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ARAŞTIRMA / RESEARCH

Effect of subcutaneous high-dose methotrexate treatment on the management of rheumatoid arthritis

Romatoid artrit yönetiminde subkutan yüksek doz metotreksat tedavisinin etkisi

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Abstract

Purpose: Methotrexate (MTX) is still the main treatment option for rheumatoid arthritis (RA). There is no consensus on drug administration routes and dosage when administered alone or in combination with other drugs. This study aims to identify the effects of early administration of a combination therapy containing high dose subcutaneous (SC) MTX on RA management.

Materials and Methods: Forty-five patients with RA who newly diagnosed were divided into two groups randomly. The patients who took 12.5 mg SC MTX per week in the first 4 weeks defined as a "low dose group". The patients who took 25 mg SC MTX per week in the first 4 weeks defined as a "high dose group". Then, patients of both groups continued with 12.5 mg oral MTX per week. Clinical and laboratory findings, disease activity scores and response rates of the patients were recorded at the beginning, 3rd months and 6th months.

Results: There was no significant difference between the two groups at 3rd month's values. There were statistically significant improvements at 6th month's values. Values were as follows in low and high dose groups: mean DAS28-CRP (3.5 vs 2.7), VAS pain score (3.3 vs 1.6), and TJC28 (3 vs 1.5), respectively.

Conclusion: Early administration of high-dose SC MTX effectively controls disease activity and increases the quality of life in RA patients.

Keywords:. Drug administration routes, methotrexate, rheumatoid arthritis

Öz

Amaç: Metotreksat (MTX), romatoid artrit (RA) için hala ana tedavi seçeneğidir. Tek başına veya diğer ilaçlarla kombinasyon halinde uygulandığında ilaç uygulama yolları ve dozajı konusunda fikir birliği yoktur. Bu çalışma, RA yönetiminde erken dönemde yüksek doz subkutan (SC) MTX içeren bir kombinasyon tedavisinin etkinliğini belirlemeyi amaçlamaktadır.

Gereç ve Yöntem: Yeni tanı almış kırk beş RA'lı hasta rastgele iki gruba ayrıldı. İlk 4 haftada, haftada 12,5 mg SC MTX alan hastalar "düşük doz grubu" olarak tanımlandı. İlk 4 haftada, haftada 25 mg SC MTX alan hastalar "yüksek doz grubu" olarak tanımlandı. Daha sonra her iki gruptaki hastalar haftada 12.5 mg oral MTX ile devam etti. Hastalara ait başlangıç, 3. ay ve 6. ay klinik ve laboratuvar bulguları, hastalık aktivite skorları ve yanıt oranları kaydedildi.

Bulgular: İki grup arasında 3. ay bulguları açısından anlamlı bir fark yoktu. 6. Ay değerleri açısından istatistiksel olarak anlamlı değişiklikler saptandı. Değerler düşük ve yüksek doz gruplarında şu şekildeydi: ortalama DAS28-CRP (3.5'e karşı 2.7; p = 0.01), VAS ağrı skoru (3.3'e karşı 1.6; p = 0.02) ve TJC28 (3'e karşı 1.5; p = 0.04), sırasıyla.

Sonuç: Bu çalışma, erken dönemde yüksek doz SC MTX uygulamasının, hastalık aktivitesini etkili bir şekilde kontrol ettiğini ve RA hastalarında yaşam kalitesini arttırdığını göstermiştir.

Anahtar kelimeler: İlaç uygulama yolları, metotreksat, romatoid artrit

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INTRODUCTION

Treatment of rheumatoid arthritis (RA) aims to control synovitis and to prevent joint damage. Early diagnosis and treatment of RA can avert or substantially slow the progression of joint damage in up to 90% of patients, thereby preventing irreversible disability[1]. Joint damage that may result in disability, begins early in the course of the disease. Response to treatment is worse in patients with prolonged and uncontrolled active disease. Thus, early aggressive treatment is recommended in the early stages of disease especially for those patients with poor prognostic factors[2]. Good results have been obtained with combination therapies to induce and maintain disease control[3].

MTX is currently suggested by the European League Against Rheumatism (EULAR) and by the American College of Rheumatology (ACR) as the first-line therapy for RA[4,5]. Due to its low cost and safety profile, MTX is the first-choice treatment option in both monotherapy and combination therapy. MTX can be combined with other conventional disease-modifying antirheumatic drugs (csDMARDs) or with biological disease-modifying antirheumatic drugs (bDMARDs)[6]. The early administration of combination therapy in RA treatment is known to be more effective than MTX monotherapy[7]. The benefits and safety of MTX have been documented in randomized trials comparing the placebo and other DMARD treatments[8,9]. In patients who did not tolerated MTX; leflunomide, sulfasalazine, and hydroxychloroquine can be used according to comorbidities, patient preferences and severity of disease[9]. These treatment strategies have potential to control synovitis and slow or stop radiographic progression[9]. Compared with other nonbiologic DMARDs, MTX has also been shown to improve survival (both cardiovascular and all-cause mortality) in patients with RA[10,11].

MTX is given in a single weekly dose, usually orally. The optimal starting dose and schedule for dose escalation are uncertain. Treatment with MTX involves different starting doses (7.5–25 mg/week). Depending on the degree of disease activity, the weight and age of the patient, the presence of comorbidities, MTX dose for most of the patients varies at a dose of 7.5 to 15 mg once a week. The clinically accepted approach is to start treatment with 7.5–15 mg/week and then increase the dose according to the response status within 4–8 weeks[12]. The treatment goal is remission or low disease activity[5]. The other aims of treatment contain minimizing joint pain and swelling, preventing radiographic damage and deformity development, and maintaining work and personal activities[13]. A high dose of 20-25 mg /week MTX is recommended prior to biological therapy according to EULAR 2019[14].

In pharmacokinetic studies, SC MTX bioavailability was higher than the same dose of oral MTX[5,15]. This difference is more pronounced at doses higher than 15 mg/week[5]. SC MTX has a less side effect profile compared to oral administration. In addition, it can be better tolerated by patients [5]. SC MTX administration in RA patients may prevent or delay the need for more costly biological therapy[16]. Subcutaneous dosing for initial is an alternatively favored method by some experts[17].

Today, there are different applications regarding the use and dosage of MTX. The hypothesis of this study is to demonstrate the positive effects of early treatment with high-dose subcutaneous MTX on disease control in RA.

MATERIALS AND METHODS

This study was approved by the Başkent University Institutional Review Board and Ethics Committee (Project no: KA04/102) and supported by the Başkent University Research Fund. Informed consents were obtained from all participants. All procedures that involved human participants were in accordance with the ethical standards of the institutional research committee and in accordance with the 1975 Helsinki Declaration and its later amendments or comparable ethical standards.

Sample

Between January 2009 and June 2009, 45 adult RA patients were included in the study. The patients were diagnosed with RA according to the ACR 1987 18 criteria. The patients had not used any rheumatic drugs other than nonsteroidal anti-inflammatory drugs in the last 3 months. Moreover, the patients must have shown a positive result for three of these four parameters: ESR > 28 mm/h, morning stiffness > 45 min, tender joint count > 8, swollen joints > 3. Those with liver, kidney, hematological, pulmonary, and cardiovascular systemic diseases were excluded

from this study. Patients who have a disease duration of less than three years were included in the current study.

Procedure

Data on demographic, clinical and laboratory findings were recorded at initiation and at 3rd and 6th months. The data obtained from the patients were as follows: age, gender, duration of illness, duration of morning stiffness, TJC28, swollen joint count 28 (SJC28), erythrocyte sedimentation rate (ESR), CRP, rheumatoid factor (RF), anti-citrullinated protein antibody (ACPA), serum creatinine, alanine aminotransferase (ALT), and hemoglobin levels. In addition, patients' DAS28-CRP, VAS pain score (range: 0–10 cm), ACR20/50/70 response rates and Modified Health Assessment Questionnaire (MHAQ) scores were also evaluated.

DAS-28-CRP

The disease activity score is calculated by inputting DAS 28-CRP, tender and swollen joint count, CRP, and the patient's global health assessment data. The Turkish validity and reliability of the DAS28-CRP scale has been performed (Sunar, 2017)[19]. Cronbach's alpha value was 0.91[19]. The DAS28-CRP scores were defined as >5.1 high disease activity, >3.2 and ≤5.1 moderate disease activity, >2.6 and ≤3.2 low disease activity[11].

VAS

Pain intensity was assessed by using "Visual Analog Scale" (VAS). The Turkish validity and reliability of the VAS pain scale have been performed . Cronbach's alpha was 0.84 for VAS pain scale[20].

MHAQ questionnaire

The difficulties while performing the activities of daily living were evaluated with the MHAQ questionnaire consisting of eight questions. Patients score these questions according to their degree of difficulty. Difficulty levels were; "without difficulty" = 0, "with some difficulty" = 1, "with great difficulty" = 2, "I can't" = 3[21]. The validity and reliability of this questionnaire were proven in previous Turkish studies [22].Reliability was 0.97[22].

Grouping and treatment

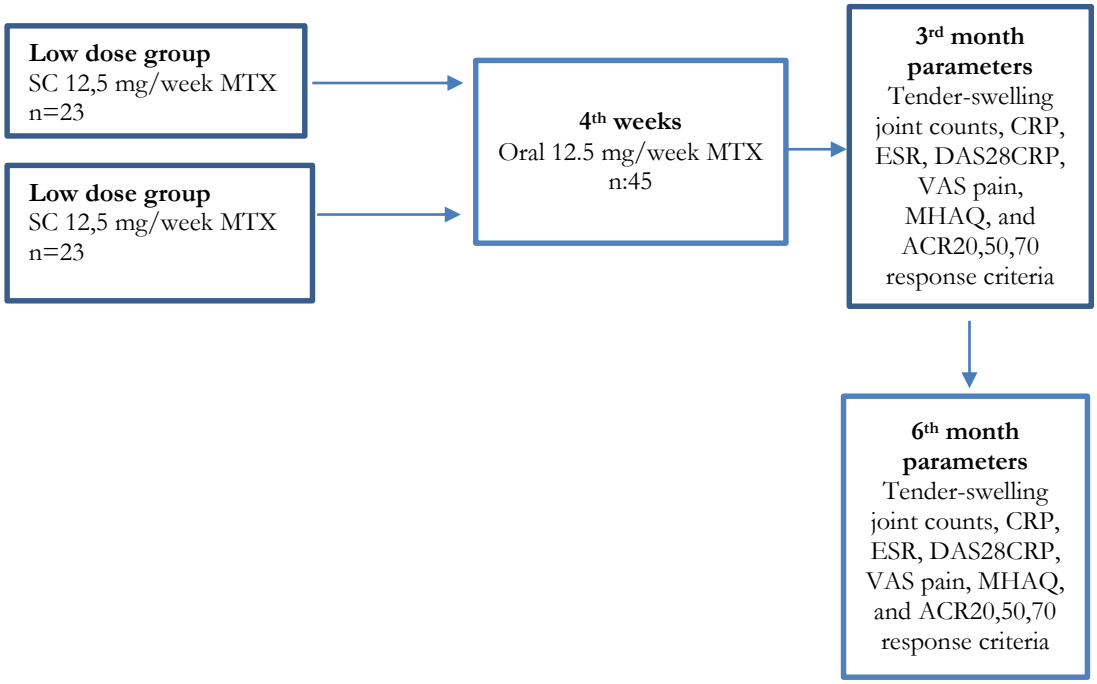
The patients were randomly divided into two groups, in this prospective study. Patients with a single last digit of the file number were inclusived in the low-dose treatment group, and the double ones were inclusived in the high-dose treatment group. The patients who received 12.5 mg SC MTX per week in the first 4 weeks defined as "low dose group". The patients who received 25 mg SC MTX per week in the first 4 weeks defined as "high dose group". Oral MTX was administrated 12.5 mg per week in both groups in the maintenance treatment. Besides the MTX treatment, 2 g/day Sulfasalazine (SSZ) and 5–7.5 mg/day prednisolone were given to both groups (Figures 1). When the DAS28 score was <3.2, the prednisone dose used by the patients was reduced by 2.5 mg / month. All patients were given 5 mg of folic acid per week.

Statistical analysis

Statistical analysis was performed using the statistical package *SPSS software* (Version 25.0, SPSS Inc., Chicago, IL, USA). If continuous variables were normal, they were described as the mean ± standard deviation (p>0.05 in Kolmogorov-Smirnov test or Shapira-Wilk (n<30)), and if the continuous variables were not normal, they were described as the median. Comparisons between groups (low dose and high dose group) were applied using Student T test or One-Way ANOVA for normally distributed data and Mann Whitney U test or Kruscall Wallis test were used for the data not normally distributed. The categorical variables between the groups were analyzed by using the Chi square test or Fisher Exc. test. Pre-post measures data (baseline, 3rd, and 6th-month data) were analyzed Paired T test or Wilcoxson test and Repeated Measure Analysis. Values of $p < 0.05$ were considered statistically.

RESULTS

This study involved 45 patients with a mean age of 53 ± 9.9 years, 75% of whom were female. The median duration of illness in these patients was 12 months (2–36 months). The two groups did not significantly differ in terms of age, gender, and disease duration. The morning stiffness before treatment was 60 min in low dose group and 150 min in high dose group. In the pre-treatment data, only the morning stiffness data significantly differed between the groups ($p = 0.01$). The patients' baseline demographic, clinical, and laboratory data are shown in Table 1.



CRP= C-reactive protein; ESR= erythrocyte sedimentation rate; DAS28= Disease Activity Score28; VAS pain= Visual Analog Scale pain; MHAQ= Modified Health Assessment Questionnaire; ACR20,50,70= American College of Rheumatology 20,50,70 response criteria

Figure 1. Study flowchart

Table 1. Patients' baseline demographic, clinical and laboratory data

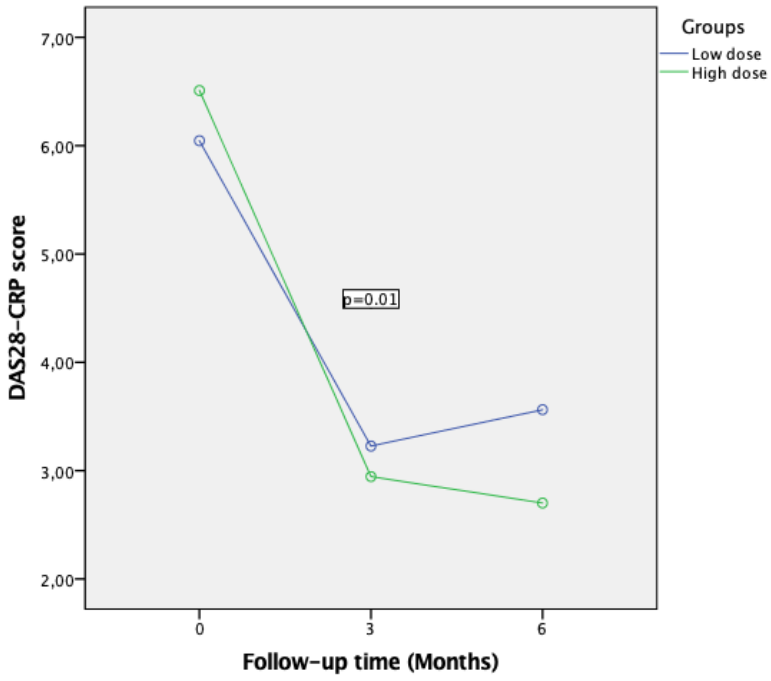
	Low Dose Group (n=23)	High Dose Group (n=22)	*P*
Demographic characteristic			
Age (years)**	55.6 ± 8.3	51.4 ± 11.1	0.19
Gender (female)*	17 (73)	17 (77)	1.00
Clinical characteristics			
Symptom duration (month)***	12 (2-36)	12 (3-32)	0.13
Morning stiffness (minute)***	60 (0-240)	150 (0-240)	0.01
SJC28**	4.6 ± 3.2	6.5 ± 4.2	0.10
TJC28**	10.8 ± 5.0	13.7 ± 5.9	0.08
VAS pain (0-10 cm) **	8.3 ± 1.7	8.2 ± 1.8	0.99
MHAQ**	15.8 ± 4.9	17.8 ± 5.3	0.26
DAS28 - CRP**	6.0 ± 0.7	6.5 ± 0.9	0.06
Laboratory characteristics			
CRP, mg/L***	22 (6-94)	29 (9-89)	0.22
ESR, mm/h***	36 (13-81)	41 (14-88)	0.27
RF positivity*	20 (87)	18 (81)	0.69
ACPA positivity*	17 (74)	17 (77)	1.00

SJC28= swollen joint count; TJC28=tender joint count; VAS pain= Visual Analog Scale pain; MHAQ= Modified Health Assessment Questionnaire; DAS28= Disease Activity Score28; CRP= C-reactive protein; ESR= erythrocyte sedimentation rate; RF= Rheumatoid factor; ACPA= anti-citrullinated protein antibody; *n (%), **mean ± SD, ***median (min-max)

A statistically significant improvement was found in morning stiffness, TJC28, and SJC28 at 3rd and 6th months when compared to baseline values in both groups. In addition, a statistically significant improvement was determined in the values of ESR, CRP, DAS28-CRP, VAS pain score, and MHAQ scores at 3rd and 6th months compared to baseline values.

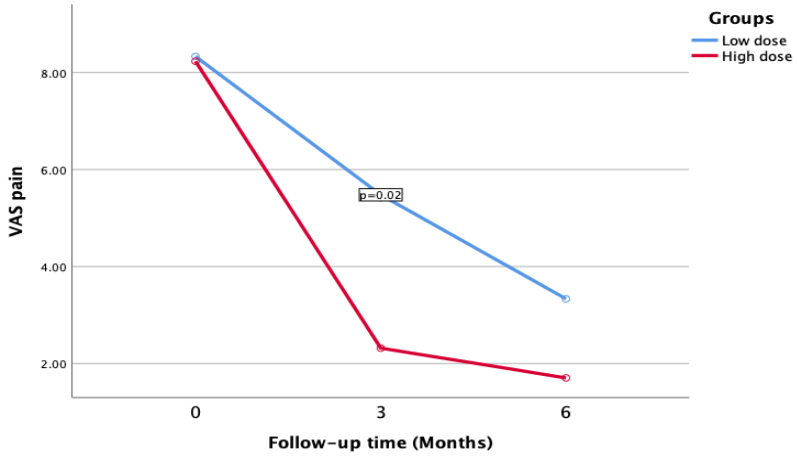
When both groups were compared with each other in terms of disease activity scores at 3rd months, no statistically significant difference was found. However, in the 6th months, a statistically meaningful response was found in the high dose group in terms of DAS28-CRP, VAS pain, and TJC28 values compared to the low dose group. The values for low dose and high dose groups at 6th months were as follows: mean DAS28-CRP (3.5 vs 2.7; p = 0.01), VAS pain (3.3 vs 1.6; p = 0.02), and TJC28 (3 vs 1.5; p = 0.04) (Figures 2 and 3). Table 2 compares the treatment groups' data obtained at baseline, 3rd and 6th months. At 3rd months, low disease activity and remission rate were observed as 52% in the low-dose group and 63% in the high-dose group (p = 0.23). At 6th months, low disease activity and remission rate were observed as 30% in the low dose group and 68% in the high dose group (p = 0.025).

ACR20 response rates at 3rd months were 96% vs 95% (p = 1.00) in the low and high-dose group, respectively, and 78% vs 91% at 6th months (p = 0.41). ACR50 response rates at 3rd months were 61% vs 82% in the low and high-dose group, respectively (p = 0.12). At 6th months, it was found to be 56% vs 77%, respectively (p = 0.14). ACR70 response rates at 3rd months were 48% vs 50% (p = 0.88) in the low and high-dose group, respectively, and 43% vs 45% at 6th months (p = 0.89).The ACR20, ACR50, and ACR70 response rates at 3rd and 6th months in the treatment group are compared in Figures 4-5.



DAS28= Disease Activity Score28

Figure2. DAS28-CRP scores according to groups



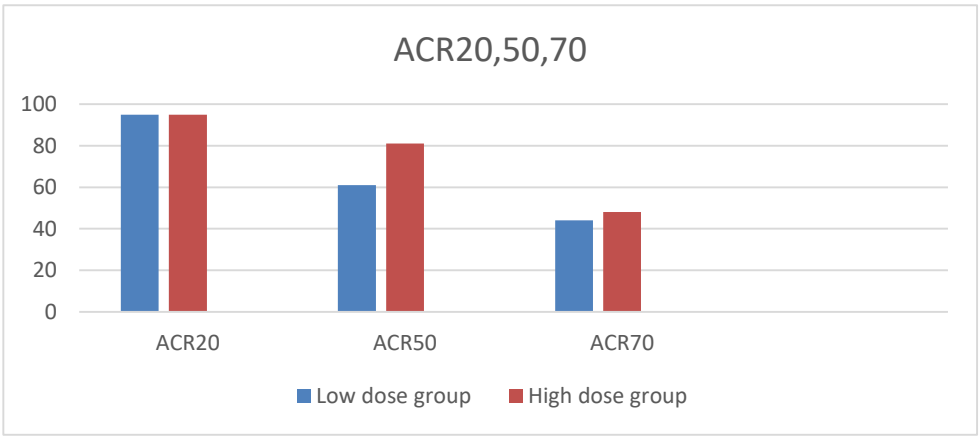
VAS pain= Visual Analog Scale pain

Figure 3. VAS pain according to groups

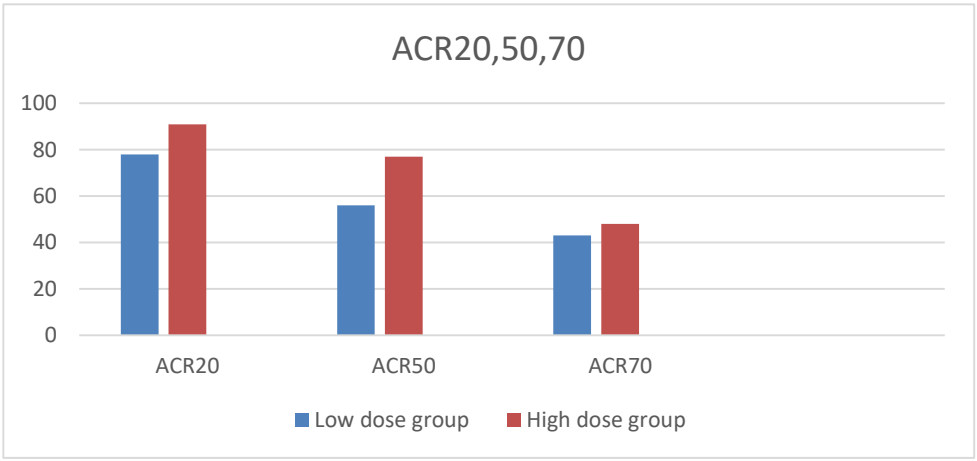
Table 2. Comparison of 3rd and 6th month data of treatment groups

	Months	Low Dose Group	High Dose Group	*p*
Morning stiffness (min) ***	Baseline	60 (0-240)	150 (0-240)	0.01
	Third month	0 (0-180)	0 (0-60)	0.49
	Sixth month	0 (0-180)	0 (0-60)	0.88
SJC28**	Baseline	4.6 ± 3.2	6.5 ± 4.2	0.10
	Third month	0.1 ± 0.4	0.2 ± 0.9	0.51
	Sixth month	0.5 ± 1.0	0.5 ± 1.2	0.95
TJC28**	Baseline	10.8 ± 5.0	13.7 ± 5.9	0.08
	Third month	2.5 ± 2.3	1.9 ± 2.1	0.37
	Sixth month	3.0 ± 2.4	1.5 ± 2.2	0.04
VAS pain** (0-10 cm)	Baseline	8.3 ± 1.7	8.2 ± 1.8	0.99
	Third month	5.4 ± 12.0	2.3 ± 1.6	0.13
	Sixth month	3.3 ± 2.7	1.7 ± 1.9	0.02
MHAQ**	Baseline	15.8 ± 4.9	17.8 ± 5.3	0.26
	Third month	5.0 ± 3.9	5.4 ± 4.5	0.96
	Sixth month	6.7 ±5.0	4.5 ± 4.7	0.12
DAS28-CRP**	Baseline	6.0 ± 0.7	6.5 ± 0.9	0.06
	Third month	3.2 ± 0.8	2.9 ± 0.9	0.28
	Sixth month	3.5 ± 1.1	2.7 ± 0.9	0.01
CRP, mg/dl***	Baseline	22 (6-94)	29 (9-89)	0.22
	Third month	8 (2-41)	7 (3-18)	0.67
	Sixth month	10 (4-48)	6 (2-20)	0.29
ESR, mm/h***	Baseline	36 (13-81)	41 (14-88)	0.27
	Third month	20 (10-38)	19 (8-44)	0.49
	Sixth month	24 (7-49)	19 (2-44)	0.18

SJC28= swollen joint count; TJC28= tender joint count; VAS pain= Visual Analog Scale pain; MHAQ= Modified Health Assessment Questionnaire; DAS28= Disease Activity Score28; CRP= C-reactive protein; ESR= erythrocyte sedimentation rate; **mean ± SD, ***median (min-max)



ACR20,50,70= American College of Rheumatology 20,50,70 response criteria
Figure 4. Comparison of ACR 20, 50, and 70 responses at third months in treatment groups



ACR20,50,70= American College of Rheumatology 20,50,70 response criteria
Figure 5. Comparison of ACR 20, 50, and 70 responses at sixth months in treatment groups

When the two groups were compared in terms of side effects, nausea, vomiting and fatigue were observed in 17% and 9% in the low dose group and high dose group, respectively (p = 0.66). Liver enzyme elevation was observed as 13% versus 18.2% (p = 0.69). The rate of patients requiring to switch treatment due to active disease at 6 months was 17.3% in the low dose group and 4.5% in the high dose group, respectively (p = 0.34).

DISCUSSION

The goal of treatment in RA patients is to achieve remission and low disease activity. It is important to optimize the therapy for patients and to use the appropriate MTX dose[23]. Although MTX has been used to treat RA for over 50 years, the optimal dose is not clear[1]. We compared the effectiveness of different doses and drug administration routes of use of MTX in combined therapy. We speculate that early

administration of the appropriate dose of MTX will reduce the need for biological therapy provide more permanent remission. A large proportion of patients (25-40%) significantly improve with MTX monotherapy, and in combination with glucocorticoids almost half of patients can attain low disease activity or remission in early RA, a rate similar to that achieved with biologic DMARDs[1]. In some early RA studies, approximately 30 percent of patients achieve low disease activity, where the dose of MTX is rapidly increased to 20 mg/week and the drug is continued for at least three months [24]. In patients whom 15 to 25 mg of MTX orally once weekly is ineffective or poorly tolerated due to gastrointestinal symptoms, a trial of subcutaneous administration of MTX is an alternative to another conventional DMARD or a tumor necrosis factor inhibitor[25]. EULAR recommendations favor combining biologic DMARDs and targeted cDMARDs with MTX. ACR70 responses are 35-40% with the combination of MTX and bDMARDs[1]. In our study, the ACR70 response was similar to the biological-MTX combination in those using combined csDMARDs. Currently, the combination therapy for RA (MTX–csDMARDs or MTX–bDMARDs) is more effective than monotherapy in controlling disease activity[26]. In the Cochrane meta-analysis[6], the triple combined therapy (MTX–SSZ–HCQ) demonstrated higher ACR50 response rates than the biological–MTX combination (67% vs 56%), although the difference was not significant. In another study, the oral triple csDMARDs (MTX–SSZ–HCQ) treatment was found to be as effective as the biological therapy–MTX combination[15,26,27]. In the FIN-RACo study[28], an ACR50 response rate of 75% was achieved in the first year of the quadruple (MTX-SSZ-HCQ-prednisolone) combined treatment with 15 mg oral MTX per week. In our study, the ACR50 response rate was found to be similar to this study. The mean age, RF, and ACPA positivity rates in our patients were similar to those obtained in other MTX studies[13,29,30-32].

In previous studies, the duration of symptoms was reported as 2.5–8 months[30-32]. In our study, the median symptom duration was longer than in other studies (12 months). In a study conducted in the early stage of RA disease, the MTX dose was recommended as 20-25 mg per week[23]. The CAMERA study[23], clearly demonstrated that the use of MTX with close monitoring can lead to a significant improvement in disease activity in early RA. It is aimed to increase the MTX dose rapidly to 20-25 mg per week. Thus, earlier identification of patients who would respond to MTX and benefit from combination therapy was provided[23]. In our study, while there was no difference in the early period with weekly 25 mg SC MTX treatment initiated without titration, a significantly lower disease activity and a higher remission rate were obtained in the 6th month.

Braun et al[31], compared SC and oral MTX therapy in RA patients. They were obtained the following ACR responses in patients treated with SC MTX and those treated with oral MTX: ACR20 (78% versus 70%), ACR50 (62% versus 59%), and ACR70 (41% versus 33%). In this study, at 6-months ACR responses rates were higher in the SC MTX group than oral MTX group[31]. In our study, 6-month ACR responses were also higher in the SC MTX group compared to the oral MTX group. However, it was not statistically significant.

In the Canadian Early Arthritis Cohort study[32] comparing SC MTX and oral MTX, it was reported that better response was obtained in the DAS28 score in the SC group. A statistically better response was also obtained in the SC MTX group at DAS28-CRP, VAS pain and TJC28 values in our study. High dose SC MTX was found to be safer and more effective in the early period in our study.

A study has found that 60%–65% of RA patients are dissatisfied with pain management[33]. In this study, it was reported that pain was still continuing in one third of the patients with improvement in treatment criteria. This finding indicates the need for a better treatment strategy[33]. In our study, a significant improvement was found in the pain score in the 6th month in the high-dose SC MTX group.

The factors limiting the use of MTX are the drug's side effects and the poor response to treatment. Life-threatening MTX-related toxicities are very rare at doses used in RA. Approximately 20-30% of patients in the treatment of RA have been reported to discontinue MTX within the first year of treatment because they cannot tolerate the side effects[34]. Drug withdrawal due to adverse events has been reported less frequently in csDMARDs compared to bDMARDs[15].

Side effects of high-dose SC MTX were better tolerated than oral doses of MTX. Gastrointestinal system side effects were observed more commonly because Mtx was administered orally in low-dose

group patients. Therefore, we think that the rate of drug withdrawal is higher in this group.

The limitations of our study are that it is a single-center study and the number of patients is limited. Another limitation is that the study was conducted by a single physician and was not designed as double-blind. Meanwhile, the strength of our study is that it included a homogeneous patient group and the patients were followed up regularly.

MTX can be considered as a stone bridge that serves as a link between the traditional and the current RA treatment. Our results showed that early administration of high doses of SC MTX results in more efficient disease control and leads to a more significant improvement in the patients' quality of life. In order to boost the significance of our study, prospective and multi-center studies involving a larger patient population are needed.

Yazar Katkıları: Çalışma konsepti/Tasarımı: AEY; Veri toplama: EDE; Veri analizi ve yorumlama: MAT; Yazı taslağı: MAT; İçeriğin eleştirel incelenmesi: HKK; Son onay ve sorumluluk: MAT, EDE, HKK, AEY; Teknik ve malzeme desteği: MAT; Süpervizyon: MAT; Fon sağlama (mevcut ise): yok.
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Ethical Approval: Ethical approval for this study was obtained from the Ethics Committee of Başkent University Faculty of Medicine with the decision dated 06.07.2004 and numbered 2004/99-07.
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