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

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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 immunoadsorption 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 protocol 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

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Amaç: Sepsis gibi ağır enfeksiyonlu aktif sistemik lupus erytematozuslu (SLE) olgularda yüksek mortalite nedeniyle uygun tedavi modalitesini seçmek zordur. Burada aktif SLE’li ve sepsisi 5 hastada yeni bir tedavi yaklaşımının sonuçlarını değerlendirdik.


Bulgular: Bu protokol ve uygun antibiyotik rejimi ile, 3 hasta da remisyon elde edildi ve enfeksiyonlan tedavi edildi. Hastaların immünolojik ve serolojik laboratuvar parametrelerinde belirgin düzelmeye gözlendi. Tüm hastalarda ortalama C3c ve C4 düzeyleri yükselirken (sirasıyla, 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 titeleri azaldı (sirasıyla, 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 sepsisi 5 hastanın 3’ünde olumlu sonuçlar elde etti. Ancak bu yaklaşımın etkinliği hakkında kesin sonuçlara varmak için daha büyük hasta gruplarında başka araştırmaların yapılması gerekmektedir.

Anahtar Kelimeler: Lupus eritematozus, Immunoadsorbsiyon, immunoglobulin, Sepsis

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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 immunoglobulin (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 where 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 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 were determined as follows: Hb: 8.6 g/dl, leukocyte: 3400 /mm³, erythrocyte sedimentation rate (ESR): 114 mm/hour, proteinuria: 1.2 gr/day, the positivities 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) 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. 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 right 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 CRP. 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. Pyoderma 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 18 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 had edema, fever, pleuritis, ascites, hepatomegaly, seizure attacks, anemia with a haemoglobin concentration of 8.6 g/dl, leukopenia of 3600 /mm³, thrombocytopenia of 76000 /mm³, 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, fluorokinolon 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 immunoabsorbance treatment using Immusorba PH-350 membrane with Plasauto IQ machine (Asahi Medical Co., Ltd., Tokyo, Japan). This immunoabsorbent consisted of polyvinylalcohol as a carrier and aminoacid ligand such as phenylalanine. Just after every immunoabsorbent 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 protocol 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-double strain DNA, leukocyte, peripheral blood smear, serum protein electrophoresis and creatinin clearance 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

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<tr>
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<th>Pre-treatment</th>
<th>Post-treatment</th>
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<tr>
<td>Leukocyte, /mm³</td>
<td>5720 ± 2559</td>
<td>5025 ± 2145</td>
</tr>
<tr>
<td>Platelet, x10³/mm³</td>
<td>213 ± 153</td>
<td>225 ± 55</td>
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<tr>
<td>ESR, mm/hr</td>
<td>52 ± 55</td>
<td>58 ± 20</td>
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<tr>
<td>Proteinuria, gr/day</td>
<td>5.9 ± 6.5</td>
<td>4.9 ± 4.3</td>
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<tr>
<td>Serum urea, mg/dl</td>
<td>205 ± 76</td>
<td>155 ± 27</td>
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<tr>
<td>Serum creatinine, mg/dl</td>
<td>3.5 ± 2.5</td>
<td>1.7 ± 1.0</td>
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<tr>
<td>Creatinine clearance, ml/min</td>
<td>30 ± 28</td>
<td>49 ± 48</td>
</tr>
<tr>
<td>Serum albumin, gr/dl</td>
<td>2.4 ± 0.7</td>
<td>2.9 ± 0.7</td>
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<tr>
<td>C3c, mg/dl</td>
<td>84 ± 62</td>
<td>98 ± 4.5</td>
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<tr>
<td>C4, mg/dl</td>
<td>32 ± 33</td>
<td>39 ± 26</td>
</tr>
<tr>
<td>ANA titer</td>
<td>1/176 ± 1/87</td>
<td>1/132 ± 1/116</td>
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<tr>
<td>Anti-dsDNA titer</td>
<td>1/50 ± 1/30</td>
<td>1/36 ± 1/28</td>
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<tr>
<td>CRP, mg/dl</td>
<td>30.5 ± 13.7</td>
<td>22.4 ± 5.7</td>
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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 protocol. 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 immunoadsorption 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 pathogenic antibodies and circulating immune complexes as well as reticuloendothelial system de-blockage; 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 immunosuppressive therapy were treated with IV Ig. Recently, it has been reported that the administration of IV immunoglobulin (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, rynaud 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.

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REFERENCES