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Original Research Article

A study on steroids and immunosuppressants as risk factors for infections in SLE patients

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ABSTRACT

Introduction: Systemic lupus Erythematosus (SLE) patients are inherently at risk for infections. Steroids and other immunosuppressants used for treating SLE patients further increase the chances of infections. This study was done to find the association of immunosuppressants with the risk of development of infections in patients with SLE.

Materials and Methods: Appropriate samples were collected from 110 SLE patients with various infections and processed in Microbiology laboratory. Treatment history was also collected from the patients and analysis was done on infections in these patients.

Results: Daily prednisolone dosage $\geq$20 mg was associated with increased risk of infection with p value of $<$ 0.05 and in patients receiving Cyclophosphamide with steroids also risk of infection was higher with p value $<$0.05 which is also statistically significant.

Conclusion: Since there is strong association between higher dose of steroids and Cyclophosphamide therapy with risk of infections in SLE patients, judicious use of these drugs is recommended.

1. Introduction

SLE is the prototype of a systemic autoimmune disorder in which there is production of autoantibodies. SLE affects almost all organs of the body and it occurs mainly in women in their peak reproductive age. SLE may present with varying symptoms ranging from skin and joint involvement to those involving major organs. In a genetically predisposed individual infections play a key role in disease manifestation. The disease runs a course of flare -ups and remissions which may extent over a period of years or sometimes even decades. [1]

SLE is not a curable disease. Hence the treatment is aimed to control severe exacerbations and to develop maintenance strategies so as to suppress symptoms and prevent damage to organs. Nonsteroidal antiinflammatory drugs (NSAID), antimalarial (hydroxychloroquine), glucocorticoids and in severe cases immunosuppressants like Azathioprine, Mycophenolate mofetil (MMF), Methotrexate and Cyclophosphamide (CYC) are used for treating mild SLE without major organ involvement. Treatment of moderate to severe SLE consists of a period of induction therapy in which intensive immunosuppressive therapy is given which is followed by a longer period of maintenance therapy using less intensive immunosuppressants.

Corticosteroids are used either as single or as background therapy in combination with immunosuppressive agents at prednisolone doses ranging from 0.5 to 1.0 mg/kg/day in a single dose followed by gradual dosage tapering. When doses more than 0.6 mg/kg/day are used or in rapidly progressing severe disease bolus therapy of 1000 mg of methyl prednisolone i.v. daily for three days followed by 0.5 mg/kg/day of prednisolone is given.

Intermittent pulse CYC therapy (Intravenous route) is effective for moderate to severe proliferative nephritis.

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The treatment is usually given in one of the three ways: 1) Once monthly IV for 6 months followed by two years of quarterly doses 2) CYC for 12 weeks followed by Azathioprine 3) CYC for 6 months follo wed by Azathioprine or MMF. MMF is used to treat manifestations of SLE like proliferative nephritis, skin disease, refractory thrombocytopenia and pulmonary haemorrhage.[2]

Steroids predispose to infection by decreased inflammatory response and effector cell response in cell mediated immunity, lysis of lymphoid follicles and decreased immunoglobulin synthesis. Prolonged administration of steroids causes chronic changes in tissues such as skin atrophy which allow increased access of microorganisms into circulation further increasing risk of infection.

There is inherent risk for infections in SLE patients due to the presence of immunological dysfunctions. This susceptibility to develop infection is further enhanced by the immunosuppressive therapy. 30% to 50% of SLE patients develop infections during the course of their disease. The recognition and treatment of infections in this patient population are particularly difficult tasks because the clinical manifestations of infection may mimic those of the underlying disease, the effects of immunosuppressive therapy may decrease the usual manifestations of an infection such as fever and localizing signs of imflammation and the spectrum of pathogens is large making empiric treatment difficult. Diagnosing infections at an early stage is important as they may mimic SLE flares leading to a delay in diagnosis or inappropriate increase in doses of immunosuppressants with dreadful consequences.

There are not many published articles on relationship between daily dose of steroids and immunosuppressants with infections in SLE patients. Hence the p resent study was done to find the association of immunosuppressants with occurrence of infections in patients with SLE.

2. Materials and Methods

A total of 110 SLE patients with clinically suspected infections were included in this study. Clinical history, demographic information and treatment history were collected using specially designed questionnaire. Appropriate samples were collected from the patients under strict aseptic precautions and transported to the laboratory without delay and processed.

The samples were inoculated on suitable bacterial and fungal culture media. After incubation overnight, bacterial and fungal pathogens were identified by standard techniques as recommended by CLSI (Clinical and Laboratory Standards Institute).[3]

Infections occurring in patients taking prednisolone dose $<$20 mg/day were compared with those in patients taking dosage of $\geq$20 mg/day. Also analysis was done on infectious complications in patients on CYC with steroids and also in SLE patients on MMF.

3. Results

From the 110 SLE patients the main samples collected were urine 84 (56%), sputum 22 (14.67%), and blood 21 (14%). 60 SLE patients included in the study had infectious episodes. Out of 150 samples processed, significant growth was observed in 74. Urinary tract infections 40 (54%) were common followed by respiratory tract infections 12 (16%). Other sites of infection in decreasing order of frequency were blood, skin & soft tissue, ear, oral cavity and peritoneum. Bacterial infections were common than fungal infections.

74 patients were on Prednisolone dose $<$ 20 mg. Out of them infections were recorded in 31 (42%) patients. In this study 36 patients were on prednisolone dosage $\geq$ 20 mg and 29 (81%) of them presented with various types of infections. Daily prednisolone dosage $\geq$ 20 mg was associated with an increased risk of infection with a p value of 0.0003 ($<$ 0.05 which is statistically significant).

Urinary tract infection (UTI) was the predominant infection and Escherichia coli was the common organism causing infection both in patients on steroids $<$20 mg/day and $\geq$20 mg/day.

29 patients were on treatment with CYC & Prednisolone, out of which 22 suffered from infections. In this group of patients Blood stream infections and UTI occurred in equal number and Pseudomonas aeruginosa was the predominant organism causing infections. In the remaining 81 patients who were not on CYC only 39 patients developed infections. Thus the risk of infections was higher in patients receiving both CYC & Prednisolone with a p value of 0.0183. ($<$0.05) which is statistically significant). Only 8 patients were on treatment with MMF and 4 of them developed infectious episodes. No association was found between MMF intake and infection with a p value of 0.7472. ($>$0.05 which is statistically not significant).

4. Discussion

In the present study out of 110 SLE patients 60 (55%) patients suffered from various infectious complications which is comparable to studies done by deluis et al[4] and H – Al-Rayes et al.[5] Urinary tract and respiratory tract were the most common sites of infection. (Tables 2, 3, 5 and 6) This finding is supported in other studies conducted by Ginzler e et al,[6] Staples P J et al[7] and de Luis et al.[4] In this study bacterial infections were common than fungal infections which is in agreement with studies conducted from India and other countries.[8–10]

In the present study, daily prednisolone dose of $\geq$ 20 mg was associated with an increased risk of infection with a p value of $<$ 0.05 which is statistically significant. (Table 1) Also in studies done by Noel et al[10] and Gladman et al[11] Pryor et al,[12] Bosch et al,[13] steroid intake was identified as a risk factor for infection in SLE patients. Ruiz- Irastorza et

Table 1: Steroid vs. infection (n = 110)

	Total no. of patients	Infected		Not Infected	
Daily Prednisolone dosage ↓		**No.**	**%**	**No.**	**%**
< 20 mg	74	31	41.89%	43	58.11%
≥ 20 mg	36	29	80.56%	7	19.44%
Total	**110**	**60**		**50**	

Table 2: Infections in patients on prednisolone dose < 20 mg/day

Infection site	**No of infections**
Urinary tract	18
Respiratory tract	4
Skin & soft tissue	4
Others	5
Total	**31**
Organisms isolated from patients on prednisolone dose $<$**2**0 mg/day	
Organism	**Number**
Escherichia coli	12
Pseudomonas aeruginosa	6
Klebsiella pneumoniae	5
Candida albicans	3
Staphylococcus epidermidis	1
Acinetobacter baumannii	1
Proteus mirabilis	1
Enterococcus faecalis	1
Aspergillus flavus	1
Total	**31**

Table 3: Infections in patients on prednisolone dose $\geq$20 mg/day

Infection site	**No of infections**
Urinary tract	12
Respiratory tract	8
Blood	6
Others	3
Total	**29**
Organisms isolated from patients on prednisolone dose $\geq$ **2**0 mg/day	
Organism	**Number**
Escherichia coli	8
Klebsiella pneumoniae	7
Staphylococcus aureus	5
Pseudomonas aeruginosa	4
Staphylococcus epidermidis	1
Acinetobacter baumannii	1
Salmonella typhi	1
Enterococcus faecalis	1
Candida tropicalis	1
Total	**29**

Table 4: Cyclophosphamide + steroid vs. Infection (n = 110)

		Infected		Not Infected	
	Total no. of patients	**No.**	**%**	**No.**	**%**
No. of patients on Cyclophosphamide + Prednisolone	29	22	75.86%	7	24.14%
No. of patients not on Cyclophosphamide	81	39	48.15%	42	51.85%
Total	**110**	**61**		**49**	

Table 5: Infections in patients on cyclophosphamide+steroids

Infection site	**No of infections**
Blood	**7**
Urinary tract	7
Respiratory tract	4
Others	4
Total	**22**
Organisms isolated from patients on CYC+Steroids	
Organism	**Number**
Pseudomonas aeruginosa	6
Klebsiella pneumoniae	5
Staphylococcus aureus	5
Escherichia coli	4
Acinetobacter baumannii	1
Salmonella typhi	1
Total	**22**

Table 6: Infections in patients not on CYC

Infection site	**No of infections**
Urinary tract	**24**
Respiratory tract	7
Skin & soft tissue	5
Others	3
Total	**39**
Organisms isolated from patients not on CYC	
Organism	**Number**
Escherichia coli	10
Pseudomonas aeruginosa	8
Klebsiella pneumoniae	6
Staphylococcus aureus	5
Candida albicans	3
Enterococcus faecalis	2
Proteus mirabilis	2
Citrobacter freundii	1
Candida tropicalis	1
Aspergillus flavus	1
Total	**39**

Table 7: MMF vs. infection (n=110)

		Infected		**Not Infected**	
	Total no. of patients	**No.**	**%**	**No.**	**%**
No. of patients on Mycophenolatemofetil	8	4	50.00%	4	50.00%
No. of patients not on Mycophenolatemofetil	102	57	55.88%	45	44.12%
Total	**110**	**61**		**49**	

al[14] found that prednisolone dose increases risk of infection in patients with SLE. The present study is comparable to the findings from above mentioned studies.

In the current study, the risk of infection was higher in patients receiving CYC with a p value <0.05 which is statistically significant. (Table 4) Pryor et al[12] reported a higher rate of infection in patients receiving CYC and steroids. The present study is in line with the above study. In this study, eight patients were on treatment with MMF out of which four developed infection. No significant association was found between infection and MMF with a p value more than 0.05. (Table 7) In the study by Hu et al.[15] it was found that the frequency of infection in SLE patients treated with MMF was less compared with patients on CYC.

Disease activity along with prednisolone dose more than 10 mg/day, methyl prednisolone in high doses and CYC therapy are well documented causes of increased risk of infection.[16] Long term steroid use in SLE patients

significantly increase morbidity due to permanent damage to organs.[17] Compared to daily regimen, alternate day steroid administration is believed to decrease risk of infection.[1] In Singapore a prospective study did not show an association of infection and cytotoxic therapy in patients with SLE.[8] It was found that patients treated with plasmapheresis and CYC had more chances of developing infections compared to patients treated with CYC alone. Recent clinical trials suggest infections are less frequent in patients treated with MMF as compared to CYC.[1]

In a retrospective analysis, infection rate was found to be higher among patients receiving CYC and higher doses of steroids compared to patients on MMF.[18] In a study on SLE infection predictive index, CYC infusion was found to be a major risk factor for infection. The cytotoxic action of CYC on lymphocytes could be a reason for this increased risk.[19] In a large multi centric study on SLE patients, corticosteroids dose $\geq$ 10mg/day and immunosuppressants were associated with infection whereas antimalarial use was found to be protective.[20] Complement deficiency, use of steroids and cytotoxic drugs were attributed to infections in Saudi patients with SLE.[5] The immune response to microorganisms is very much suppressed in patients receiving CYC in combination with high dose steroids. CYC regimen causes reduction in WBC count. This increases risk of serious infection in SLE patients.[12]

A high index of suspicion is essential as the symptoms of SLE and infection are often similar. The helpful clues which help to diagnose infections are presence of the following like chills, leukocytosis, increased C Reactive Protein (CRP) levels[21] and absence of SLE involving multiple systems. SLE patients are at high risk for developing infection. Hence all fevers must be evaluated in SLE patients because the most common causes of fever in them are infections and active lupus. Also the signs of inflammation in these patients may be altered by steroids and NSAIDs which are used for treating disease manifestations. Thus careful use of steroids and other immunosuppressive agents in SLE patients is recommended to limit infections.

5. Conclusion

Since there is strong association between increased dose of steroids and CYC with risk of developing infections in SLE patients judicious use of steroids and other immunosuppressants is recommended. Also it is very important to diagnose infections at an early stage as they may mimic SLE flares which may lead to a delay in diagnosis or inappropriate increase in doses of immunosuppressants with dreadful consequences.

6. Conflict of interest

None.

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