Original Article

Lupus Nephritis, the therapy and the role of Rituximab in resistant cases

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Summary:

BackgroundSystemic lupus erythematosus (SLE) is a common autoimmune disease that affects mainly young females and nephritis is an important complication of the disease that may end with end stage renal disease (ESRD). Early diagnosis and proper treatment is important in decreasing the morbidity. Multiple immunesupressor agents used and according to the histopathology stage of the disease, still the proper drug used and the duration and dose required not settled. Rituximab which is monoclonal antibody that reacts against CD20 antigen on lymphocytes that cause B cells depletion is recently introduced in treatment of lupus nephritis .

Objectives: to see the effect of different immunosuppressive agents in lupus nephritis and any response of resistant cases to Rituximab

Methods sixty three systemic lupus erythematosus (SLE) patients' age 3-45 years, 54 females and 9 males referred to the Nephrology Center in AL Sader Hospital in AL-Najaf governorate from April 2009- June 2013 enrolled in this study. All patients had renal biopsy and had categorized in different histopathological classes, the patients in stages I and II were treated with prednisolone while patients with other stages were treated with prednisolone and immunosuppressive therapy. The patients were followed up clinically and by laboratory results for response to the therapy, those who respond to the treatment tapering of the steroid was done and patients follow up were continued. Patients who showed no response to prednisolone or to the immunosuppressive agent were given Rituximab.

Results –Mean age of patients was 22 years with a standard deviation+ 9 years. The association between sex and prednisolone was statistically not significant. The association between immunosuppressor therapy and sex was statistically not significant. The association between rituximab and sex was statically significant (p value 0.03(.The response to steroid therapy & age was statistically not significant. The association between response to immunosuppressor therapy and age was statistically not significant .The response to immunosuppressor therapy in different histopathological stages was statistically significant (P value 0.03). Response to Rituximab therapy was statistically significant (P value 0.048).

Conclusion: Immunosuppressor therapy may have an effect in treatment of lupus nephritis and Rituximab may be useful in treatment of resistant cases of lupus nephritis.

Key words: Lupus nephritis, Rituximab.

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Introduction:

Systemic lupus erythematosus (SLE) is a common autoimmune disease that can affect the kidneys through pathological damage to the glomeruli. 1 The presence of lupus nephritis (LN) significantly reduced survival to approximately 88% at 10 years with even lower survival in African American. 2 The disease is commonly affected young females. 3 Nephritis remains one of the most devastating complications of Lupus 1, 4. The major objective is to standardize definitions, emphasize clinically relevant lesions, and encourage uniform and reproducible reporting between centers.5, 6, 7Cyclophosphamide(CYC) has severe and life threaten adverse effects including acute myeloid leukemia ,bladder cancer and permanent infertility alopecia.8 Infusion reactions to rituximab occur in 20-40% and are mostly mild ,although severe especially in higher doses less side effects include nausea, vomiting, bone marrow suppression,
hemorrhagic cystitis, darkening of skin and nails and reactions including meningesium, anaphylaxis and serum sickness have been reported.9 In 2006 the Food and Drug Administration reported the occurrence of progressive multifocal leukoencephalopathy in two patients with lupus after rituximab. Both had prolonged previous and concurrent immunosuppressive exposure, and this severe viral infection is a rare but recognized complication of systemic lupus.10 Drugs that inhibit and suppresse the immune reaction include Mycophenolate (CellCept, Myforic) which inhibits inosine monophosphate dehydrogenase and suppresses de novo purine synthesis by lymphocytes thereby inhibiting their proliferation. It inhibits antibodies production11. Although

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Azathiaprim (AZA) has been used to treat Lupus Nephritis, the Task Force Panel did not recommend it as of first choice in induction therapy.12

Patients and Methods:

The study enrolled all 63 Lupus nephritis cases who were consulted the Nephrology department in AL Sader teaching hospital in Najaf city .Their age from 3 years to 45 years. females number 55 and males 8, all patients were diagnosed as SLE by clinical and immune laboratory study .The criteria in diagnosing the nephritis based on laboratory tests and include hypercholestremia, hypoalbuminemia and protienurea with>1 gm/24 hours or albumin creatinine ratio in nephritic range . All patients had undergo renal biopsy and histopathological classification of nephritis was established according to the criteria of .The start of treatment with corticosteroid therapy was established for all patients, started with 3 doses solumedrol in dose 30 mg/Kg/day ,maximum 1 g then prdinsolon 2 mg/Kg /day for 1 week and tapering the dose to 0.5 mg/Kg/day every other day for 2 months, those who did not respond within 8 weeks immunosuppressant therapy was added in patients with normal renal function , using Azathiaprim (AZA) 2-3 mg/Kg/ day or Cyclophsphamide (CYC) 2-3 mg/Kg/day. In patients with active stage III or stage IV and patients not responding to the steroid treatment then i.vcyclophsphamide 250-1000 mg/ m2 with renal function monitoring, while if renal function is impaired the treatment was with use of Mycophenolate or 500 mg-750 mg or Myfortl 150 mg/m2 and the respond to treatment was followed for 3 months. The patients who did not respond to immunosuppressant treatment rituximab 375mg/ m2 for 6 doses were used.Theprdinsolon dose tapered to dose 0.5 mg/Kg/day. The patients were followed with renal function test.WBC count kept >5000. 3 patients had Hemodialysis when the GFR<30mg/minute/1.73m2 and 1 patient was treated with peritoneal dialysis (GFR< 10mg/minute/1.73m2). Infection developed during the therapy include 4 patients with pneumonia, 2 patients with Herpes Zoster and 3 had oral thrush .Two of the patients developed fit and treated with anticonvulsant Carbamazepine .One child 3 year age in stage I disease not responding to steroid was shifted to cyclosporine therapy in dose 3-4 mg /kg/day for one year and then treated to steroid therapy only. Two patients died in stage III and stage IV treated with predinsolon and shifted to Immuran therapy as the patient decided to become pregnant .The respond of the patients to the therapy had been classified as a good response when the serum cholesterol, the serum albumin and protienurea return to normal .The partial response means that serum albumin increase while the protienurea decreases to more than half of the previous reading while the patient had no response to the therapy when the above mentioned parameters failed to return to the normal range. The American college of rheumatology criteria was depended in this study & as follow:

Class I is defined as minimal lupus nephritis with mesangial deposition of immune complexes identified by immunofluorescence, or by immunofluorescence and electron microscopy, without concomitant light microscopic alterations.

Class II is defined as mesangial proliferative lupus nephritis characterized by any degree of mesangialhypercellularity in association with mesangial immune deposits

Class III is defined as focal lupus nephritis involving less than 50% of all glomeruli. Affected glomeruli usually display segmental endocapillary proliferative lesions or inactive glomerular scars, with or without capillary wall necrosis and crescents with subendothelial deposits .The lesion could be A active one, A/C active and chronic, while C When the lesion is chronic.

Class IV is defined as diffuse lupus nephritis involving 50%or more of glomerulo in the biopsy, the lesion may be segmental defined as sparing at least half of the glomerular tuft ,or

global defined as involving more than half of the glomurular tuft .The lesion could be either in A active or A/C active and chronic or C chronic one.Class V is defined as membranous lupus nephritis with global or segmental continuous granular subepithelial immune deposits often with concomitant mesangial immune deposits

Class VI advanced –stage lupus nephritis designates those biopsies with >90% gloalglomerulosclerosis and in which there is clinical or pathologic evidence that the sclerosis isattributable to lupus nephritis there should be no evidence of ongoing active glomerular disease.

Statistical methods: - Descriptive statistics was done by mean, standard deviation & bar charts for continuous variable and chi-square, Fischer exact test for categorical variable.

P value = or below 0.05 was regarded significant.

Results:

12patients in class I (2 males and 10 females); 16 patients in class II (2 males and 14 females); 18 in class III (2 males and 16 females, include 14 active, 1 chronic lesion and 3 active on chronic lesion) : 15 patients in class IV (3 males and 12 females , include 11 active,1 Chronic and 3 active on chronic lesion) ; 2 patients in class VI(2 female).

The mean age of patients was 22 years with a standered deviation $\pm$ 9 years.

The association between gender & response to prednisolone (response vs non response) was statistically not significant.

Good response to predinsolon in class I and II were 6 all females

Partial response to predinsolon in class I and II were 2 males and 9 females

No response to predinsolon in class I and II were 2 males and 9 females

The association of response to prednisolone vs the histopathological class was statistically not significant (table 1).

Table(1) response to prednisolone &histopathological class

		histopathological class		Total
		Class1&2	Class 3&4	
response to prednisolone	Respond	3	1	4
	not respond	25	32	57
	Total	28	33	61
response to immunosuppressor	Respond	17	12	29
	not respond	8	20	28
	Total	25	32	57

Good responses to immunosupressor in class III were 2 one male and one female.

Partial responses to immunosupressor in class III were 4 females.

No responses to immunosupressor in class III were 11 females.

Good responses to immunosupressor in class IV were 1 female.

Partial responses to immunosupressor in class IV were in 3 females and1 male.

No responses to immunosuppressor in class IV were 8females and 2 males.

2cases in class VI one female with partial response to immunosuppressor and one female did not respond.

The association between response to immunosuppressor&histopath class was statistically significant (P=0.03)(Table 1).

The association between response to immunosuppressor& age was statistically not significant(Table 2).

Table -2: The association of age and gender with response to immunosuppressor

		Response to immunosuppressor		Total
		Respond	Not respond	
Age	Below 20	12	13	25
	Above 20	18	16	34
	Total	30	29	59
Gender	male	3	5	8
	female	27	24	51
	Total	30	29	59

The association between immunosuppressor& gender was statistically not significant (Table 2).

Rituximab used in 27 resistant cases and showed the following results

Class I 2cases with partial response (1 male and 1 female).

Class II 6 cases (3 females good response). (3partial response1male and 2 females).

Class III 9 cases (6 females with good response). (2 partial response 1 male and 1 females), (no response in female).

Class IV 10 cases (4 females with good response) and (6 cases showed partial response 2 males and 4 females).

The response to rituximab (good &poor) was 26/27(96.2%), while the no response was only1/27(3.7%).

Theassociationbetweenresponsetorituximab&histopathologic class was statistically significant(0.048)(Table 3)(Figure2).

Table- 3: The association of response to rituximab &histopathologic class

			Histopathological class		Total
			class1&2	class3&4	
response to rituximab	responders	Count	8	18	26
		% within response to rituximab	30.8%	69.2%	100.0%
		% within histopathologic class	28.6%	56.2%	43.3%
	not respond	Count	0	1	1
		% within response to rituximab	0.0%	100.0%	100.0%
		% within histopathologic class	0.0%	3.1%	1.7%
	No receive	Count	20	13	33
		% within response to rituximab	60.6%	39.4%	100.0%
		% within histopathologic class	71.4%	40.6%	55.0%
Total		Count	28	32	60
		% within response to rituximab	46.7%	53.3%	100.0%
		% within histopathologic class	100.0%	100.0%	100.0%

P value = 0.048 (statistically significant)

The association between response to rituximab & gender was statistically significant (p=0.03) (Table 4).

Table- 4: The association between gender and response to rituximab

			Response to rituximab				Total
			Not used rituximab	good response to rituximab	poor response to rituximab	no response to rituximab	
Gender	male	Count	4	0	5	0	9
		% within gender	44.4%	0.0%	55.6%	0.0%	100.0%
	female	Count	32	13	8	1	54
		% within gender	59.3%	24.1%	14.8%	1.9%	100.0%
Total		Count	36	13	13	1	63
		% within gender	57.1%	20.6%	20.6%	1.6%	100.0%

P value =0.03 (statistically significant)

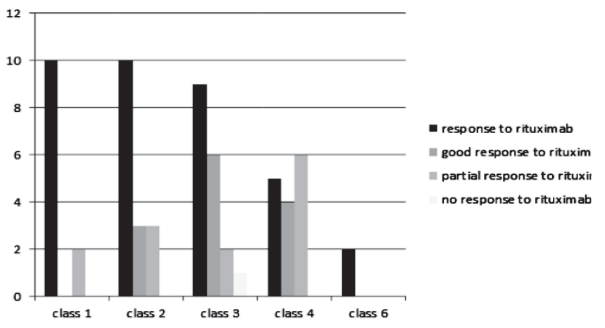

Figure - 1: The association of response to rituximab and histopathological class

The association between response to rituximab & age was statistically not significant (Figure -2).

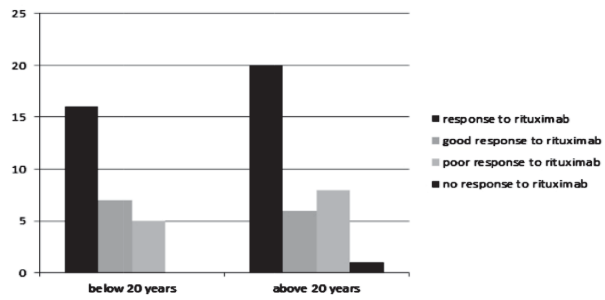

Figure -2:The association between age and response to retoximab

Discussion:-

Lupus Nephritis is the most important complication of SLE. Since the Lupus Nephritis can be sever and the treatment is toxic one should predict the patients who most benefit from long term treatment.13 Corticosteroid used in histopathalogical class I and II as it suppresses the immune system by reducing the putative soluble factors that posited to affect podocyst.14In this study we noticed high number of resistant cases and the response to the predinsolon therapy was only in 6 patients. This disagrees with studies like study of Bruchfield. A et al were the relapses and not responding to steroid in about 20-30% range in minimal change nephropathy14. This may be explained by delay the in presentation of cases to the Nephrology center and actually many of them got hypertension and hematuria at the time of presentation.

In cases of focal segmental one the respond to the steroid is limited when the lesion is chronic and there is element of fibrosis.15 Sex differences showed no effect on the response to the steroid in different stages and this may be explained by small number of the male cases were the disease affects mainly female gender and this was noticed also with the immunesupressor therapy. This is consistent with the study of Fredmanet al.16

The current study showed no significant relation between age and response to therapies &this may be explained by younger age group in the study as the cases <45 years age.

The difference in response in older people may be related to changes in liver & kidneys function. 17 The current study showed a significant response to immunesupressor therapy and this goes with Gourley et al &Dolley et al studies.18, 19 The Egyptian experience was in finding the same clinical results with use of large or small dose of i.v Cyclophosphamide. 20, 21 The last study raised the question of optimal dose required to get the prefer result. Early response to immunosuppressive therapy in 24 weeks predict good renal outcome Euro Lupus Trail.22, 23 This 24 weeks duration was depended by many physicians to decide the response of the patient in the right way of treatment. In recent studies researchers put a new strategy to decide earlier time that is as early as 8 weeks by testing new biomarkers and to concentrate on the complement3 (C3) ,complement4 (C4) and C3/C4 ratio.24 The B cell depletion by using Ritxuimab therapy in resistant cases of Lupus Nephritis used in this study the cases were followed for 1-3 years and there was a good and partial response in 26 cases out of 27 cases (92%)which is a good result &consistant with Davis et al study were 18 patients treated with Ritxuimab therapy, 13 patients showed a good response while the patients not responding were those with Crescentic proliferative histopathological type. Generally cases that did not show complete response in stages III and IV were those with chronic lesion.25, 26 The response to Rituximab therapy with sex was significant as sex has dependent effect and higher weight of the male contribute to their faster rituximab clearance.27 Pneumonia ,Herpes zoster ,oral thrush and one case developed convulsion after starting treatment with rituximab were reported during this study & all were controlled, the same was reported by Merril et al. 28, 29 Weledenbusch M et al study>s the efficacy of rituximab in resistant cases of lupus nephritis cases treated with rituximab & were followed for 60 weeks for the response (partial or complete) showed 87% in stage III 76% in stage IV 67% in mixed type which reflects a good results that goes with the current study. 30 In this study there were good results for 3 years duration with no relapse, while in many studies on rituximab therapy for resistant cases ended within one year duration. 31 In the study of Merrill et al in SLE patients with SLE in phase II/III in EXPLORER Trial it showed that less flare up with use of Rituximab after one year compared with the use of immunosuppressive therapy 29still we need longer time to see the success of Rituximab on a long run.

Conclusion:-

Immunosuppressive therapy may have good effect on lupus nephritis in different stages of the disease, rituximab therapy may be helpful in treating resistant cases of lupus nephritisand corticosteroid may be of no value if used in delay stages of the disease.

Recommendations:-

Cases of lupus Nephritis should be early diagnosed & referred to the Nephrology Center , use of biomarkers early and after a short period of the treatment to see cases which respond to the therapy and those which are resistant to the treatment.

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