of pulse dose 3 grams of methylprednisolone intravenously the therapy continued with oral prednisolone and IV pulse CYC. The patient were invited to follow up examinations after remission of the disease with this therapy. After 8 months the patient visited us because of fever, disuria, cough and sputum, dyspnea and polyarthritis. She was hospitalised with the diagnosis of pneumonia, urinary tract infection and active SLE. She had edema, anemia, a high ESR, proteinuria, azothemia, hypocomplementemia, the positivities of ANA, anti-dsDNA and CRP. Enterococci cultured from blood and Escherichia coli from urine.

Case 5; Forty five years old female patient was hospitalised by the dermatology clinic because of having rash in her face and trunk in June 1994. With a diagnosis of discoid lupus erythematosus a topical corticosteroid treatment was considered. In January 1996 a therapy with prednisolone plus azathioprine was started by her doctor with diagnosis of SLE and her clinical condition improved. But her symptoms recurred and she was hospitalised for fever, malaise, arthralgia, photosensitivity and raynaud phenomenon. She had edema, fever, pleuritis, ascites, hepatomegaly, seizure attacks, anemia with a haemoglobin concentration of 8.6 g/dl, leukopenia of 3600 /mm^3, thrombocytopenia of 76000 /mm^3, a high ESR of 134 mm/h, a proteinuria of 5.8 g/day, microscopic hematuria, pyuria and the positivities of ANA, anti-dsDNA and CRP. Enterococci cultured from blood and urine.

Immunosuppressive drug doses were reduced as much as possible because of severe infections. In all patients, the ampiric antibiotic treatment was started after the appropriate cultures of blood, urine and sputum were taken. Their antibiotic regimens were changed according to the culture results, if required. The mono- or combined antibiotherapies consist of 3rd generation cefalosporin, aminoglycoside, flourokinolon and vancomycin was given to all patients. Immunoadsorption and IV Ig treatments were administered if there had been an unresponsiveness to the usual treatments within 3 to 5 days.

All of them had 5 sessions of immunoadsorbance treatment using Immusorba PH-350 membrane with Plasauto IQ machine (Asahi Medical Co., Ltd., Tokyo, Japan). This immunoadsorbent consisted of polyvinylalcohol as a carrier and aminoacid ligand such as phenylalanine. Just after every immunoadsorbent therapy session, 0.4 g/kg/day native human immunoglobulin (Sandoglobulin, 6 gr bottle, Sandoz Pharma Ltd., Switzerland) was applied for five times. The same protocole was repeated after 24 hours. In all patients daily arterial blood pressure, pulse rate, temperature and diuresis were noted. Serum urea, creatinine, electrolytes, total protein, albumin, C3c and C4 levels, CRP, ANA, anti-doublestrain DNA, leukocyte, peripheral blood smear, serum protein electrophoresis and creatinin clearence were measured in the pre-treatment and 3rd week of the treatment. In addition, the clinical signs such as arthritis, arthralgia, myalgia, skin changes, oral ulcers, psychosis, seizures and serositis were followed-up during the treatment period.

Table **1.** The changes in laboratory values after the treatment

	Pre-treatment	Post-treatment
Leukocyte, /mm³	5720 ± 2559	5025 ±2145
Platelet, x103/mm³	213 ± 153	225 ± 55
ESR, mm/hr	52 ±55	28 ±20
Proteinuria, gr/day	5.9 ±6.5	4.9 ±4.3
Serum urea, mg/dl	205 ± 76	155 ±27
Serum creatinine, mg/dl	3.5 ±2.5	1.7 ± 1.0
Creatinine clearence, ml/min	30 ±28	49 ±48
Serum albumin, gr/dl	2.4 ±0.7	2.9 ± 0.7
C3c, mg/dl	84 ±62	98 ±45
C4, mg/dl	32 ± 33	39 ±26
ANA titer	1/176 ± 1/87	1/132 ± 1/116
Anti-dsDNA titer	1/50 ± 1/30	1/36 ± 1/28
CRP, mg/dl	30.5 ± 13.7	22.4 ± 5.7

Results

The results of laboratory values were shown in Table 1. All serological and immunological parameters were improved after the treatment. But in 2 patients who died, CRP values were still high.

Partial or complete remission of the primary disease and the cure of infection was succeeded in three patients with this protocole. In all patients, the changes in laboratory values after the treatment were shown in Table 1. Serological and immunological improvements were observed. The other two cases (Case 4 and 5) died because of multiple organ failure, septic shock and disseminated intravascular coagulation in 10th and 15th days of the immunoadsorption and IV Ig therapy, despite intensive medical treatment. In 2 patients who died CRP values were still high.

Complications such as hypersensitivity, anaphylactic, pyrogenic and minor systemic reactions, and vasomotor and/or cardiovascular manifestations were not observed during the immunoadsorbtion therapy.

Discussion

Although SLE no longer has the very poor prognosis as it had 50 years ago, active disease and sepsis remain the most important factors in mortality in SLE (7). The majority of infections are due to typical gram-positive and negative bacteria (8). In our previous study, we evaluated infectious complications in 1511 patients with SLE (9). Bacterial infections were determined in 48.4%, viral infections in 23.2%, fungal infections in 22.2% and parasitic infections in 6%. Disease activity and treatment are responsible for the extensive defects of the immune defense system in lupus patients that increase their susceptibility to an extensive range of infections (10).

We performed a different treatment modality in 5 patients with sepsis and active disease in order to treat a serious infection and to induce a remission of the disease. It has been demonstrated that the life-threatening bacterial and viral infections and mortality in patients with SLE treated with plasmapheresis in addition to IV pulse CYC occurred more frequently than the patients with similarly active SLE treated with IV CYC alone (11). Immunoadsorption comprises removal of pathogenetic antibodies and circulating immune complexes as well as reticuloendothelial system deblockage; modification of immune complex structure and processing can be induced by changing the antigen/antibody ratio and by modulation of immune complex solubility via complement activation (12). The results of controlled trials performed with IMPH-350 and Ig-Therasorb in SLE indicated excellent biocompatibility and good clinical responses (13). In our cases, immunosuppressive therapy could exacerbate the infection and solely immunoadsorbance treatment could fail to exert an immunosuppressive effect because of decreasing Ig levels of patient and leading to a rebound phenomenon.

IV Igs contain idiotypic antibodies directed against pathologic autoantibodies and appear to be an interesting source of immunomodulating antibodies, which could be useful in the treatment of autoimmune diseases (14,15). The efficacy of IV Ig in the treatment of rheumatic and connective tissue diseases remains to be confirmed in double-blind placebo-controlled studies. Corvetta et al. (16) reported that three patients with life-threatening manifestations of SLE, unresponsive to conventional high-dose corticosteroid and/or immunosupressive therapy were treated with IV Ig. Recently, it has been reported that the administration of IV immunglobulin (Ig) to septic patients has a potential beneficial effect (17). Its action mechanism is the ca-

parity of specific antibodies contained in IV Ig to bind to the infectious organism followed by opsonophagocytosis. IV Ig preparations have been shown, both in vitro and in vivo to profoundly affect the homeostasis of the cytokine network, probably in a way which directs this network from disturbed to regulated functioning. Excessive production and insufficient removal of cytokines due to multiorgan failure of sepsis patients are now known to play a decisive role in progression of sepsis to septic shock. However, several clinical studies to determine efficacy have failed to prevent fatal outcome, even when IV Ig was given at high doses (18). In our cases it could be possible to keep the Ig levels of patients in acceptable amounts in case of combining immunoadsorbance treatment with IV Ig's. Also immunomodulatory effect of IV Ig's would have additional benefits.

In our previous, IV Ig and immunoadsorbance treatment was combined in patients with active SLE who had no infection. Euler and Schroeder (19) investigated the effect of S-sulfonated and native IV Ig preparations in addition to previous immunosuppressive drugs (prednisolone and/or azathioprine and/or non-steroidal antirheumatic drugs) in the treatment of 18 patients with mild to moderately active SLE. They gave 30 gr of one of the two preparations on 4 consecutive days, followed by the same regimen on days 21- 24. They reported a reduction in the systemic lupus activity measure (SLAM) score or an improvement of an organ manifestation (thrombocytopenia, arthritis, facial erythema, raynaud phenomenon) of at least 50% in ten of 18 patients (responders) and 30-50% in 2 patients (partial responders). In our two patients the cause of death was fatal progressive infection. The titers of ANA and anti-dsDNA, and the complement levels remained unchanged in 2 patients who died. We observed the reduction in other three patients. In other study, Welcker et al. (20) treated 7 patients with SLE with 10 gr 7S-immunoglobulin infusions on three consecutive days after three sessions of immunoadsorption. They reported that this treatment regimen did not provide a benefit to patients with end-stage kidney involvement but the patients with moderate kidney involvement improved. In an other report, IV Ig treatment of SLE had led to an improvement in three patients, while exacerbations or new onsets occured in three patients (21). Therefore, in SLE patients with renal disease, it should be used cautiously because some patients have worsening of their renal function with IV Ig infusions. The renal functions of our three patients with diffuse proliferative lupus nephritis did not worsen. Only one of them together with another patient without the renal biopsy died due to severe infection. The mean serum creatinine levels and daily protein excretions of the patients decreased mild or moderately.

In our study we had limited number of patients with succesfully treated 3 patients (60%) and 2 of our patients died. The primary prognostic factor in these cases was probably the course of the present infection, that was the rapidly progression of pathogens as staphylococcuc aureus and the presence of more than one pathogen. This form of treatment is expensive and is not free of complications. In case of absolute failure of other therapies in active SLE patients with serious complications, this modality of treatment may be considered.

As a result, we concluded that this new regimen could be useful in some patients for controlling active disease and severe infection. But, the role of this approach in the overall treatment strategy of SLE remains to be further defined, and clearly more controlled data are needed.

REFERENCES

1. Godfrey F, Khamashta MA, Hughes GR. Therapeutic advances in systemic lupus erythematosus. Curr Opin Rhematol 1998; 10:435-41.

2. Strand V. New therapies for systemic lupus erythematosus. Rheum Dis Clin North Am 2000 May;26(2):389-406.

3. Le Moing V, Leport C. Infections et lupus. Rev Prat 1998; 48: 637-42.

4. Cunha BA. Infections in nonleukoemic compromised hosts (diabetes mellitus, SLE, steroids, and asplenia) in critical care. Crit Care Clin 1998; 14: 263-82.

5. Duffy KN, Duffy CM, Gladman DD. Infection and disease activity in systemic lupus erythematosus: a review of hospitalised patients. J Rheumatol 1991; 18: 1180-4.

6. Petri M, Genovese M. Incidence of and risk factors for hospitalizations in systemic lupus erythematosus: a prospective study of the Hopkins Lupus Cohort. J Rheumatol 1992; 19: 1559-65.

7. Cohen MG, Li EK. Mortality in systemic lupus erythematosus: active disease is the most important factor. Aust N Z J Med 1992; 22(1): 5-8.

8. Paton NI. Infections in systemic lupus erythematosus patients. Ann Acad Med Singapore 1997; 26: 694-700.

9. Güllülü M, Dilek K, Yavuz M, Karakoc Y, Dilek S, Yücel A, Mistik R, Yurtkuran M. Sistemik lupus eritematozuslu olgulardaki infeksiyonlar. Medikai Network Doktor 1995; 3: 319-22.

lO. Iliopoulos A G, Tsokos GS. Immunopathogenesis and spectrum of infections in systemic lupus erythematosus. Semin Arthritis Rheum 1996; 25: 318-36.

11 Aringer M, Smolen JS, Graninger WB. Severe infections in plasmapheresis-treated systemic lupus erythematosus. Arthritis Rheum 1998; 41: 414-20.

12. Bosch T. Current status in extracorporeal immunomodulation: immune disorders. Artiforgans 1996; 20: 902-5.

13. Schneider M, Gaubitz M, Perniok A. Immunoadsorption in systemic tissue diseases and primary vasculitis. Ther Apher 1997;1: 117-20.

14. Sany J. Intravenous immunoglobulin therapy for rheumatic diseases. Curr Opin Rheumatol 1994; 6: 305-10.

15. NIH Consensus Conference. Intravenous immunoglobulin: Prevention and treatment of disease. JAMA 1990; 264: 3189-93.

lö. Corvetta A, Delia Bitta R, Gabrielli A, Spaeth PJ, Danieli G. Use of high-dose intravenous immunoglobulin in systemic lupus erythematosus: report of three cases. Clin Exp Rheumatol 1989; 7: 295-9.

17. Dominioni L, Bianchi V, Imperatori A. Severely septic surgical patients. In: Kazatchkine MD, ed. Intravenous Immunoglobulin Therapy: Clinical benefits and future prospects. London: The Parthenon Publishing Gfoup, 1995: 85-8.

18. Nydegger UE. Sepsis and polyspecific intravenous immunoglobulins. J Clin Apheresis 1997; 12: 93-9.

19. Euler HH, Schroeder JO. Dermatomyositis and systemic lupus erythematosus. In: Kazatchkine MD, ed. Intravenous Immunoglobulin Therapy: Clinical benefits and future prospects. London: The Parthenon Publishing Group, 1995: 53-7.

20. Welcker M, Helmke K. Immunologic therapy for glomerulonephritis with combined immunoadsorption and IVIG therapy (Abstract). Immun Infekt 1995; 23: 140-1.

21. Barron KS, Sher MR, Silverman ED. Intravenous immunoglobulin therapy: magic or black magic. J Rheumatol Suppl 1992;33: 94-997.