Clinical Rheumatology (2019) 38:949–954
https://doi.org/10.1007/s10067-018-4355-0

BRIEF REPORT

# The effect of methotrexate versus other disease-modifying anti-rheumatic drugs on serum drug levels and clinical response in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors

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Received: 18 July 2018 / Revised: 20 September 2018 / Accepted: 29 October 2018 / Published online: 6 November 2018


## Abstract

To investigate the effect of concomitant conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) with adalimumab or infliximab on maintaining serum drug and clinical outcomes after the first year of treatment in patients with rheumatoid arthritis (RA). Second, to assess the influence of methotrexate (MTX) dose on these outcomes. Ninety-two patients with RA starting infliximab ($n = 67$) or adalimumab ($n = 25$) tumor necrosis factor inhibitor (TNFi) with available drug levels and clinical improvement assessment (European League Against Rheumatism [EULAR] response) after 12 months were included. Patients were grouped according to concomitant csDMARD use: (i) TNFi monotherapy; (ii) TNFi+MTX; (iii) TNFi with csDMARDs other than MTX (TNFi+OD). Patients receiving MTX were also classified by dose as < 15 mg/week (TNFi+MTX<15) and ≥ 15 mg/week (TNFi+MTX≥15). Logistic regression analyses were employed. More TNFi+MTX patients had circulating serum TNFi at 12 months (71% TNFi+MTX vs. 20% TNFi+OD vs. 9% TNFi monotherapy). Of these, the probability of maintaining serum TNFi levels was twice (OR 2.3; $p = 0.06$) than that of patients without MTX. However, statistically significant results were observed only for the highest MTX dose (OR 4.9; $p = 0.02$). Most patients achieving good EULAR response were treated with TNFi+MTX (81%). The probability of achieving this response was three times higher in patients within the TNFi+MTX group (OR 3.4; $p = 0.03$); however, no differences were found with regard to MTX dose. The persistence of serum TNFi and the probability of achieving clinical response are influenced by MTX but not by OD in patients with RA treated with infliximab or adalimumab.

**Keywords** csDMARDs · EULAR response · MTX dose · Rheumatoid arthritis · TNF inhibitors

## Introduction

Several factors influence tumor necrosis factor inhibitor (TNFi) pharmacokinetics [1]. Among these, the development of anti-drug antibodies has been highlighted because they are associated with low circulating drug levels and therefore with a decrease in clinical efficacy. Previous studies on patients with rheumatoid arthritis (RA) [2–4] have demonstrated a beneficial effect of concomitant use of methotrexate (MTX) in patients undergoing TNFi therapy, at least in part, through the reduction of immunogenicity. However, few studies have investigated whether patients cotreated with MTX also have higher serum TNFi concentrations than patients receiving TNFi monotherapy [1, 5].

The effect of concomitant MTX on the clinical response to TNFi is widely known, as reflected in the 2016 European

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s10067-018-4355-0) contains supplementary material, which is available to authorized users.

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League Against Rheumatism (EULAR) recommendations update, which recommends the use of MTX with all TNFis [3]. Other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), such as leflunomide, sulfasalazine, and hydroxychloroquine, have also demonstrated clinical efficacy in patients with RA and are recommended if MTX cannot be used or has no clinical efficacy [3, 4]. However, scant data are available about the influence of these csDMARDs on TNFi pharmacokinetics and immunogenicity. In this regard, csDMARDs have been demonstrated to influence drug pharmacokinetics in patients treated with adalimumab; however, no study with another TNFi has been performed [1, 5, 6]. Moreover, despite infliximab being one of the most common TNFis used in inflammatory diseases, there is no evidence on the effect of concomitant use of csDMARDS on serum infliximab levels in patients with rheumatism.

The main objective of this study was to investigate the effect of concomitant csDMARD use on the presence of serum drug levels in patients with RA treated with adalimumab or infliximab after the first year of treatment. Second, we aimed to evaluate whether there was an association between the use and type of concomitant csDMARD and the clinical response achieved after the first year of TNFi administration. Finally, we investigated whether MTX has a dose-dependent effect on these two outcomes.

## Methods

### Study design and population

For this study, baseline and 1-year data from the RA-Paz cohort were used. This is a prospective cohort including patients with RA since 1999 who started biological DMARD (bDMARD) treatment in a tertiary hospital. In this cohort, patients are evaluated every 6 months. In each visit, clinical and laboratory parameters are assessed, including tender and swollen joint counts, patient's visual analog scale for disease activity and overall health and acute phase reactants. In addition, since 2010, serum samples have been collected to determine serum drug levels and the presence of anti-drug antibodies. For this study, the dataset was locked in April 2016. Patients receiving infliximab or adalimumab who had available data on serum drug and anti-drug antibodies levels evaluated at 6 and/or 12 months after initiating TNFi treatment were included. All patients fulfilled the 1987 revised criteria of the American College of Rheumatology [7] and received the standard dose of each drug. The study was approved by the La Paz University Hospital Ethics Committee and all the patients signed an informed consent document.

### Collected data and measurements

At baseline, the following data were recorded: patient variables (age, sex, and body mass index), disease characteristics (disease duration since diagnosis, rheumatoid factor, and anti-cyclic citrullinated peptide antibody [ACPA]) and treatment (bDMARDs, csDMARDs, and prednisone).

At baseline, 6 and 12 months, disease activity was measured using the Disease Activity Score for 28 joints (DAS28). Clinical improvement was calculated through ΔDAS28 and the clinical response was defined according to the European League Against Rheumatism (EULAR) criteria as nonresponse, moderate response, and good response [8].

### Measurements of serum drug and anti-drug antibodies levels

Serum drug levels were measured by a capture enzyme-linked immunosorbent assay (ELISA) and serum anti-drug antibodies levels by a bridging ELISA (drug-sensitive assay) at 6 and 12 months of treatment. Blood samples were obtained just before drug administration or at a maximum of 24 h before injection in the case of adalimumab. In total, 92 samples were analyzed. Both assays were performed as previously described [9]. Serum infliximab levels > 10 ng/ml and serum adalimumab levels > 5 ng/ml (mean + 6 SD control group) were considered positive.

### Statistical analysis

First, a descriptive analysis was performed. The results of this analysis were reported as median and interquartile range for continuous variables or as absolute number and relative frequencies for categorical variables. To investigate the association between the concomitant use of csDMARDs and the presence of serum drug levels, patients were first grouped into one of three categories according to the concomitant use of csDMARDs at baseline: (i) TNFi monotherapy; (ii) TNFi with concomitant oral MTX (TNFi+MTX); or (iii) TNFi with other concomitant csDMARDs different from MTX (OD), including leflunomide, sulfasalazine, and hydroxychloroquine at baseline (TNFi+OD). In the group (ii), there is a subgroup of patients with TNFI+MTX+OD. Preliminary statistical studies did not demonstrate a superior effect for the different studied outcomes compared with the group TNFi+MTX (data not shown); therefore, it was decided to group these two populations (TNFi+MTX+OD and TNFi+MTX− without OD−). Furthermore, sensitivity analyses were performed to evaluate whether there was a dose-dependent effect of MTX on the various outcomes. For this purpose, patients within the TNFi+MTX group were further classified into one of two groups using the median dose received in our cohort (15 mg/week) as the cut-off point: MTX dose < 15 mg/week

(TNFi+MTX<15) and MTX dose ≥ 15 mg/week (TNFi+MTX≥15).

Second, the percentage of patients with a presence of drug levels in serum (as a dichotomous variable: presence/no detection) and achieving a clinical response (as a categorical variable: nonresponse, moderate response, and good response) were determined for each group.

Third, logistic regression models were employed to investigate the association between the concomitant use of csDMARDs with the presence of serum drug levels and clinical response, reporting odds ratio (OR) as the estimate of association.

Finally, treatment survival was studied using Kaplan-Meier curves, and all groups were compared using the log-rank test. In case of drop-outs or missing data at 12 months, the last observation carried forward using data at 6 months was performed for 34 patients.

All analyses were performed with SPSS 24.0 software and a cut-off of $< 0.05$ was employed to determine statistical significance. Graphs were performed with GraphPad Prism 6 (San Diego, CA, USA).

## Results

### Patient characteristics

A total of 92 patients with RA starting TNFi treatment with adalimumab ($n = 25$) or infliximab ($n = 67$) were included in this study (Supplementary fig. 1). Demographic and clinical baseline characteristics are summarized (Table 1). Median age and disease duration were 55 years and 8 years, respectively. Most patients were female (84%) and positive for rheumatoid factor (74%) and for ACPA (82%).

The number and percentage of patients in each group according to the use of concomitant csDMARDs were as follows: 12 (13%) TNFi monotherapy patients; 59 (64%) TNFi+MTX patients, of which 26 (44%) were also receiving OD; and 21 (23%) TNFi+OD patients. Among the patients within the TNFi+MTX group were 18 (31%) TNFi+MTX<15 patients and 41 (69%) TNFi+MTX≥15 patients.

### Association between concomitant csDMARDs and the presence of serum TNFi

Figure 1a shows the percentage of patients based on detectable serum TNFi in each group at 1 year according to the use of concomitant csDMARDs. The proportion of patients with detectable TNFi levels at 1 year was higher in the TNFi+MTX group (71%) than in the other groups (20% TNFi+OD and 9% TNFi monotherapy) (Fig. 1a). Along these lines, the probability of maintaining circulating TNFi levels was twice that of patients with MTX compared with patients without MTX (OR 2.3; $p = 0.06$).

Moreover, the percentage of patients with circulating TNFi at 1 year was higher among those treated with TNFi+MTX≥15 (54%) than in patients receiving TNFi+MTX<15 (17%), TNFi+OD (20%), or TNFi monotherapy (9%) (Fig. 1b). Accordingly, the probability of serum TNFi persistence at 1 year in the group with TNFi+MTX≥15 was five times higher than that observed in patients with TNFi monotherapy (OR 4.9; $p = 0.02$). Conversely, receiving MTX doses below

**Table 1** Demographic and baseline characteristics of 92 patients with rheumatoid arthritis

| Characteristics | Monotherapy ($n = 12$) | MTX¥ ($n = 59$) | OD ($n = 21$) | $p$ |
|---|---|---|---|---|
| Age, years* | 63.5 (49–72.8) | 52 (45–63) | 64 (47.5–71.5) | 0.2 |
| Body mass index* | 24 (21.8–28.3) | 24.2 (22.2–29.5) | 24.5 (20.7–25.9) | 0.3 |
| Female** | 7 (58%) | 52 (88%) | 18 (86%) | 0.03 |
| Smoker** | 5 (42%) | 17 (29%) | 4 (19%) | 0.4 |
| Disease duration, years* | 9.5 (3.5–20.8) | 8(5–14) | 10 (4.5–15.5) | 0.3 |
| Rheumatoid factor** | 11/12(92%) | 40/58 (69%) | 17/21 (81%) | 0.2 |
| ACPA** | 11/12 (92%) | 46/58 (79%) | 18/21 (86%) | 0.5 |
| DAS28 at baseline* | 5.2 (4.6–6.2) | 5.3 (4.4–1.3) | 5 (4.1–5.8) | 0.5 |
| CRP at baseline* | 5 (3–36) | 7.3 (3–23.1) | 10.6 (4.6–19.7) | 0.2 |
| TNF inhibitor:** | | | | 0.08 |
| Infliximab | 11 (92%) | 44 (75%) | 12 (57%) | |
| Adalimumab | 1 (8%) | 15 (25%) | 9 (43%) | |
| Prednisone** | 4 (33%) | 35 (59%) | 14 (42%) | 0.1 |

*MTX*, methotrexate; *OD*, other DMARDs; *BMI*, body mass index (kg/m$^2$ ); *ACPA*, anti-citrullinated protein antibodies (IU/ml); *CRP*, C-reactive protein (mg/L); *DAS28*, Disease Activity Score in 28 joints; *DMARD*, disease-modifying anti-rheumatic drug

¥ Include patients in treatment with TNFi and MTX or TNFi plus MTX plus OD

*Median (interquartile range)

**$n$ (%)

15 mg/weekly or OD was not significantly associated with this outcome (OR 1.7; $p = 0.5$ and OR 1.8; $p = 0.6$, respectively).

### Association between concomitant csDMARDs and the clinical response to TNFi

At 1 year, ΔDAS28 data were available for 86 patients: 12/12 (100%) patients in the TNFi monotherapy group, 16/18 (89%) patients in the TNFi+MTX<15 group, 38/41 (93%) patients in the TNFi+MTX≥15 group, and 20/21 (95%) patients in the TNFi+OD group.

According to EULAR response criteria, 27 (32%) patients did not respond to bDMARDs, whereas 33 (38%) and 26 (30%) achieved a moderate and good response, respectively. Most patients achieving a good EULAR response belonged to the TNFi+MTX group (81% TNFi+MTX vs. 11% TNFi+OD vs. 8% TNFi monotherapy) (Fig. 2a). Overall, patients with MTX had more than three times the probability of achieving a good EULAR response compared with patients without MTX (OR 3.4; $p = 0.03$).

In addition, the majority of good EULAR responders were patients in the TNFi+MTX≥15 group (58% TNFi+MTX≥15 vs. 23% TNFi+MTX<15 vs. 11% TNFi+OD vs. 8% TNFi monotherapy) (Fig. 2b). Compared with patients undergoing TNFi monotherapy, the probability of achieving a good EULAR response for the various groups was TNFi+MTX≥15: OR 3.2, $p = 0.2$; TNFi+MTX<15: OR 3.0, $p = 0.2$; and TNFi+OD: OR 0.8, $p = 0.9$.

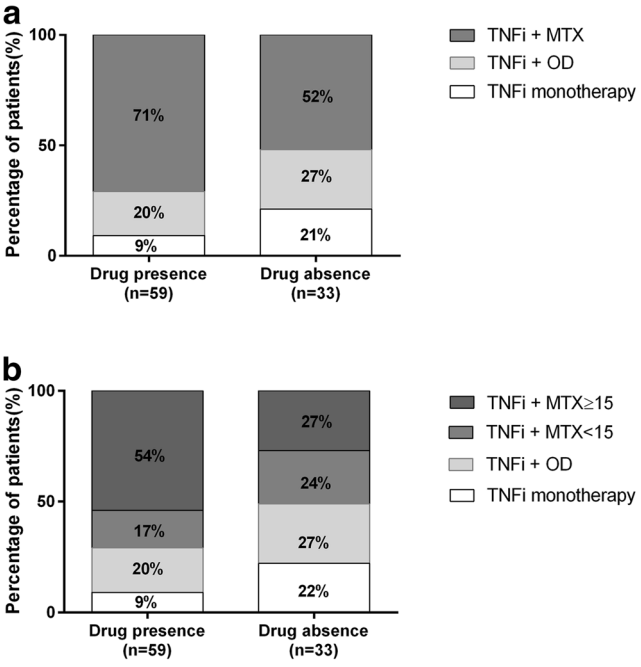


**Fig. 1** Percentage of patients with or without detected serum drug levels at 1 year stratified by treatment. **a** TNFi monotherapy ($n = 12$); TNFi+OD ($n = 21$); TNFi+MTX ($n = 59$). **b** TNFi monotherapy ($n = 12$); TNFi+OD ($n = 21$); TNFi+MTX<15 ($n = 18$); TNFi+MTX≥15 ($n = 41$)

### Effect of concomitant csDMARDs on TNFi survival

Figure 3 shows drug survival curves for each treatment group. A total of 71 (77%) patients dropped out TNFi treatment due to the following: primary inefficacy (22 patients, 31%), secondary inefficacy (14 patients, 20%), and due to other reason (adverse events, loss of follow-up…) (35 patients, 49%).

Overall, the median survival time (mst) was significantly higher in patients with TNFi+MTX than in patients receiving TNFi+OD or TNFi monotherapy (5.00 years vs. 2.00 years vs. 2.15 years, respectively; $p = 0.03$) However, the mst was not found to be longer in patients undergoing TNFi+MTX≥15 therapy compared with patients undergoing TNFi+MTX<15 therapy.

## Discussion

This study investigated the effect of concomitant csDMARD administration on circulating serum TNFi persistence and clinical outcomes in patients with RA receiving infliximab or adalimumab. It also evaluated whether the type of administered csDMARD or its dose influences this effect.

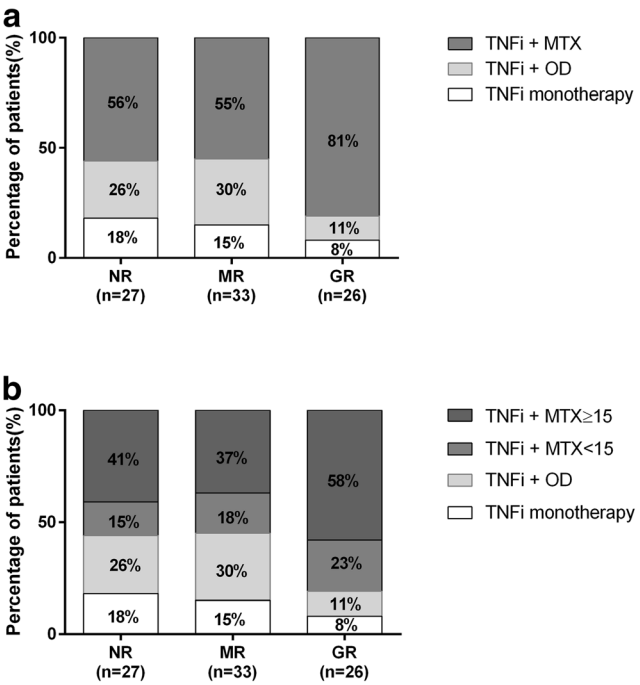


**Fig. 2** EULAR response at 1 year stratified by treatment. **a** TNFi monotherapy ($n = 12$); TNFi+OD ($n = 20$); TNFi+MTX ($n = 54$). **b** TNFi monotherapy ($n = 12$); TNFi+OD ($n = 20$); TNFi+MTX<15 ($n = 16$); TNFi+MTX≥15 ($n = 38$); NR, nonresponse; MR, moderate response; GR, good response

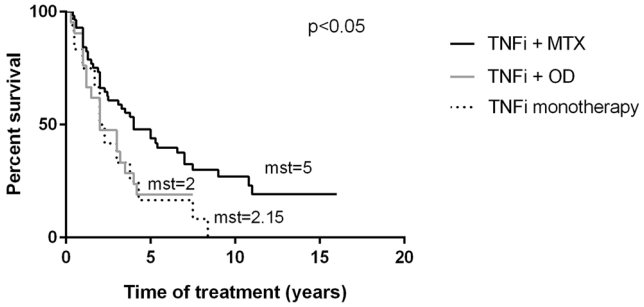


**Fig. 3** Survival curve of TNFi treatment stratified by concomitant use of csDMARDs. TNFi monotherapy ($n = 12$); TNFi+OD ($n = 21$); TNFi+MTX ($n = 59$); mst, median survival time. Differences assessed by log-rank (Mantel-Cox) test

First, the results of this study showed an effect of csDMARDs on serum TNFi (infliximab or adalimumab) presence after the first year of treatment. The use of MTX was associated with more frequent detection of circulating drug levels at 1 year. A dose-dependent effect of MTX was also found; patients with MTX > 15 mg/weekly were five times more likely to have circulating TNFi in serum compared with patients receiving monotherapy, whereas doses of MTX under 15 mg/weekly or OD did not represent superiority over monotherapy in terms of circulating TNFi.

Serum drug levels are known to be closely correlated with TNFi clinical efficacy in patients with RA, showing that low or absent drug levels are associated with poor clinical responses in patients with RA [1, 9–11]. Previous data investigating the additional value of concomitant csDMARDs on serum drug levels in patients receiving TNFis are scarce, most found in patients treated with adalimumab [1, 6]. Our results, including patients with RA also treated with infliximab, are consistent with published data, showing that patients with more frequently detectable drug levels are receiving concomitant MTX (with or without other DMARDs). This effect could be explained by the role of MTX in reducing TNF bioactivity and anti-drug antibodies development [1, 2, 5, 12]. In a cohort of patients with RA starting infliximab, we demonstrated that the nonuse of MTX was associated with more rapid infliximab clearance after 1 year of treatment [13]. Interestingly, we have now observed that the effect of MTX on circulating infliximab and adalimumab serum levels is dose-dependent, with the probability of maintaining drug levels five times higher in patients receiving a high MTX dose than in patients receiving TNFi monotherapy [6]. A plausible explanation of this could be that it is known that higher doses of MTX have more bioavailability than low doses.

This is the first study to investigate the association between clinical response and the concomitant use of various csDMARDs. Moreover, we also show the probability of achieving a good EULAR response. However, this effect appears to be restricted to MTX, achieving good clinical response the 81% of patients with concomitant MTX and with a higher probability (3.4 times more) of obtaining a good EULAR response than patients on monotherapy. The probability of achieving a good clinical response was twice as high in patients receiving a high dose (at least 15 mg weekly) compared with those receiving lower doses. However, a dose-dependent effect for MTX on the clinical response was not found. Additionally, the mean survival time on TNFi therapy was observed to be twice as long in patients receiving MTX compared with patients receiving other csDMARDs or TNFi monotherapy [14].

The observed results of this study are relevant for clinical practice and are in agreement with other published data [15]. Current guidelines reflect that previous clinical trials of TNFi monotherapy have not been consistently found to be superior to MTX alone, whereas combination therapy appears to be effective and appropriate for use with adalimumab or infliximab [3]. We clearly show the importance of the administered MTX dose from the beginning of treatment, and a positive effect of MTX on the permanence of infliximab in the circulation has been elucidated for the first time.

The main limitation of this study is the relatively low number of included patients, meaning no adjustments for possible confounders could be made. Nevertheless, it is important to remark that the populations under various treatment regimens (monotherapy, MTX, or OD) were fairly homogeneous at baseline. Moreover, in the case of the MTX group, only patients who received oral MTX were included to avoid a possible bias related to different bioavailability. In addition, clinical improvement was assessed by EULAR response, a validated index that also depends on baseline clinical activity. On the other hand, this limitation could be the reason why, despite observing substantial numerical differences, no statistically significant differences were found for some variables. Also, to overcome the fact that patients were treated with two different TNFis, drug levels and anti-drug antibodies levels at 1 year were dichotomized as presence or absence and not assessed as a continuous variable. Regarding anti-drug antibodies, as it was performed a drug-sensitive assay (bridging ELISA) [16], the analysis of presence/absence of anti-drug antibodies is equivalent to analyze presence/absence of drug levels. This approach could have influenced the results of the study for this outcome.

In conclusion, in patients with RA starting infliximab or adalimumab biological treatment, the use of concomitant MTX has a beneficial effect on maintaining circulating serum TNFi and on the clinical response after 1 year of treatment. Concomitant MTX use is also associated with longer TNFi survival. Importantly, the effect of MTX on drug persistence is dose-dependent. Finally, the concomitant use of csDMARDs other than MTX appears to have a beneficial but limited effect

on TNFi serum levels. In order to confirm these results, further long-term studies including broader cohorts and also including patients in treatment with other TNFi are warranted.

**Acknowledgements** Chamaida Plasencia-Rodríguez has received speaking fees or funding for research projects from Pfizer, Lilly, Novartis, and Roche. Victoria Navarro-Compán has received speaking fees or funding for research projects and attending congresses from AbbVie, BMS, Lilly, MSD, Novartis, Pfizer, Roche, and UCB; Dora Pascual-Salcedo has received speaking fees of Abbvie, Pfizer, Takeda, Menarini, and Grifols. Alejandro Balsa has received unrestricted grants from Pfizer, Roche, and AbbVie and speaker fees from Pfizer, Janssen, AbbVie, MSD, BMS, UCB, Nordic, Sandoz, and Roche.

## Compliance with ethical standards

The study was approved by the La Paz University Hospital Ethics Committee and all the patients signed an informed consent document.

**Disclosures** None

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