Study on the effect of Mycophenolate Mofetil in lupus nephritis treatment

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Abstract: Introduction: Lupus nephritis is one of the most common and important complications of SLE. Regimens of glucocorticoids combined with cytotoxic drugs are effective for the treatment of severe lupus nephritis, however they have adverse effects. Mycophenolate mofetil acid (MMF) is an effective and immunosuppressive drug that has been used in renal and other organs grafts. Recently this drug has been used in treatment of lupus nephritis and limited studies show more benefits in comparison with currently used treatments. **Objective:** to study the effect of MMF in treatment of lupus nephritis. **Methods and materials:** this study has been performed prospectively on 15 patients with lupus nephritis symptoms that SLE was established in them. Patients with grade 3 & 4 lupus nephritis after receiving of 3 pulse of Methylprednisolone have been treated with MMF. At first, third, sixth and twelfth months after initiation of treatment patients have been examined clinically and also CBC-diff, ESR, CRP, BUN, Cr, serum protein and albumin levels, urinary analysis, complement components such as C3,C4, Ch50 levels, titers of ANA and anti-dsDNA, cryoglobulins, anticardiolipin and antiphospholipids was measured and finally all data analyzed statically. **Results**: All symptoms except of cerebritis were improved in 6 months after initiation of treatment. As well as inflammatory indicators such as ESR and CRP were decreased during treatment period. BUN, Cr and studied antibodies measurements were decreased significantly that shows improvement in renal function. Also improvement in condition of blood pressure of patients is another characteristic of improvement in renal function. Complement components (C3, C4 and Ch50) levels were increased significantly during treatment procedure. By other side amounts of blood cells never decreased under normal limits during treatment period and even in case of hemoglobin, results of this study show that its amounts increased during treatment period. Conclusion: treatment with MMF is as effective as Cyclophosphamide in regression of clinical symptoms and improvement of renal function, additionally serious adverse effects such as pancytopenia and opportunist infections are not seen in treatment with MMF.

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1. Introduction

LN (Lupus Nephritis) is one of the most common and important results and complications of SLE (systemic lupus erythematosus) and severe renal diseases can directly and indirectly (i.e. through treatment side effects) lead to mortality and morbidity (Apple, 2004). The annual outbreak of SLE in women is 5.4 cases per 100000 women while it is equal to 1 case per 100000 men. The highest incidence rate of SLE is in the 15-24 years age group. In addition, the maximum annual prevalence of this disease is 7.5 cases per 100000 people while the minimum incidence rate is in the 55-74 years age group with an annual prevalence of 1.2 cases per 100000 people. Lupus is 10 times more prevalent in women than men (Edworthy Steven, 2005). Almost 25 to 50% of lupus patients are suffering from renal involvement at the time of diagnosis and more than 60% of adults with SLE experience a sort of renal involvement in the course of the disease (Apple, 2004). Although kidney biopsy is feasible in specialized medical centers, urinary tests (including examination of proteinuria, presence of cells and casts in urine) and blood serum tests (including examination of blood azotemia) are known as the most effective means of monitoring patients through normal visits. Clinical findings such as signs of hypertension, reduced complement levels, and lymphopenia can reflect the advancement of diseases and a shift toward reduced renal function (Edworthy Steven, 2005). Glomerular involvement in SLE is usually caused by a human prototype of classic chronic immune complex which leads to glomerulonephritis (Apple, 2004). Chronic sedimentation of circulating immune complexes plays an important role in the development of certain types of lupus nephritis such as its mesangial and proliferative forms (Apple, 2004).

Levels of albumin and serum cholesterol are suitable markers that reflect the development of the nephrotic syndrome and determine the degree of proteinuria (Edworthy Steven, 2005).

Currently, intravenous Cyclophosphamide is known as the standard treatment for severe lupus glomerulonephritis (Ginzler, 2005). It is also used generally for the treatment of diffuse proliferative glomerulonephritis that is caused by systemic lupus erythematosus (SLE) (Kapitsinou, 2004). Immunosuppressive treatment diets composed of glucocorticoids and cytotoxic drugs (especially Cyclophosphamide) are effective for the treatment of LN. However, these diets are accompanied by rapid side effects and negative outcomes of conglomeration of drugs in body such as suppression of bone marrow, gonadal toxicity, hemorrhagic cystitis, opportunistic infections, and malignant diseases (Ginzler, 2005; Kapitsinou, 2004; Chan, 2005; Chan, 2000). Moreover, 18-57% of patients receiving Cyclophosphamide experience failure with the reoccurrence of the disease and increased advancement of the disease toward renal failure (Ginzler, 2005).

More than 15% of patients are resistant to treatment with Cyclophosphamide and 30-50% of patients develop ESRD (End Stage Renal Disease) (Mok and Lai, 2002). MMF is an effective immunosuppressive drug which is used in renal transplantation and other organ transplants (Kapitsinou, 2004; Zhao, 2003; Schanz, 2002). Mycophenolic acid is the active metabolic of MMF (Chan, 2000; Morath and Zeier, 2003) and is a selective non-competitive reversible inhibitor of the IMPDH enzyme (Morath and Zeier, 2003 ; Ishikawa, 1999). This medicine selectively suppresses the proliferation of the B and T lymphocytes, formation of antibodies, and glycosylation of binding molecules through reversible inhibition of the aforementioned enzyme (Chan, 2000; Morath and Zeier, 2003; Ishikawa, 1999; Jonsson and Carlsten, 2002). Recently, this drug has been used for the treatment of LN and the very few studies on the effectiveness and side effects of this drug for lupus patients reflect the higher advantages of this medicine over the common treatments (Ginzler, 2005; Kapitsinou, 2004; Chan, 2000; Mok and Lai, 2002; Zhao, 2003; Schanz, 2002; Morath and Zeier, 2003; Ishikawa, 1999; Jonsson and Carlsten, 2002; Ramos, 2003; Lui, 2002; Kingdon, 2001; Zoja, 2001).

2. Material and Methods

The present study was a prospective descriptive study that was carried out from 2009 to 2010 on 15 patients with LN symptoms who visited the renal diseases clinic or the nephrology section of Imam Reza Hospital and were definitively diagnosed with SLE.

The criteria for confirming the diagnosis of SLE in patients included 4 of the 11 diagnostic criteria defined for the diagnosis of lupus.

After confirming the diagnosis of lupus in patients and after proving the presence of LN through renal biopsy, patients with class 3 and 4 LN were exposed to MMF treatment after receiving 3 rounds of pulse therapy with methylprednisolone.

One, three, six and twelve months after the start of the treatment patients were subjected to clinical examinations for follow-up reasons.

Moreover, ESR, CRP, BUN, Cr, and CBC-diff tests were performed on all the patients while levels of serum protein, serum albumin, complement elements (including C_3, C_4, and Ch_{50}), ANA, Anti-dsDNA, cryoglobulins, anticardiolipin, and antiphospholipids were measured in the patients. Results of all the measurements and tests were also recorded.

Since complement changes about one month after the administration of MMF were slight and negligible the complement was only measured in the third and sixth months due to the high costs of the experiments.

Exclusion criteria for the study included the following.

- Showing any contradictions to the intake of MMF such as several wounds, upper gastrointestinal bleeding, and severe pancytopenia
- Lack of control over the clinical symptoms of the patient for three months after starting the treatment with MMF
- Development of any lethal condition after starting the treatment with MMF

Statistical Analysis:

The collected data were analyzed by SPSS-17 statistical software. The collected data were expressed as percentage and mean ± SD. Continuous (quantitative) variables were compared by Independent samples and Paired t test.

Categorical (qualitative) variables were compared by contingency tables and Chi-square test or Fisher's exact test. P-value ≤ 0.05 was considered statistically significant.

3. Results

In this research, 15 patients with LN were selected to study the effect of MMF on patients with this disease. The average age of patients was 28.8±9.25 years. 86.7% of patients were also female. The clinical and experimental findings about the patients along with their immunological parameters are presented in tables (1) to (3).

Moreover, 3 patients were diagnosed with stage-III LN and 12 patients had stage-IV LN.

Table 1: Physical finding of patients

	Before	1 month late	3 month late	6 month late	12 month late
SBP	141.3±17.16	146.33	144.67	137.60	134
DBP	9.33±7.67	90.07	81.53	81.67	78.53
Arthritis	26.7%	26.7%	13.4%	-	-
Cerebritis	53.4%	53.4%	20%	13.4%	-
Plevritis	26.7%	26.7%	-	-	-
Pericartitis	40%	-	-	-	-
CNS involvement	60%	46.7%	46.7%	-	-
Pulmonary involvement	40%	33.4%	6.7%	-	-
Cardiac involvement	33.4%	33.4%	-	-	-
Mouth ulcer	40%	13.4%	-	-	-
Photosensitivity	60%	60%	53.4%	-	-

Table 2: Laboratory finding of patients

		Before	1 month late	3 month late	6 month late	12 month late
ESR		59.33±33.47	51.13±29.19	49.66±29.73	29.33±25.28	20.80±11.08
Hb		11.26±1.99	12±1.65	12.37±1.18	12.85±0.98	12.93±1.27
WBC		6713±2111	8020±2964	8360±2508	6846±1752	6243±1956
PLT		119533±68116	158200±11538	139666±65280	252133±35971	181533±55550
Pr		2916±1158	2430±779	1740±707	1086±309	267±148
Alb		3.39±0.59	3.33±0.60	4.28±0.33	4.37±0.25	4.5±0.23
BUN		27.64±5.28	19.50±6.89	13.29±3.50	19.36±5.83	13.09±3.45
Cr		2.04±2.44	1.72±0.66	1.44±0.49	1.45±0.45	1.27±0.47
Urine WBC		14±3.54	13.93±3.43	11.87±2.72	4.66±1.23	1.4±0.63
Urine	0	0	0	0	0	10(66.66%)
Pr	1±	0	0	0	0	4(26.7%)
	2±	0	0	3(20%)	14(93.33%)	1(6.66%)
	3±	12(80%)	13(86.66%	12(80%)	1(6.66%)	0
	4±	3(20%)	2(13.33%)	0	0	0

Table 3: Immunological finding of patients

	Before	1 month late	3 month late	6 month late	12 month late
C3	13.27±3.43	-	69.47±18.36	88.93±36.03	-
C4	10.60±2.13	-	26.13±6.89	43.06±6.97	-
Ch50	67.80±4.72	-	101.96±29.96	123.21±22.29	-
ANA	8.5±6.29	6.19±4.44	3.61±2.20	2.89±1.17	1.38±0.45
Anti-ds DNA	60.13±50.87	36.60±17.13	27.13±11.83	16.73±6.43	9.67±4.25
Anticardiolipin	8(53.33%)	-	-	5(33.33%)	3(20%)
antiphospholipids	7(46.7%)	-	4(26.7%)	3(20%)	3(20%)
Crayoghlo	6(40%)	-	4(26.7%)	4(26.7%)	4(26.7%)

4. Discussions

Among the clinical signs and examples of involvement of different organs, which were addressed in this study, the quickest response to treatment was seen in the treatment of Pericartitis. That is to say, within one month after the start of the treatment, of all of the patients with Pericartitis recovered. The second clinical signs that showed quick response to treatment with MMF were mouth ulcers.

In sum, all of the signs and symptoms under study were addressed six months after the start of treatment except for cerebritis. At the end of the 12th month, all of the patients with cerebritis recovered from the condition. Therefore, clinical response to treatment with MMF was completed 12 months after the start of treatment.

Compared to human studies, the clinical responses from the present study were similar to the study by Zhan.

Although full remission was achieved after 6 months in the present study, 11 of the 19 patients under study showed signs of remission in the first 4 weeks of the treatment (Mok and Lai, 2002).

In addition, in the study by Ding (which was carried out in China) and the study by Burrati similar

results were obtained. In other studies no explicit reference was made to the remission of the clinical symptoms or the time required for the remission.

Regarding the experimental signs, inflammatory criteria (ESR-CRP) declined significantly in the course of treatment and the decline can be considered a sign of a proper response to treatment. In none of the studies the criteria were assessed and therefore it was not possible to compare the results with the findings of other studies.

One of the major side effects of Cyclophosphamide is the decline in the number of blood cell lines and pancytopenia (Ding, 2004). However, research results indicated that the number of blood hemoglobin not only does not decline in the course of treatment but also increases progressively. That is to say, at the end of the 12^{th} month of treatment the level of hemoglobin in the patients increased. This finding is comparable to the result of the study by LI et al. (Li, 2002) who reported that the level of hemoglobin increases in a 6 months period. On one hand, as seen in the trend of changes in the number of white blood cells (WBC), no significant variation is caused by MMF. On the other hand, the number of WBCs was always within the normal limits. This finding first of all suggests that MMF does not cause leukopenia and also indicates that no inflammatory and infectious condition is caused by the consumption of this drug(Hu, 2002). These results are similar to the findings of the research by Chan (Chan, 2000) because in this study the difference between the number of patients in the control group and MMF group who develop leukopenia is significant. In the MMF group (i.e. the group receiving MMF) no signs of leukopenia were observed. However, in the studies by Li (Li, 2002) or Buratti (Buratti, 2001) leukopenia was reportedly seen in patients treated with MMF. The difference between the study by Li and the present study is that the number of patients examined by Li (75 patients from 9 different hospitals) was higher which increased the reliability of their study.

In the study by Buratti all of the patients were children and perhaps it can be concluded that the chances of outbreak of leukopenia in children is higher than adults. However, in none of the aforementioned studies the resulting leukopenia was so dangerous that could lead to cessation of the treatment or emergence of lethal complications. When the number of plackets was counted, only in one of the patients the number had declined drastically and had reached 13000. The trend improved with continuation of the treatment and therefore it cannot explain the effect of MMF on the number of plackets. Moreover, the number of plackets in none of the aforementioned previous studies was measured and therefore no information is available for comparing the results of the present study with similar studies. Hence, it can be concluded that one of the major advantages of administration of MMF for treat lupus patients over administration of Cyclophosphamide is prevention of pancytopenia or a reduction in any blood cell line.

Concerning the number of serum proteins research results revealed that in spite of the significant decrease in the serum protein in the course of treatment, the level of serum albumin not only did not decline but also increased gradually and the increase was also significant. These two findings are contradictory because the level of albumin is expected to decline with a decrease in the level of serum protein. Hence, it seems necessary to carry out studies centered on this finding.

In the studies by Ginzlet and Chan (Chan, 2000) the level of serum albumin increased significantly. Their results are therefore in line with the results of the present study in this sense. However, the total serum protein was not measured in those studies and therefore the results obtained from our study in this regard cannot be compared to other results.

Concerning the level of complement components it can be said that all of the complements under study (C3, C4, and CH50) increased significant as a result of administration of MMF. This increase reflects a reduction in the sedimentation of complements in glomerulars and prevention of hypocomplementemia in patients. In another study in which the level of complement components was assessed similar results were obtained. In the studies by Ginzler (Ginzler, 2005) and Chan (Chan, 2000) the levels of C3 and C4 were in the normal range while in the studies by Li and Buratti the levels of complement components were also in the normal range. This reflects the similarity of results obtained from the aforementioned studies. In none of these studies the level of CH50 was measured separately and it is one of the strengths of the present study(Li, 2002; Buratti, 2001).

Concerning the antibodies under study it can be said that all of these antibodies decline in the course of the treatment. This reduction complies with the nature of the treatment in use and is therefore expectable. Results of the studies by Li (Li, 2002), Buratti (Buratti, 2001), Johnsson (Jonsson, 1999), Chan (Chan, 2000), and Ginzler (Ginzler, 2005) also confirm this finding.

On the other hand, factors associated with nephritis such as anti-dsDNA, anticardiolipin, antiphospholipids, and cryoglobulins also declined significant in the course of treatment with MMF. Therefore, at the end of the sixth month the reduction in these factors was statistically significant. This

finding indicates that treatment with MMF is fully effective for these antibodies.

Of the aforementioned factors only cryoglobulins was measured by Hu et al. (Hu, 2002) and the results showed a reduction in the level of cryoglobulins similar to the present study.

Hence, the present study can be considered a pioneering study because of measuring levels of anticardiolipin and antiphospholipids as factors associated with nephritis.

Analysis of renal tests revealed that values of BUN and Cr decline gradually and significantly, which reflects the improvement of renal function. These findings, especially with regard to the level of Cr, comply with the findings of Kapitsinou et al. (Kapitsinou, 2004), Ginzler (Ginzler, 2005), and Chan (Chan, 2000). However, in the aforementioned studies the level of BUN was not measured. The reduction in the level of BUN in this study complies with results of the research by Zoja et al. (Zoja, 2001).

In addition, the effect of treatment on hematuria and proteinuria was fully evident at the end of the third months in the patients and was statistically significant. The increasing trend of improvement of the function of glomerulars continues to the end of the 12-month treatment period. Regarding the findings about proteinuria it can be said that results of the present study are consistent with the results reported by Ginzler (Ginzler, 2005), Chan (Chan, 2000), Morath (Morath and Zeier, 2003), Li (Li, 2002), and Zoja (Zoja, 2001). However, hematuria was only studied by Johnsoon and Hu whose findings complied with the findings of our study.

Modification of the SBP and DBP values in the course of treatment indicated recovery of the natural functionality of the kidneys. Therefore, at the end of the sixth month the reduction in these values was statistically significant concerning both types of blood pressure.

The levels of blood pressure were only assessed by Kapitsinou (Kapitsinou, 2004) whose findings are in line with the results of this study.

Conclusion

Since the outcome of the disease changes depending on the criteria for its activity and since the fully examined activity criteria were also omitted or improved, the effect of MMF on the outcome of the disease was found to be positive. Moreover, since lupus is a life time disease and cannot be fully treated it can only be controlled. Hence, control of this disease is considered a form of treatment.

Administration of MMF as an alternative treatment for SLE is as effective as the use of Cyclophosphamide for the remission of clinical signs and recovery of renal function. Moreover, the dangerous side effects of Cyclophosphamide such as pancytopenia and outbreak of opportunistic infections are reduced with the use of MMF.

Suggestions

Due to the low number of patients with SLE, the reliability of studies can be improved by conducting studies with cooperation of several treatment centers to gain access to a larger number of patients.

Unification of the subject matters of different studies facilitates the comparison of results obtained from different studies.

Since biopsy is necessary for final verification of renal improvement, it is recommended to plan on studies that provide for a second time biopsy at the end of the treatment period.

The use of approved indices such as the activity-index and chronicity-index is recommended.

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