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Etanercept for patients with juvenile idiopathic arthritis: drug levels and influence of concomitant methotrexate: observational study

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Abstract

Background Etanercept (ETN) is widely used tumour necrosis factor (TNF) blocker in the treatment of juvenile idiopathic arthritis (JIA) when traditional synthetic disease modifying antirheumatic drug (sDMARD) therapy is not sufficient. There is limited information about the effects of methotrexate (MTX) on serum ETN concentration in children with JIA. We aimed to investigate whether ETN dose and concomitant MTX would effect ETN serum trough levels in JIA patients, and whether concomitant MTX have an influence on the clinical response in patients with JIA receiving ETN.

Methods In this study, we collected the medical record data of 180 JIA patients from eight Finnish pediatric rheumatological centres. All these patients were treated with ETN monotherapy or combination therapy with DMARD. To evaluate the ETN concentrations, blood samples of the patients were collected between injections right before the subsequent drug. Free ETN level was measured from serum.

Results Ninety-seven (54%) of the patients used concomitant MTX, and 83 (46%) received either ETN monotherapy or used sDMARDs other than MTX. A significant correlation was noted between ETN dose and drug level [$r = 0.45$ (95% CI: 0.33–0.56)]. The ETN dose and serum drug level were correlated ($p = 0.030$) in both subgroups – in MTX group [$r = 0.35$ (95% CI: 0.14–0.52)] and in non-MTX group [$r = 0.54$ (95% CI: 0.39–0.67)].

Conclusion In the present study, we found that concomitant MTX had no effect on serum ETN concentration or on clinical response. In addition, a significant correlation was detected between ETN dose and ETN concentration.

Keywords Juvenile idiopathic arthritis, Etanercept, Drug concentration, Methotrexate

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Background

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory arthritis in childhood [1]. In Finland, with a population of 5.5 million, including 922 000 children under 16 years of age, nearly 200 children are diagnosed as having JIA every year [2] according to International League of Associations for Rheumatology (ILAR) criteria [3]. Treatment of JIA is usually initiated with conventional, synthetic disease-modifying antirheumatic drugs (sDMARDs), typically methotrexate (MTX) [4]. More than half of patients with JIA benefit from this treatment and achieve remission. Nearly all of those who do not achieve remission with sDMARDS benefit from biological disease-modifying antirheumatic drug (bDMARD) treatment [5]. According to the American College of Rheumatology (ACR) recommendations [4, 6], when traditional sDMARD therapy is not sufficient for treating JIA, a tumour necrosis factor (TNF) blocker, including etanercept (ETN), can be added. The treatment of JIA in Finland is based on the ACR treatment recommendation and is in line with European care practices [7].

ETN, a dimeric fusion protein that comprises two extracellular portions of the TNF receptor 2 linked to the Fc portion of human immunoglobulin G1, was introduced nearly 30 years ago for treating rheumatoid arthritis (RA) [8] and for treating JIA [9]. In Finland, ETN has been used for JIA since February 2000, and the normal procedure is subcutaneous administration once a week, occasionally twice a week, according to the manufacturer's instructions https://www.ema.europa.eu/en/medicines/human/EPAR/enbrel.

In a clinical trial simulation, subcutaneous ETN injections 0.8 mg/kg weekly and 0.4 mg/kg twice a week produced overlapping steady-state time-concentration profiles and corresponding clinical outcomes [10]. Similar results were reported by Langley et al. in their study of pediatric patients with psoriasis who received ETN 0.8 mg/kg weekly and pediatric patients with arthritis who received ETN 0.4 mg/kg twice weekly [11]. ETN can be administered alone or in combination, usually with MTX. Nevertheless, the effect of MTX on the serum trough concentration of ETN remains unclear [12].

In this study, we aimed to investigate whether concomitant MTX and ETN doses affect ETN serum trough levels in patients with JIA and whether concomitant MTX affects clinical response in patients with JIA receiving ETN.

Methods

Patients and methods

This observational retrospective study collected the medical record data of patients from eight Finnish pediatric rheumatological centres: five university hospitals and three within secondary referral hospitals. Patients who received ETN regularly from July 2014 to November 2017 for at least two weeks and were under 18 years old were included in the study. ETN treatment was accomplished by the decision of the pediatric rheumatologist. Serum samples for the concentration measurement were taken for clinical reasons, mainly to assist in dose adjustment to optimise the use of ETN and/or verification of individual compliance. Pharmacological treatment comprised ETN monotherapy or combination therapy, with or without sDMARD. All analysed patients were diagnosed as having JIA according to ILAR criteria [3].

The following patient data were collected: ETN initiation date, dose of the drug (mg/kg), body surface area using Mosteller modulation [13], concomitant sDMARDs, previous bDMARDs, height, weight, age, sex, diagnosis date, and type of JIA. Basic clinical disease information included the following: antinuclear antibody (ANA), human leucocyte antigen B27 (HLA-B27) result, rheumatoid factor (RF) level, cyclic citrulline peptide antibody (CCP-ab), patient's global assessment of wellbeing (PaGA), measured on a visual analogue scale (VAS) from 0 to 100, physician's global assessment of disease activity (PhGA) on a VAS from 0 to 100, 10-joint juvenile disease activity score (JADAS10) at the time of ETN concentration measurements, and possible comorbidities (uveitis or inflammatory bowel disease).

To evaluate the ETN concentrations of the patients, blood samples were collected between injections right before the subsequent drug dose to enable trough concentration measurement. This was the first ETN concentration measurement. Free ETN level was measured from serum with the ELISA method by Sanquin Diagnostics (Amsterdam, the Netherlands) [14] subcontracted by the United Medix Laboratory (Helsinki, Finland). The target value for residual ETN concentrations was above 1.5 μg/mL [15–17].

Ethics

This register-based study was performed by collecting clinical data from patient records. Therefore, according to Finnish legislation, no approval by an ethical committee or informed consent was required. Each hospital granted permission to collect the patient data.

Statistics

Data are presented as means with standard deviation (SD), medians with interquartile range (IQR), or counts with percentages. Statistical significance between groups was evaluated using t test or chi-square test. When adjusting for confounding factors, an analysis of covariance or logistic regression model was applied. Relationship between ETN dose and concentration estimated

according to the use of MTX by tuota moni ei mut intissäusing two separate univariate regression models. In the case of violation of the assumptions (e.g., non normality) for continuous variables, a bootstrap-type method or Monte Carlo p-values (small number of observations) for categorical variables were used. Correlation coefficients were calculated using the Spearman method, using Sidak-adjusted (multiplicity) probabilities. ETN dose adjusted (partial) correlation between dose of MTX and ETN serum trough level was calculated by the Pearson method. The normality of the variables was evaluated graphically and by using the Shapiro–Wilk W test. All analyses were conducted using Stata 17.0 (StataCorp, College Station, TX, USA).

Results

Overall, 182 patients with JIA receiving ETN were eligible in the study. Two patients with inadequate compliance were excluded. Finally, 180 patients were included: 109 (61%) girls and 71 (39%) boys. The mean patient age was 8.0 years (range: 2–17 years).

The characteristics of the patients are presented in Table 1. Ninety-seven (54%) of the patients used concomitant MTX, and 83 (46%) received either ETN monotherapy or used sDMARDs other than MTX. Twenty-three patients used leflunomide, eight used sulfasalazine, and three used hydroxychloroquine (Table 2). Compared with the non-MTX group, patients in the MTX group were younger and had shorter disease duration at ETN treatment initiation. No significant difference was observed between the groups in body composition measures, disease activity, neither in the presence of ANA nor HLA-B27 antigen. CCP-ab was positive in all patients with RF-positive polyarthritis.

Median (Q1, Q3) time point for the measurement of ETN concentration was 12 (4, 30) months after ETN initiation. At that time point, median (range) MTX dose was 13.0 mg/m^2 (5.5–24.2 mg/m^2) and median ETN dose was 0.75 (0.49–1.47) mg/kg/week and median ETN concentration was 1.60 (0.40–6.30) µg/mL in the MTX group and 1.70 (0.60–4.90) µg/mL in the non-MTX group ($p=0.52$ after adjusted ETN dose). Correlation between MTX dose and ETN concentration adjusted with ETN dose was 0.01 (95% Cl: -0.16 to 0.19).

A significant correlation was revealed between ETN dose and drug level [$r=0.45$ (95% CI: 0.33–0.56)] (Fig. 1). The ETN dose and serum drug level were correlated ($p=0.03$) in both subgroups – in MTX group [$r=0.35$ (95% CI: 0.14–0.52)] and in non-MTX group [$r=0.54$ (95% CI: 0.39–0.67)]. No correlation was detected between ETN concentration and patients' weight or body surface area.

No significant correlation was found between disease duration and ETN concentration when ETN dose was adjusted, neither in the MTX group $r=0.01$ (95% CI:

Table 1 Clinical and demographic characteristics of the patients at the time of ETN measurement

	MTX group $n=97$	non-MTX group $n=83$	*p* value
Female (%)	62 (64)	47 (57)	0.32
Age (years), mean (SD)	7.5 (3.6)	8.6 (3.8)	0.037
Height (cm), mean (SD)	122 (23)	128 (239)	0.11
Weight (kg), mean (SD)	26.5 (13.0)	28.6 (13.7)	0.27
BMI, kg/ m^2	16.6 (2.8)	16.5 (2.5)	0.77
BSA (m^2), mean (SD)	0.94 (0.31)	1.00 (0.33)	0.17
Disease duration (years), mean (SD)	2.3 (2.4)	3.2 (2.8)	0.019
Diagnosis			0.74
Oligoarthritis, persistent	17 (18)	18 (22)	
Oligoarthritis, extended	15 (15)	14 (17)	
Polyarthritis, RF-negative	57 (49)	40 (48)	
Polyarthritis, RF-positive	2 (2)	1 (1)	
Enthesitis related arthritis	4 (4)	7 (8)	
Psoriatic arthritis	1 (1)	2 (2)	
Undifferentiated arthritis	1 (1)	1 (1)	
Uveitis, n (%)	9 (9)	2 (2)	0.066
Inflammatory bowel disease, n (%)	1 (1)	1(1)	0.99
Previous bDMARD, n (%)	10 (10)	15 (18)	0.13
Etanercept	7	10	
Adalimumab	3	4	
Infliximab	2	4	
Tocilizumab	0	2	
Concomitant treatment n (%)			
Other sDMARDs	6 (6)	32 (39)	< 0.001
Prednisolone	4 (4)	7(8)	0.23
ESR (mm/h), mean (SD)	13.2 (14.0)	12.1 (12.1)	0.61
CRP (mg/l), mean (SD)	4.9 (12.6)	5.9 (13.5)	0.63
JADAS10, mean (SD)	10.0 (5.6)	9.7 (5.8)	0.56
PaGA, mean (SD)	3.3 (2.6)	2.6 (2.2)	0.10
PhGA, mean (SD)	3.1 (1.8)	2.7 (1.9)	0.14
HLA-B27 positive, n (%)	27 (28)	25 (30)	0.58
ANA, n (%)	31 (32)	23 (28)	0.54
Erosions, n (%)	21 (22)	16 (19)	0.60

ETN etanercept, *MTX* methotrexate, *BMI* Body mass index, *BSA* Body surface area, *RF* Rheumatoid factor, *bDMARD* biological disease-modifying antirheumatic drug, *sDMARD* synthetic disease-modifying antirheumatic drug, *ESR* Erythrocyte sedimentation rate, *CRP* C-reactive protein, *JADAS10* 10-joint Juvenile Arthritis Disease Activity Score, *PaGA* Patient's global assessment of wellbeing measured on a linear analogue scale (VAS), *PhGA* Physician's global assessment of wellbeing measured on a VAS scale, *HLA* Human leucocyte antigen B27, *ANA* Antinuclear antibody

Table 2 Other sDMARDs of the patients at the time of ETN measurement

sDMARD	MTX group *n* = 97	non-MTX group *n* = 83	*p* value
Leflunomide, n (%)	1(1)	23(28)	< 0.001
Hydroxychloroquine, n (%)	5(5)	3(4)	0.73
Sulfasalazine, n (%)	2(2)	8(10)	0.046
Azathioprine, n (%)	0(0)	1(1)	0.46
Prednisolone, n (%)	4(4)	7(8)	0.35

sDMARD synthetic disease-modifying antirheumatic drug, *MTX* Methotrexate

Table 3 Correlations (Spearman) between ETN concentration and disease activity

	ETN concentration	
	MTX group *r* (95% CI)	non-MTX group *r* (95% CI)
ESR	-0.04 (-0.24 to 0.16)	-0.01 (-0.23 to 0.21)
CRP	-0.20 (-0.39 to -0.01)	-0.06 (-0.28 to 0.15)
PaGA	0.02 (-0.18 to 0.22)	-0.25 (-0.44 to -0.04)
PhGA	0.19 (-0.01 to 0.37)	-0.09 (-0.30 to 0.12)
JADAS10	0.13 (-0.07 to 0.32)	-0.22 (-0.42 to -0.01)

No significant correlations after Sidak adjustment

ETN etanercept, *MTX* methotrexate, *ESR* Erythrocyte sedimentation rate, *CRP* C-reactive protein, *PaGA* Patient's global assessment of wellbeing measured on a linear analogue scale (VAS), *PhGA* Physician's global assessment of wellbeing measured on a VAS scale, *JADAS10* 10-joint Juvenile Arthritis Disease Activity Score

-0.15 to 0.15) nor in the non-MTX group $r = -0.03$ (95% CI: -0.23 to 0.18). Neither was significant correlation observed between disease activity and ETN concentration (Table 3).

Discussion

To our knowledge, this is the first study to analyse ETN treatment and the effects of concomitant MTX usage on serum ETN concentration in pediatric patients with JIA receiving ETN with or without concomitant MTX. The main findings of this study are that concomitant MTX had no effect on serum ETN concentration and significant correlation was observed between ETN dose and ETN concentration. We did not observe any positive influence on clinical response in ETN-treated patients in MTX group compared with non-MTX group.

When sDMARDs are insufficient to provide remission in patients with JIA, bDMARDs are regularly used. TNF inhibitors, such as ETN, are the first choice of bDMARDs [18]. ETN has been used in JIA for over 30 years, and it has been shown to be effective and safe for long-term use [19, 20]. In a pilot study of 40 JIA patients treated with ETN, there was a clear association between circulating ETN levels, and the dose received [21], consistent with our results: increase in ETN dose was associated with increase in ETN concentration. Similarly to our study, Alcobendas et al. [21] did not

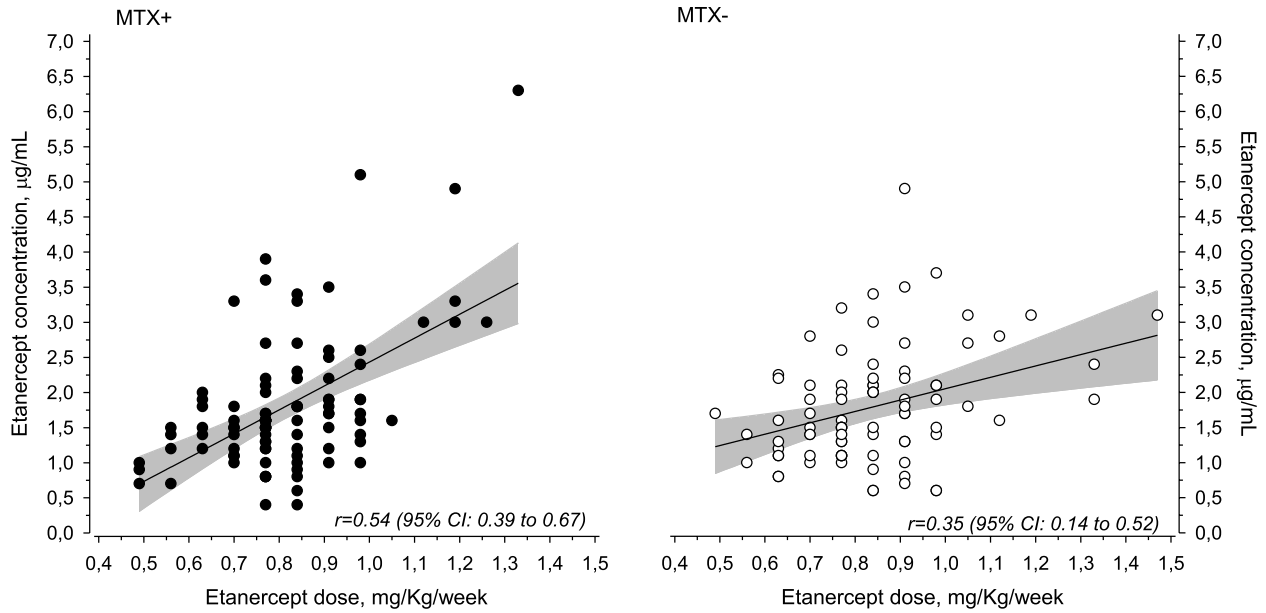

Fig. 1 Relationship between ETN (etanercept) dose and concentration according to MTX (methotrexate) use. The grey area represents 95% confidence intervals of linear prediction

find any relationship between ETN concentration and disease activity. Results of the study by Bader-Meunier et al. support these findings [22]. Also in adult patients with RA, ETN concentration did not correlate significantly with good clinial response [12].

Variation in the response to drug treatment among patients with JIA has awaken expectations to get support from therapeutic drug monitoring for decision-making during bDMARD treatment. Similar to other drugs, serum ETN concentration can be affected by several factors. ETN is administered subcutaneously, when the absorption and bioavailability is not necessarily complete. The injection site might have a minor effect on absorption accompanied by factors affecting ETN metabolism [23–25]. Moreover, it remains unclear whether body mass affects ETN concentrations, whether patients with higher body mass have higher volume on distribution [26], and whether obese patients with JIA may have difficulties in achieving remission [27]. In the present study, we did not find any correlation between ETN concentration and patients' weight or body surface area, consistent with the results of Langley et al. [11].

ETN is a nonimmunogenic TNF inhibitor. Although antibodies are generated, they are nonneutralising and do not influence drug efficacy or safety [11, 22]. In the present study, considering the above, we did not measure anti-etanercept antibodies.

Apparently, drug concentrations in general vary widely within patients on the standard treatment dose. This intrapatient variability (IPV) is common during bDMARD treatment. Higher ETN doses might lower IPV by generating higher serum ETN concentrations and thus ensuring constant drug levels [28]. Parallel results have been reported in patients with JIA treated with ETN [29].

To our knowledge, no study has evaluated pediatric patients receiving ETN or the possible effect of concomitant MTX dosing on serum ETN concentration. In adult patients with RA receiving ETN treatment, concomitant MTX did not increase ETN concentration [12]. Deng et al. reported the influence of higher TNF-alpha concentration on ETN clearance in adult patients with ankylosing spondylitis [30], but another study revealed no association between circulating ETN concentration and concomitant MTX usage [31]. If concomitant MTX does not improve treatment outcome, it is worth of consider to taper off MTX in such patients.

In a case of a treatment failure, the problem can be that drug is ineffective and should be changed or that drug is effective, but the dose or frequency is too low. This can be determined by measuring drug concentrations. Drug trough level measurements can help in the decision of dose and frequency, and drug selection, as well as in situations where the patient is in remission, but it remains unknown whether continuing the drug administration is feasible. If the drug trough level is under the recommended level, it would be sensible to discontinue the treatment.

This study has some limitations. First, the present study was a register-based study, and clinical data were collected retrospectively from the patients' records. On the other hand, this kind of data is valuable real-life data for clinicians. Second, considerable variation existed between the time of diagnoses of JIA and the initiation of ETN.

In conclusion, in a case of uncertainty of drug effectiveness in patients with increase disease activity, it is critical to determine whether to increase the drug dose or frequency or whether the drug is ineffective and should be altered. One possibility is to add sDMARD to the therapy if not added earlier. In the present study, we observed that MTX did not affect serum ETN concentration, but increase of the ETN dose increased its serum concentration. We found that ETN concentration did not correlate with disease activity. This might be explained by patients' lower disease activity, when a lower ETN dose may be sufficient, or even a drug-free period. Moreover, based on the results of this study, it seems that concomitant MTX do not improve the treatment outcome. Further studies are needed to confirm our findings.

Abbreviations

ACR	American College of Rheumatology
ANA	Antinuclear antibody
bDMARD	Biological disease-modifying antirheumatic drug
CCP-ab	Cyclic citrulline peptide antibody
ETN	Etanercept
HLA-B27	Human leucocyte antigen B27
ILAR	International League of Associations for Rheumatology
IQR	Interquartile range
JADAS10	10-Joint juvenile disease activity score
IPV	Intrapatient variability
JIA	Juvenile idiopathic arthritis
MTX	Methotrexate
PaGA	Patient's global assessment of wellbeing
PhGA	Physician's global assessment of disease activity
RF	Rheumatoid factor
SD	Standard deviation
sDMARD	Synthetic disease modifying antirheumatic drug
TNF	Tumour necrosis factor
VAS	Visual analogue scale

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Authors' contributions
The final manuscript has been read and approved by all the authors, and they all have given necessary attention to ensure the integrity of the work, including: 1) substantial contributions to conception and design of, or acquisition of data or analysis and interpretation of data, 2) drafting the article or revising it critically for important intellectual content. Each author listed on the manuscript takes full responsibility for the manuscript. TL has written the first draft of the manuscript, she participated in making statistical analysis and in

interpretation of the results. JK has written the first draft of the manuscript, she participated in collecting and studying the patients and in making statistical analysis and in interpretation of the results. KR participated in collecting and studying the patients and was critically revising of the manuscript and participated in making statistical analysis and in interpretation of the results. PV participated in designing the study and participated in collecting and studying the patients and was critically revising of the manuscript. MM, participated in collecting and studying the patients and was critically revising of the manuscript. LK participated in collecting and studying the patients and was critically revising of the manuscript. MMG participated in collecting and studying the patients and was critically revising of the manuscript. MB participated in collecting and studying the patients and was critically revising of the manuscript. HP participated in collecting and studying the patients and was critically revising of the manuscript. HK participated in designing the study, participated in carrying out statistical analysis and interpretation of the results, and in drafting and revising the final version. SJ was designing the study and was critically revising of the manuscript. KA participated in designing the study, in studying the patients and in making statistical analysis and in interpretation of the results, and in drafting and revising the final version.

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Availability of data and materials
The dataset used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
According to Finnish legislation, no approval by an ethical committee or informed consent was required. Each hospital granted permission to collect the patient data.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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