COMPARISON OF THE EFFICACY AND SIDE EFFECTS OF CYCLOSPORINE-A AND METHOTREXATE IN THE TREATMENT OF THE PATIENTS WITH RHEUMATOID ARTHRITIS

Romatoid artritli hastaların tedavisinde metotreksat ve siklosporin-A nın etkinlik ve yan etkilerinin karşılaştırılması

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Abstract

Purpose: *This study was carried out to compare the efficacy and the side effects of cyclosporine A (CyA) and methotrexate (MTX).*

Patients and Method: *Twenty-nine patients with RA, who applied to Erciyes University, Medical Hospital, Physical Medicine and Rehabilitation Department between 1996--1997, were included in the study. The patients were divided into two groups. The first group of 15 patients was treated with CyA, 3 mg/kg/day and the second group of 14 patients with MTX, 7.5 mg/week . Patients were followed up for clinical and laboratory parameters for a period of six months. During the follow-up period, the groups were compared with each other for these parameters.*

Results: *At the end of six months, both medical treatments were found to be effective in clinical parameters, but no statistically significant difference was observed. In laboratory parameters, a statistically significant decrease was found in the erythrocyte sedimentation rate of the group treated with MTX ($p<0.05$). The study was evaluated for side effects. Systolic and diastolic blood pressure and serum creatinine values in the group treated with CyA, and AST values in the group treated with MTX were found to be increased with a statistically significance ($p<0.05$).*

Conclusion: *As a result, we conclude that both of the medicines used for RA treatment were effective at low toxic levels which could be tolerated. We also coclude that MTX must be used as a first choice since it is more economical.*

Key Words: *Arthritis, rheumatoid; Cyclosporine A, Methotrexate*

Özet

Amaç: *MTX ve CyA'nın etkinlik ve yan etkilerini karşılaştırmak amacıyla bu çalışma yapıldı.*

Hastalar ve Metod: *Çalışmaya, 1996-1997 yılları arasında Erciyes Üniversitesi Tıp Fakültesi Fiziksel Tıp ve Rehabilitasyon (FTR) Anabilim Dalı'na başvuran 29 romatoid artritli (RA) hasta alındı. Hastalar iki gruba ayrıldı onbeş hastadan oluşan ilk grup 3 mg/kg/gün dozunda Siklosporin A (CyA) ile, 14 hastadan oluşan ikinci grup 7.5 mg/hafta dozunda metotreksat (MTX) ile tedavi edildi. Hastalar 6 aylık tedavi süresince klinik ve laboratuar parametreler ile takip edildi. Gruplar, takipler sırasında bu parametreler bakımından karşılaştırıldı.*

Bulgular: *Her iki tedavi yöntemi, 6 aylık takip sonunda klinik parametreler yönünden etkili bulundu ve aralarında anlamlı fark bulunmadı. Laboratuar parametreleri incelendiğinde, MTX grubunda sadece eritrosit sedimentasyon hızında anlamlı şekilde azalma saptandı ($p<0.05$).*

İlaçların yan etkileri gözden geçirildiğinde; CyA tedavisi alan grupta sistolik ve diastolik kan basıncı ve serum kreatinin seviyelerinde, MTX tedavisi alan grupta ise AST değerlerindeartma olan olgu sayısı anlamlı şekilde fazlaydı ($p<0.05$).

Sonuç: *Her iki ilacın da RA tedavisinde etkili olduğu ve tolere edilebilir derecede düşük toksik etkileri olduğu sonucuna varıldı. Ayrıca daha ekonomik olması nedeniyle, RA tedavisinde bu ilaçlardan öncelikle MTX'ın tercih edilmesi gerektiği düşünüldü.*

Anahtar Kelimeler: *Metotreksat, Romatoid artrit, Siklosporin A*

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Rheumatoid arthritis (RA) is a systemic condition characterized by inflammatory synovitis, elevated acute phase response, and extra articular manifestations. It has a variable course which often

leads to functional decline, work disability, and increased mortality rates (1,2). Many second-line agents including cyclosporine A (CyA) and methotrexate (MTX) are now available to treat RA and they have been shown in clinical trials to be more effective than a placebo. The choice of which slow-acting drug to prescribe for patients with RA depends on both its efficacy and toxicity (3).

MTX is an effective agent in the short-term treatment of refractory RA (4,5). MTX has proved to be a major advance since the 1980s for the treatment of RA (6). The number of patients who can continue to take MTX for long periods of time is quite favorable when compared with other second-line therapies (7,8).

CyA is a potentially useful agent for the treatment of RA both in early and advanced disease stages. It is superior to conventional second-line agents in slowing radiological progression of the disease (9). CyA, which has revolutionized the management of rejection in solid organ transplantation, was first studied in patients with RA by Hermann and Muller in 1979 (10,11).

PATIENTS AND METHODS

Twenty nine patients, with a mean age 44.1±12.7 years (27-65), with RA diagnosed according to ARA-1988 criteria (12) were included in the study. The patients were admitted to the Physical Medicine and Rehabilitation Department of Erciyes University Medical Faculty between February 1996--September 1997. The ARA-1988 criteria for the classification of RA (12) consists of morning stiffness of at least one hour, arthritis of three or more joint areas, arthritis of hand joints, symmetric arthritis, rheumatoid nodules, positive serum rheumatoid factor (RF), and radiographic changes typical of RA. Radiographic changes and physical findings must be present for at least six weeks. Four of seven criteria are required to establish the diagnosis of RA. Patients who were over 65 years old, pregnant, those who took second line medicine treatment within the last six months, and whose results of hepatic and renal functions were unsatisfactory, were excluded from the study. The treatment was explained to the patients and informed consent was obtained, before the study was applied. The patients were divided into two groups; the first group included 14 patients who were treated with 3 mg/kg/day CyA p.o., the second group included 15 patients, who were treated with 7.5 mg/week MTX p.o. Remission was defined according to clinical remission criteria of 1981-ACR Committee, (13) . which consisted of absence of fatigue, absence of joint pain, absence of synovial swelling, absence of joint tenderness, normal sedimentation rate, and morning stiffness of less than 15 minutes. The patient were required to meet five of these criteria to be classified as being in remission(13). Disease duration was 4.6±2.8 (1--8) years in the CyA and 3.6±4.2 (1--5) years in the MTX group.

The first group included 15 patients who were treated with 3 mg/kg/day CyA p.o. The second group included 14 patients who were treated with 7,5 mg/week MTX p.o. For a period of six months, patients were followed up for visual analog scale (VAS), Lee Functional Index (LFI), Ritchie Articular Index (RAI), morning stiffness, and swollen joint number as clinical parameters, Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF) as laboratory parameters. During the follow-up period, the groups were compared with each other for these parameters.

Student-t test was used for statistical evaluation. Values are expressed as mean ± SE.

RESULTS

Mean age of the patients were 45.4±6.7 years (range: 27-56) in the CyA group including 14 patients (12 women, 2 men), and 43.3±15.2 years (range: 28--65) in the MTX group including 15 patients (12 women, 3 men). In both groups, the mean duration of disease was similar (4.6±2.8 years in CyA group, 3.6±4.2 in MTX group, $p>0.05$). The number of the patients who received disease-modifying antirheumatic drugs (DMARDs) previously were six in CyA group, and five in the

MTX group. The groups proved to be well balanced with regard to demographic characteristics.

At the end of the six month follow up, both treatments were found to be effective in clinical parameters, but no statistically significant difference was found (Table I). In laboratory parameters, a statistically significant decrease was found in only ESR of the group treated with MTX (Table II).

CyA dose was increased to 4 mg/kg/day in two patients, and MTX dose was raised to 15 mg/week in two patients. Only one patient in CyA group needed to stop taking the drug because of serum creatinine elevation, and one patient in the MTX group due to high elevation of the liver enzymes. The drug side effects are shown in Table III. In the CyA group, as shown in Table III, there is serum creatinine elevation in four patients, hypertension in six, hypertrichosis in four, headache in three, gastrointestinal intolerance in two, and gingival hypertrophy in one; in the MTX group, elevation of serum liver enzymes in three patients, headache in two, skin rash in one, and gastrointestinal intolerance in three.

Table I. Comparison of clinical parameters in CyA and MTX groups

	Before Treatment				After Treatment			
PARAMETERS	**CyA**	**MTX**	**t**	**p**	**CyA**	**MTX**	**t**	**p**
VAS	6,4 ± 1,3	7,2 ± 1,6	-1,3	>0,05	1,3 ± 1,8	1,6 ± 1,3	-0,5	>0,05
LFI	14,5 ± 6,6	14,9 ± 8,7	-1,4	>0,05	1,9 ± 3,5	2,3 ± 5,5	-0,2	>0,05
RJI	21,07 ± 6,7	20,2 ± 11,0	0,234	>0,05	3,6 ± 5,0	3,7 ± 4,3	-0,05	>0,05
NSJ	4,4 ± 2,8	6,3 ± 4,3	-1,3	>0,05	0,4 ± 0,8	0,7 ± 1,6	-0,4	>0,05
MS	67,5 ± 41,9	67,0 ± 37,1	0,034	>0,05	4,6 ± 12,8	5,0 ± 0,8	-0,08	>0,05

VAS: visual analog scale LFI: Lee functional index RJI: Ritchie joint index NSJ: Number of swollen joints MS: Morning stiffness

Table II. Comparison of laboratory parameters in CyA and MTX groups

	Before Treatment				After Treatment			
Parameters	**CyA**	**MTX**	**t**	**p**	**CyA**	**MTX**	**t**	**p**
ESR	48,2 ± 24,4	60,2 ± 52,8*	-0,7	>0,05	32,4 ± 21,3	23,1±19,6*	1,8	>0,05
CRP	34,2 ± 28,8	39,2 ± 40,0	-0,387	>0,05	1,0 ± 19,3	9,8 ± 16,9	0,1	>0,05
RF	56,6 ± 29,6	93,0 ± 151,007	-0,8	>0,05	35,6 ± 28,4	32,2 ± 27,1	0,3	>0,05
BUN	17,8 ± 4,2	19,4 ± 4,5	-0,9	>0,05	21,4 ± 7,9	20,2 ± 2,7	0,5	>0,05
Cr.	0,6 ± 0,1**	0,7 ± 0,2	-1,4	>0,05	1,0 ± 0,2**	0,7 ± 0,1	3,4	0,002
Uric A.	4,0 ± 1,6	4,1 ± 0,8	-0,056	>0,05	5,2 ± 1,6	4,1 ± 1,2	1,9	0,06
Na+	140,1 ± 3,9	141,6 ± 3,0	-1,1	>0,05	143,5 ± 3,2	139,1 ± 8,8	1,6	>0,05
K+	4,7 ± 0,5	4,2 ± 0,4	2,4	>0,05	5,0 ± 0,3	3,9 ± 0,6	5,1	0,0001
Bil.	0,5 ± 1,9	0,6 ± 0,2	-7	>0,05	0,7 ± 0,2	0,6 ± 0,1	1,2	>0,05
GGT	16,1 ± 12,7	19,6 ± 9,1	-0,8	>0,05	19,2 ± 11,1	19,4 ± 11,4	-0,04	>0,05
AST	17,0 ± 5,3	15,4 ± 7,1***	0,6	>0,05	18,7 ± 4,1	20,0 ± 9,0***	-0,04	>0,05
ALT	13,7 ± 5,1	15,8 ± 7,7	-0,8	>0,05	17,0 ± 3,9	22,8 ± 14,2	-1,4	>0,05

** There was a significant difference (p<0.05), **There was a significant difference (p<0.05), ***There was a significant difference (p<0.05)*

Table III. Distribution of side effects in CyA and MTX groups

SIDE EFFECTS	CyA Group No. of patients (%)	MTX Group No. of patients (%)
Hypertension	6 (%42.8)*	0 (%0)
Hypertrichosis	4 (%28.5)	0 (%0)
serum CK elevation	4 (%28.5)*	0 (%0)
Gingival hypertrophy	1 (%7.1)	0 (%0)
Headache	3 (%21.4)	2 (%13.3)
GIS intolerance	2 (%14.2)	3 (%20)
Serum liver enzyme elevation	0 (%0)	3 (%20)
Skin rash	0 (%0)	1 (%6.6)

**Significantly increased ($p<0.05$) compared to the pretreatment group*

DISCUSSION

The optimum program for the management of RA would rapidly control inflammation, prevent joint damage, preserve function and quality of life, be safe, inexpensive, and convenient to use over an extended period of time (14). Current therapy for RA generally consists of NSAID and a second—line agent including methotrexate (MTX), oral and intramuscular gold, antimalarial agents, azathioprine, D—penicillamine, sulphasalazine and more recently, cyclosporine (CyA) (15). There are some handicaps for DMARDs; these agents are usually only partially effective, and many patients discontinue therapy because of drug toxicity and/or loss of efficacy (16). The primary aim of the DMARD treatment is to reduce the activity of the disease and then to slow progression (17). In the traditional therapeutic pyramid, recommended in major textbook and reviews on the treatment of RA, approximately 5—8 are required to traverse the pyramid from bottom to top using single sequential drug in the treatment program. But in general, joint damage occurs in the first one to two years of disease (14). This explains the physicians must use the effective second—line drugs as soon as possible in the early period of the disease.

CyA and MTX, accepted effective drugs in the treatment of RA in recent studies, are two of the efficacious second—line drugs.

Some placebo-controlled trials were performed in patients who had failed previously applied second-line therapies (5,18). Weinblatt, et al. (18), reported significant improvement in efficacy parameters in a 35-patient, 24-week, double—blind crossover trial of low dose MTX versus placebo. MTX was superior to the placebo in improving the patients' response, and improvement began within three weeks. A study, which included 189 patients, who received MTX (7.5 mg to 15 mg/week) or a placebo, was reported by Williams, et al. (5). There was a significant improvement in all clinical parameters and ESR in the MTX group. When compared with other DMARDs in terms of efficacy and toxicity, MTX has been found to be less toxic than parenteral gold salts and D—penicillamine, and as toxic as sulphasalazine and oral gold salts, but more toxic than hydroxychloroquine (19). MTX exhibited the best efficacy:toxicity ratio among the efficacious DMARDs. MTX has not been definitely established to prevent radiographic progression of the disease (20).

The most common adverse events with MTX are gastrointestinal toxicity including anorexia, nausea, vomiting, diarrhea, and weight loss (21,22). Central nervous system side effects including headache, fatigue and malaise are surprisingly common (23). Cirrhosis may occur, although its incidence is controversial (24). ACR recommended liver

biopsies only after five years, or if liver enzymes were frequently elevated (24). Hematological toxicity including leukopenia, thrombocytopenia, megaloblastic anemia, and pancytopenia may occur (22).

CyA exerts a number of pharmacologic effects; its most interesting action is to selectively modulate subpopulations of immunocompetent cells. The compound is known to exhibit the capacity of T cells to synthesize and release interleukin-2 (11). The prompt in vitro and in vivo reversibility of its immunosupressive activity demonstrates that the response is not due to a lymphocytotoxic action (25). CyA can therefore be considered to be the first drug of a new generation of immunosupressive agents. The findings of the recent studies suggest that CyA is effective in the treatment of RA (25). CyA showed a clear benefit over placebos, and improvement in all clinical parameters was noted (9). CyA produced little effect on ESR; around an average of 40% improvement in CRP levels over a period of six months. The lack of effect of CyA on ESR has been noted in almost all studies. It probably reflects the drug's inability to affect certain acute-phase reactants, fibrinogen, which determines the sedimentation rate. The practical implication for this is that the ESR cannot be used as a reliable guide for response in clinical practice. The drug has been employed extensively as an immunosuppressive agent for organ transplants (26). The optimum dose with regard to the efficacy balanced against toxic side effects has not been precisely determined, but most protocols employ doses of 3.0 to 5.0 mg/kg/day, with close monitoring of CyA blood levels (27).

Open label trials in RA were initiated in the early to mid-1980s. Van Rijthoven, et al. (28), reported on a double-blind, placebo-controlled trial in 36 patients with established RA. There was significant clinical improvement in the patients treated with CyA, 10 mg/kg/day initial dose, compared to those treated with a placebo. In that study, a 30% increase in serum creatinine over baseline levels was observed. Dougados, et al.(29), reported on a double-blind, placebo-controlled trial starting at dose of CyA 5.0 mg/kg/day to 7.5 mg/kg/day if the serum creatinine level allowed. Clinical efficacy in this study was similar to that reported by Van Rijthoven, but serum creatinine rose only 23% above baseline. Tugwell, et al. (30), reported a double-blind, placebo-controlled trial using "go low, go slow" method. The CyA was started at a dose of 2.5 mg/kg/day, then increased to a maximum dose of 5.0 mg/kg/day. Efficacy was significant compared to the placebo, and only 17% serum creatinine elevation was observed. When compared to the other DMARDs including auranofin, antimalarials, i.m. gold and D-penicillamine, there was a statistically significant reduction in erosions and radiological joint damage maintenance on CyA, even though the percentage of side-effects was slightly higher (31).

The most common adverse effects associated with CyA in clinical practice are disturbances of renal function and hypertension (2). In the initial studies, due to high dosage of CyA (up to 12.5 mg/kg/day), disturbances of renal function were seen (32). The risk of nephropathy can be reduced by the following measures: 1) using cyclosporin at a dosage of 2.5 to 5.0 mg/kg/day; and 2) monitoring serum creatinine levels. If serum creatinine levels persistently increase to above 30% of pretreatment levels, the dose of CyA should be reduced (33).

Recently, some studies were performed to compare MTX and CyA. CyA (2.5 to 5.0 mg/day) was compared with MTX (7.5 to 15 mg/kg/week) in a double-blind, placebo-controlled study of 264 patients who failed at least one prior DMARD (34). Both agents were superior to the placebo. MTX was superior to CyA in improving clinical parameters. In the study performed by Morina, et al. (35), MTX (7.5 mg/week) was found slightly more effective than CyA (2.9 mg/kg/day). In a study performed to compare CyA with MTX and azathioprine, CyA was accepted as an effective DMARD, comparable with azathioprine and MTX, and might be of benefit in the therapy of some recalcitrant RA cases refractory to all other DMARDs (36). Güzel et al.(37), reported in their study that significant clinical

improvement was observed in MTX (7.5 to 15 mg/week) and CyA (2.0 to 4.0 mg/kg/day) groups at the end of 6 months, but more significant improvement in ESR was observed in the MTX group.

In the present study, both medical treatments were found to be effective in clinical parameters, but no statistically significant difference was found. In laboratory parameters, a statistically significant decrease was found in only ESR of the group treated with MTX.

When the study was evaluated for the side effects; systolic and diastolic blood pressure and serum creatinine values in the group treated with CyA, and AST values in the group treated with MTX were increased with a statistical significance.

As a result, we conclude that both of the medicines used for RA treatment are effective at low levels with a tolerable toxicity. We also conclude that MTX must be used as the first choise since it is more economical.

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