

# The role of methotrexate as combination therapy with etanercept in rheumatoid arthritis: Retrospective analysis of a local registry

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## Abstract

**Objective:** In a real-life setting, to analyse retrospectively the effects of different methotrexate regimens on etanercept efficacy during the first year of treatment for rheumatoid arthritis (RA).

**Methods:** Demographic characteristics, clinical parameters and treatment data from patients with RA receiving the first-line biological disease-modifying antirheumatic drug, etanercept, as monotherapy or in combination with methotrexate were analysed at baseline and after 6 and 12 months. The study population was stratified into three groups according to the level of concomitant methotrexate therapy: no methotrexate, low-dose methotrexate ( $\leq 10$  mg/week) or high-dose methotrexate ( $> 10$  mg/week).

**Results:** Clinical response at 6 and 12 months and clinical outcome at 12 months were significantly better in patients concomitantly treated with high-dose methotrexate. Furthermore, this regimen was associated with the lowest discontinuation rate, suggesting a favourable safety profile.

**Conclusion:** These data confirm, in a real-life setting, the importance of methotrexate as a combination therapy with etanercept and suggest that the minimal effective dose of methotrexate is  $> 10$  mg/week.

## Keywords

Combination therapy, etanercept, methotrexate, rheumatoid arthritis

## Introduction

Methotrexate is a key drug in the treatment of rheumatoid arthritis (RA).<sup>1</sup> According to international recommendations, methotrexate should be the first choice for both first-line synthetic disease-modifying antirheumatic drug (DMARD) treatment in newly diagnosed

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RA and as combination therapy in association with biological DMARDs.<sup>2,3</sup> In particular, tumour necrosis factor (TNF) inhibitors have been shown to produce a significantly better clinical response when used in combination with methotrexate compared with their use as monotherapy.<sup>4,5</sup> However, the optimal dose of methotrexate has not been defined: doses used can range between 7.5 and 25 mg per week, depending on local guidelines and the preference of the rheumatologist. In the CONCERTO trial, in which four different methotrexate regimens in combination with adalimumab were prospectively evaluated, a statistically significant increasing trend in the proportion of patients achieving 26-week low disease activity with an increase in methotrexate dose was reported.<sup>6</sup> To date, no similar clinical studies evaluating the role of methotrexate in association with other TNF inhibitors have been performed.<sup>7</sup>

The aim of the present study was to analyse retrospectively the effects of different methotrexate regimens on the efficacy of the DMARD etanercept during the first year of RA treatment in a real-life setting.

## Patients and methods

Data from all RA patients diagnosed according to the 1987 revised American College of Rheumatology (ACR)<sup>8</sup> or the 2010 ACR/European League Against Rheumatism (EULAR)<sup>9</sup> classification criteria, and treated with TNF inhibitors between October 1999 and December 2014 in the Department of Rheumatology, Gaetano Pini Institute, Milan, Italy, were collected in a local registry. Demographic characteristics (age, sex, disease duration), clinical parameters (28-joint Disease Activity Score,<sup>10</sup> Simplified Disease Activity Index,<sup>11</sup> C-reactive protein level, erythrocyte sedimentation rate and rheumatoid factor) and treatment data (biological therapy and concomitant synthetic DMARD and steroid use) were recorded at baseline and at 6-month intervals.

Patients receiving etanercept 50 mg/week subcutaneously as monotherapy or in combination with methotrexate were included in the present study; patients receiving concomitant synthetic DMARDs other than methotrexate were excluded. The study population was stratified into three groups according to the level of concomitant methotrexate therapy: no methotrexate, low-dose methotrexate ( $\leq 10$  mg/week) or high-dose methotrexate ( $> 10$  mg/week).

Data collection in the registry was approved by the Ethics Committee of the Gaetano Pini Institute, Milan, Italy.

## Statistical analyses

Data were reported as mean  $\pm$  SD. The Simplified Disease Activity Index (SDAI) score was used as the primary endpoint for the study. Mean change from baseline in the SDAI score at 6 and 12 months and the proportion of patients achieving SDAI remission at the same timepoints were compared in the three groups using the Kruskal–Wallis and Dunn's multiple comparison tests for continuous variables and the  $\chi^2$ -test for dichotomous variables. A  $P$ -value  $< 0.05$  was considered to be statistically significant. Statistical analyses were performed using IBM<sup>®</sup> SPSS<sup>®</sup> software, version 20.0 (IBM, Somers, NY, USA).

## Results

A total of 146 patients were included in the study: 49 received etanercept monotherapy; 47 received etanercept plus low-dose methotrexate; 50 received etanercept plus high-dose methotrexate. Baseline demographic and clinical characteristics are given in Table 1. Patients in the low-dose methotrexate group were significantly older compared with both the etanercept monotherapy and the high-dose methotrexate groups ( $P = 0.0098$ ). No statistically significant differences in disease activity were observed between the three groups at baseline.

**Table 1.** Baseline demographic and clinical characteristics in patients with rheumatoid arthritis treated with etanercept alone, etanercept plus low-dose methotrexate ( $\leq 10$  mg/week) or etanercept plus high-dose methotrexate ( $> 10$  mg/week).

Characteristic	Etanercept alone <i>n</i> = 49	Concomitant methotrexate		Statistical significance
		Low dose <i>n</i> = 47	High dose <i>n</i> = 50	
Age, years	52 $\pm$ 12	59 $\pm$ 14	48 $\pm$ 12	<i>P</i> = 0.0098 <sup>a</sup>
Sex				NS <sup>b</sup>
Female	40 (81.6)	37 (78.7)	35 (70.0)	
Male	9 (18.4)	10 (21.3)	15 (30.0)	
Disease duration, years	8.8 $\pm$ 10.1	7.7 $\pm$ 7.3	7.8 $\pm$ 8.6	NS <sup>a</sup>
DAS28	5.29 $\pm$ 1.25	5.26 $\pm$ 1.28	5.37 $\pm$ 1.13	NS <sup>a</sup>
SDAI	24.20 $\pm$ 12.36	22.20 $\pm$ 11.49	24.65 $\pm$ 12.73	NS <sup>a</sup>
Positive rheumatoid factor	40 (81.6)	36 (76.5)	36 (72)	NS <sup>b</sup>

Data presented as *n* (%) of patients or mean  $\pm$  SD.

DAS28, 28-joint Disease Activity Score;<sup>10</sup> SDAI, Simple Disease Activity Index.<sup>11</sup>

NS, no statistically significant between-group differences.

<sup>a</sup>Kruskal–Wallis test; <sup>b</sup> $\chi^2$ -test.

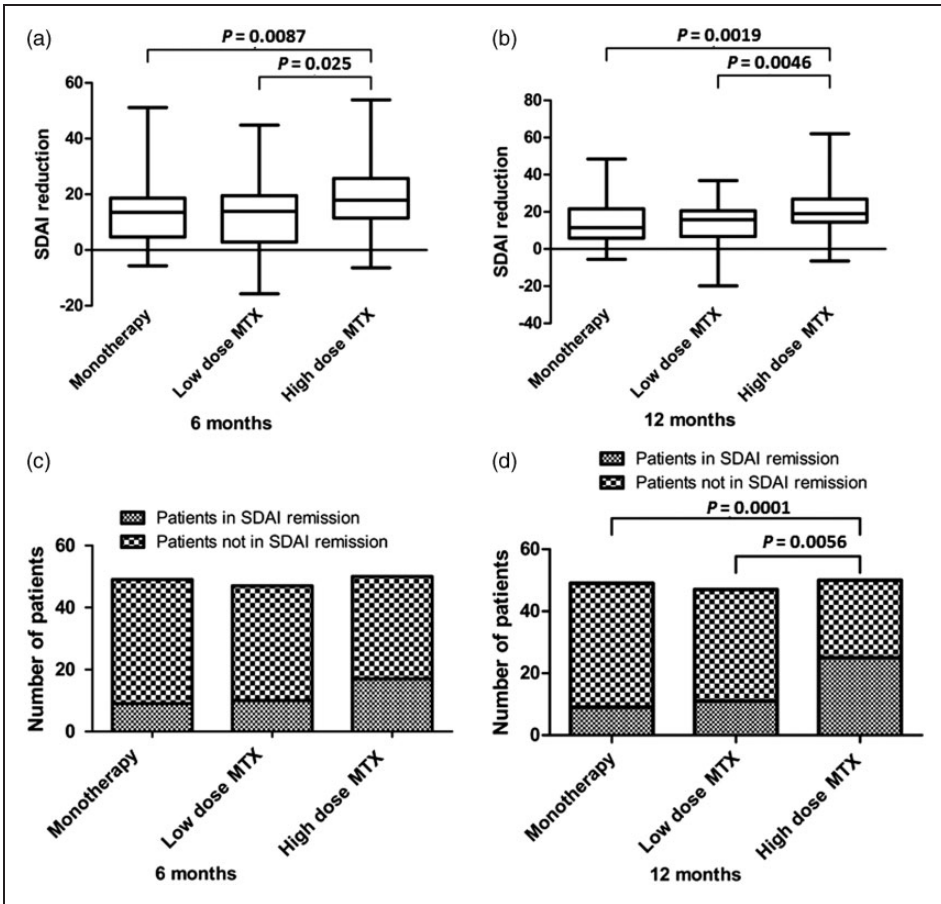
A total of 32 patients discontinued etanercept therapy during the first 12 months of treatment; the proportion of patients discontinuing etanercept was lower in the high-dose methotrexate group (14.0%, *n* = 7) compared with both the etanercept monotherapy (26.5%, *n* = 13) and low-dose methotrexate (25.5%, *n* = 12) groups, but these differences were not statistically significant. The main reason for discontinuation in all three groups was lack of therapeutic efficacy.

The mean change from baseline SDAI score was significantly greater at both 6 and 12 months in the high-dose methotrexate group compared with the etanercept monotherapy group (*P* = 0.0087 and *P* = 0.0019, respectively) and the low-dose methotrexate group (*P* = 0.025 and *P* = 0.0046, respectively) (Figure 1). No statistically significant differences in SDAI remission rates were observed between the three groups at 6 months (Figure 1). However, the proportion of patients achieving SDAI remission was significantly higher in the high-dose methotrexate group (50.0%) compared with both the etanercept monotherapy

group (22.5%; *P* = 0.0001) and the low-dose methotrexate group (30.5%; *P* = 0.0056) at 12 months (Figure 1).

## Discussion

The present study confirmed the crucial role of methotrexate in combination with TNF inhibitors in the treatment of patients with RA who exhibit an insufficient response to synthetic DMARDs, with additional value being demonstrated with increasing methotrexate doses. The 6- and 12-month clinical response to etanercept therapy, indicated by an increase in the SDAI, was significantly better in patients concomitantly treated with  $> 10$  mg/week methotrexate compared with the other regimens studied. Our data are consistent with those previously reported in randomized clinical trials comparing etanercept as monotherapy with methotrexate combination therapy. In the TEMPO trial,<sup>4</sup> the combination of etanercept and methotrexate for the treatment of late-stage RA led to a significantly better reduction in disease activity compared with both



**Figure 1.** Simplified Disease Activity Index (SDAI) responses in patients with rheumatoid arthritis treated with etanercept alone (monotherapy) etanercept plus low-dose methotrexate (MTX) or etanercept plus high-dose MTX. (a) Mean SDAI change from baseline at 6 months. (b) Mean SDAI change from baseline at 12 months. (c) Number of patients achieving SDAI remission at 6 months. (d) Number of patients achieving SDAI remission at 12 months. Long horizontal lines represent median values; boxes represent interquartile range; short horizontal lines represent maximum and minimum values (Dunn’s multiple comparison test [a and b] or  $\chi^2$ -test [c and d]).

etanercept and methotrexate monotherapies. The mean methotrexate dose in etanercept-treated patients was 16.9 mg/week, but no subanalysis according to methotrexate dose was performed.<sup>4</sup> Similarly, no significant differences in disease activity responses measured using ACR criteria (ACR 20 or ACR 50) between etanercept and methotrexate monotherapies was observed in patients

with early stage RA.<sup>12</sup> To the best of our knowledge, the CONCERTO trial<sup>6</sup> is the only published clinical study to analyse the role of four different methotrexate regimens in association with TNF inhibitor (adalimumab) therapy. This study demonstrated a statistically significant trend in improved clinical outcomes with increasing methotrexate doses, with a similar clinical response rate

observed in patients receiving 10 or 20 mg/week methotrexate.

To date, no data on the minimal effective dose of methotrexate in patients treated with etanercept have been reported. Similar to the results of the CONCERTO trial,<sup>6</sup> in the present retrospective study higher methotrexate doses were associated with better clinical outcomes. This difference was observed only in patients who received >10 mg/week methotrexate; no additional effect for lower methotrexate doses ≤10 mg/week was demonstrated. Although this finding may be due in part to the relatively small sample size, it seems to confirm that >10 mg/week methotrexate is required in order to improve the clinical response to etanercept, as suggested by current EULAR recommendations for the management of RA.<sup>2</sup> Interestingly, in the present study, high-dose methotrexate was associated with the lowest discontinuation rate, suggesting a favourable safety profile for this methotrexate regimen. As an observational study, possible limitations affecting the analysis may be the retrospective design and the absence of randomization, which are potential sources of selection bias. However, comparisons among the three study groups revealed an adequate balance of baseline characteristics.

In conclusion, the results of the present study confirmed in a real-life setting the importance of methotrexate as a combination therapy with etanercept, and suggested that the minimal effective dose of methotrexate is >10 mg/week.

### Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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