

# Evaluation of the Efficacy of Combined Therapy of Methotrexate and Etanercept versus Methotrexate as a Mono-Therapy

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## Abstract

**Citation:** Rexhepi S, Rexhepi M, Rexhepi B, Sahatçiu-Meka V, Mahmutaj V. Evaluation of the Efficacy of Combined Therapy of Methotrexate and Etanercept versus Methotrexate as a Mono-Therapy. *Open Access Maced J Med Sci.* 2018 May 20; 6(5):786-789. <https://doi.org/10.3889/oamjms.2018.173>

**Keywords:** Rheumatoid Arthritis; Methotrexate; Etanercept

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**Received:** 17-Dec-2017; **Revised:** 23-Mar-2018; **Accepted:** 24-Mar-2018; **Online first:** 24-Apr-2018

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**Funding:** This research did not receive any financial support

**Competing Interests:** The authors have declared that no competing interests exist

**AIM:** This study aims to evaluate the efficacy of Methotrexate (MTX) alone and combined therapy with Etanercept (ETN) and Methotrexate in patients with active rheumatoid arthritis (RA).

**METHODS:** In the randomised control study, conducted in the period from March 2014 until March 2016, we evaluated the efficacy of the treatment of patients with RA with MTX as monotherapy and combination treatment with MTX and ETN. In the Clinic of Rheumatology in Prishtina, 90 adult patients with RA were treated in combination with ETN (doses of 50 mg subcutaneously/weekly), with oral MTX (doses up to 20 mg weekly), and MTX alone (doses up to 20 mg weekly) during this period of two years. Clinical response was assessed using European League against Rheumatism (EULAR)/American College of Rheumatology (ACR) Criteria and the Disease Activity Score (DAS28). Radiographic changes were measured in the beginning and at the end of the study using Larsen's method.

**RESULTS:** Of the cohort groups of 90 patients, mean age of 55.63, 15 patients, (16.6 %) were treated with combined therapy (ETN plus MTX) and 75 patients (83.3%) with monotherapy (MTX). After two years of treatment the group with combined therapy resulted with improvement of acute phase reactants as erythrocyte sedimentation rate (ESR) for the first hour (41.1 vs. 10.3 mm/hour) and C - reactive protein (CRP) (40.8 vs. 6 mg/liter), and compared to the group treated with monotherapy, there were no significant changes (ESR: 45.7 vs 34.3 mm/hour; CRP: 48 vs 24 mg/liter). Before the treatment, the severity of the disease was high, wherein the group with combined therapy DAS28 was 5.32, compared to the monotherapy group whom DAS28 was 5.90. After 2 years of treatment, we had significant changes in the results of DAS28, wherein the group treated with ETN plus MTX DAS28 was  $2.12 \pm 0.15$ , while in the group of patients treated with MTX DAS28 were  $3.75 \pm 0.39$  ( $t = 13.03$ ;  $df = 58$ ;  $p < 0.0001$ ). The group with combined therapy showed no evidence of radiographic progression comparing to the group of patients with monotherapy.

**CONCLUSIONS:** Based on our results achieved during 2 years we can conclude that ETN in combination with MTX reduced disease activity, slowed radiographic progression and improved clinical manifestations more effectively than MTX alone. No serious adverse events were noticed in the group with combination treatment.

## Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder with unknown aetiology, characterised by symmetric, erosive synovitis and, sometimes multisystem involvement. The prevalence is 1 - 2% worldwide. Both, incidence and prevalence of rheumatoid arthritis, are two to three times higher in women than in men [1] [2]. The treatment goal is achieving the lowest level of activity of the disease

and longest remission, minimization of the joint damage, maintaining physical function and quality of life. Treatment of RA contains a program that includes medical, social and emotional support for the patients. ETN is effective in reducing the signs and symptoms of RA, as well as in slowing or halting the radiographic damage when used either as a monotherapy or in combination with MTX. ETN binds TNF in circulation and in the joint, preventing interaction with cell surface TNF receptors, thereby reducing TNF activity [3] [4] [5].

This study aims to evaluate the efficacy of Methotrexate (MTX) as a monotherapy versus combined therapy with Etanercept (ETN) and Methotrexate (MTX), in patients with active rheumatoid arthritis (RA).

## Patients and Methods

In this randomised controlled study conducted during a period of two years, from March 2014 to March 2016, we have evaluated the efficacy of treatment of patients with RA treated with MTX alone and the combination of MTX and ETN.

Patients were diagnosed with RA fulfilling criteria of European League against Rheumatism (EULAR)/American College of Rheumatology (ACR) and disease duration of at least one year [6]. Patients included in the study were treated with DMARDs such as Sulfasalazine and Hydroxychloroquine and they did not have a satisfactory response to the therapy. The youngest patient included in the study was aged 29 years, with function class I - III (ACR), with 8 swollen and 10 painful joints; erythrocyte sedimentation rate (ESR) of 25 mm/hour, C - reactive protein (CRP) level of 12 mg/liter, and morning stiffness more than 30 minutes. Pain on a visual analog scale (VAS: 0 - 100 mm) was evaluated for each patient, clinical response was assessed using American College of Rheumatology (ACR) criteria for 20% improvement ACR20, the ACR50 and the ACR70 in RA, and the Disease Activity Score in 28 joints (DAS28) [7][8][9]. Patients with a history of previous hepatitis, tuberculosis and active infectious disease were excluded from the study.

Study protocol Included patients treated in combination with ETN and MTX (doses of 50 mg subcutaneously weekly), oral MTX (doses up to 20 mg weekly), and alone MTX (doses up to 20 mg weekly) in two years, in the Clinic for Rheumatology in Prishtina. Patients received a low dose of corticosteroids at the beginning of the treatment during 3 months (initial dose of 20 mg and the maintenance dose was 7.5 mg). Radiographic changes were measured at the beginning and the end of the study with Larsen's methodology 1995, using a scoring system that attributes 0 to 5 points of each synovial joint evaluated on a radiograph [10] [11]. Safety assessments were based on reported adverse events, laboratory tests and physical routine examinations. The study was approved by the Ethical Committee of the University Clinical Center of Kosovo, and a written informed consent has been obtained from each patient before he/she entered the study.

All data were expressed as the mean  $\pm$  standard deviation (SD) and percentages. The significant difference from each group was analysed

by t-test of proportion, Superman's Correlation-test for calculation the radiographic changes. Statistical analyses were performed using the statistical SPSS. Significance was set up at  $p < 0.05$ .

## Results

Out of the total number of 90 patients included in the study, 15 were males, and 75 were females, with a mean age of 55.64 years. Fifteen patients or 16.6 % were treated with combined therapy (ETN plus MTX) and 75 patients or 83.3% with monotherapy (MTX). The group of combined therapy showed improvement of acute phase reactants compared to the group treated with MTX alone. ESR (normal values  $< 10$  mm/hour), of the first group (ETN plus MTX) in the first hour of ESR was 41.1 vs. 10.3 mm/hour and CRP (normal value  $< 6$  mg/liter) was 40.8 vs. 6 mg/liter ( $p = 0.001$ ) compared to the second (MTX alone) showed no significant changes (ESR: 45.7 vs 34.3 mm/hour; CRP: 48 vs 24 mg/liter),  $p = 0.17$ .

Patients treated with combined therapy achieved ACR20, ACR50 and ACR70 better response rather than patients treated with monotherapy (MTX). ACR20 responses were achieved at the level of 90% in patients with combined therapy group (ETN plus MTX) vs 84% of the monotherapy group (MTX)  $p = 0.63$ . ACR50 responses were achieved by 70% of the combination therapy group vs 46% of the monotherapy group  $p = 0.17$ . ACR70 responses were achieved by 40% of the combination group vs 16% of the monotherapy group  $p = 0.089$ . The severity of the disease, measured before treatment by DAS Score was high. The group that was treated with combined therapy (ETN plus MTX) had DAS28 of 5.32, whereas the group with monotherapy of MTX had DAS28 of 5.90. After 2 years of treatment, we had significant changes in the results of DAS28. The group treated with ETN plus MTX had DAS28 of  $2.12 \pm 0.15$ , while the group of patients treated with MTX had DAS28 of  $3.75 \pm 0.39$  ( $t = 13.03$ ;  $df = 58$ ;  $p < 0.0001$ ) (Table 1).

**Table 1: Characteristics of treatment of RA with Methotrexate and combined therapy with Etanercept and Methotrexate**

	Methotrexate (MTX)	Etanercept and Methotrexate (ETN + MTX)	T-test of proportion t-test p-value
	N (%)	N (%)	
	75 (83.3%)	15 (16.6%)	
Female	63 (84%)	9 (60%)	
Male	12 (16%)	6 (40%)	
American College of Rheumatology (ACR) criteria			
ACR20	84%	90%	$t=0.49$ ; $df=58$ ; $p=0.63$
ACR50	46%	70%	$t=1.39$ ; $df=58$ ; $p=0.17$
ACR70	16%	40%	$t=1.73$ ; $df=58$ ; $p=0.089$
Disease Activity Score (DAS28)			
Before treatment	$5.9 \pm 0.49$	$5.32 \pm 0.26$	
After treatment	$3.75 \pm 0.39$	$2.12 \pm 0.15$	$t=13.03$ ; $df=58$ ; $p<0.0001$

Radiography of hands and feet were done at the beginning and the end of the study. The scoring was done by total Larsen's score in 32 joints (total Larsen score range is 0 - 160). Mean value of total Larsen's score in the first group of patients, treated with ETN + MTX at the beginning of the study was 2.58, whereas at the end of the study was 3.54. In the second group of patients treated with MTX, at the beginning of the study, the mean value of Larsen's score was 2.84 whereas at 24 months 3.95. According to the Larsen's method, in the group of combined therapy showed no evidence of radiographic progression comparing to the group of monotherapy ( $p < 0.010$ ).

During the treatment, in the group of patients with monotherapy 8 cases were reported for transitory adverse effects such as nausea, vomiting, and gastrointestinal ache. In the group of combined therapy, there is no evidence of serious adverse events, infectious or noninfectious that was noticed. During the study, none deaths were reported.

## Discussion

Our study is based on the comparison of results from the treatment of RA with combined therapy (ETN plus MTX) and monotherapy (MTX). Results confirm the significant advantage of combined therapy over monotherapy. DMARD medications are utilised much earlier in the treatment of RA, due to their efficacy in retarding erosive damages. Biologics produce rapid and sustained amelioration of the signs and symptoms of RA, retard radiological progression, and improve quality of life more effectively than DMARDs [12].

Our study showed that combined therapy had a statistically significant benefit compared to the monotherapy for ACR20, ACR50 and ACR70 response. It also shows the significant advantage of combined therapy over monotherapy in controlling the disease activity measured by DAS28 Score. DAS28 was obviously lower in the group treated with combined therapy compared to the group treated with monotherapy.

Different authors showed the improvement of RA using combined therapy (ETN + MTX), e.g. Weinblatt ME et al., (1999). A trial of Etanercept, a recombinant tumour necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving MTX. The authors show that in 89 RA's, patients treated with ETN showed more efficacy of ETN when used a combination treatment with MTX over 6 months of treatment. Our results are similar to recent studies [13].

The reason we conducted this study was to

improve the care of our patients. Our study confirmed that combined therapy had given better improvement. Clinical studies suggest that etanercept is safe and effective as a long-term therapy for the treatment of RA, and the risk and benefit ratio of continuous etanercept treatment remains beneficial [14] [15] [16].

Limitations of the study include the small number of patients in the group of combined therapy, because of the economic limitation conditions of applying etanercept to other patients with RA. Furthermore, studies with higher number of patients need to be done.

According to our results, we can conclude that etanercept in combination with methotrexate reduced disease activity, slowed radiographic progression and improved clinical manifestations more effectively than methotrexate alone within 2 years. During the treatment, no serious adverse events were noticed with a combination treatment of etanercept and methotrexate.

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