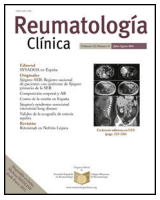
Reumatol Clin. 18 (2022) 475–479

Sociedad Española de Reumatología - Colegio Mexicano de Reumatología

Reumatología Clínica

www.reumatologiaclinica.org



Brief Report

Anti-TNFα drug levels in patients with rheumatoid arthritis and spondyloarthritis☆

Erardo Meriño-Ibarra,* Francisco Javier Manero Ruíz

Servicio de Reumatología, Hospital Universitario Miguel Servet, Zaragoza, Spain

ARTICLE INFO

Article history:
Received 7 September 2020
Accepted 3 June 2021
Available online 23 December 2021

Keywords:
Anti-TNFα levels
Rheumatoid arthritis
Spondyloarthritis

ABSTRACT

Background and objectives: Knowledge of the levels of anti-TNFa drugs can modify treatment in patients with rheumatoid arthritis (RA) and spondyloarthritis (SpA).
Objectives: To compare the levels of anti-TNFa in patients with RA vs SpA, in different clinical situations.
Materials and methods: A retrospective, observational study was conducted. Levels of anti-TNFa and the presence of anti-drug antibodies were measured in consecutively selected patients, using the ELISA technique.
Results: Fifty-three, 73 and 78 patients treated with infliximab, adalimumab and etanercept were studied, respectively. The median drug levels in patients using standard doses were infliximab 2.2 μg/mL (1.4–5.2), adalimumab 4.9 μg/mL (0.8–8.9) and etanercept 3.1 μg/mL (2.3–4.4). There were no differences in drug levels according to disease activity but we found differences in etanercept and infliximab levels according to DMARD use.
Conclusions: Levels of anti-TNFa drugs will change with DMARD treatment.

Niveles de fármacos anti-TNFα en pacientes con artritis reumatoide y espondiloartritis

Palabras clave:
Niveles de anti-TNFα
Artritis reumatoide
Espondiloartritis

RESUMEN

Antecedentes y objetivos: El conocimiento de los niveles de fármacos anti-TNFα puede modificar el tratamiento en pacientes con artritis reumatoide (AR) y espondiloartritis (EspA).
Objetivos: Comparar los niveles de anti-TNFα en pacientes con AR vs EspA, en diferentes situaciones clínicas.
Materiales y métodos: Se realizó un estudio retrospectivo, observacional donde se midieron los niveles de anti-TNFα y la presencia de anticuerpos antifármacos en pacientes seleccionados consecutivamente, utilizando la técnica de ELISA.
Resultados: Se estudiaron 53, 73 y 78 pacientes en tratamiento con infliximab, adalimumab y etanercept, respectivamente. Los niveles medios de fármaco en pacientes con dosis estándar fueron: infliximab 2,2 μg/mL (1,4–5,2), adalimumab 4,9 μg/mL (0,8–8,9) y etanercept 3,1 μg/mL (2,3–4,4). No se encontraron diferencias en los niveles fármacos según la actividad de la enfermedad, sin embargo, hubo diferencias en los niveles de etanercept e infliximab según el uso de fármacos modificadores de la enfermedad sintéticos (FAMEsc).
Conclusiones: Los niveles de fármacos anti-TNFα se verán modificados por el tratamiento con FAMEsc.

☆ Please cite this article as: Meriño-Ibarra E, Manero Ruíz FJ. Niveles de fármacos anti-TNFα en pacientes con artritis reumatoide y espondiloartritis. Reumatol Clín. 2022;18:475–479.

* Corresponding author.
E-mail address: eemerinnoi@salud.aragon.es (E. Meriño-Ibarra).

Introduction

In patients with rheumatoid arthritis (RA) treated with anti-TNF drugs (anti-TNF). A correlation has been found between drug levels and clinical response[1]. For example, in infliximab-treated patients, the presence of anti-drug antibodies (ADA) provoke loss of response, ifuional reactions and increased treatment withdrawal[2]. These data are not exclusive to RA and have also been described in spondyloarhritis (SpA), where anti-infliximab and anti-adalimumab antibodies are found in non-responders and in the case of infliximab, they are also related to infusional reactions, motivating a switch to another drug[3].

Various drug level measurement techniques are available with different standardisation[4], creating uncertainty as to the value of measuring drug levels. A consensus article has recently been published with the aim of reducing this uncertainty in the Spanish setting[5].

The aims of this study were to compare anti-TNF levels in RA patients vs. SpA, in patients in remission/low disease activity (LDA) vs. non-remission/non-LDA according to rheumatic disease, and to determine the influence of the use of conventional synthetic disease-modifying drugs (DMARDs) on these levels.

Material and methods

A total of 474 patients were being treated with anti-TNF drugs at our centre, including 51 patients with infliximab, 198 patients with adlmumab, and 225 patients with etanercept. A retrospective, observational study was conducted to measure anti-TNF levels and the presence of ADA in a group of consecutively selected patients who attended consultations at the rheumatology department of the Miguel Servet University Hospital.

Inclusion criteria

- Adult patients on anti-TNF treatment.

Exclusion criteria

- Patients who declined to participate in the study
- Patients under follow-up in other hospitals
- Diagnoses other than RA or SpA

The most commonly used methods for measuring levels are the sandwich ELISA and the indirect ELISA[4]. In our study, the sample was obtained on the day the drug was due to be administered (trough level), using the Promonitor® test from Laboratorios Grifols (sandwich ELISA), and according to the methodology described by Chen DY et al.[1]. In cases with undetectable anti-TNF levels, Acaf was measured using the Promonitor® test from Laboratorios Grifols (bridge-type ELISA).

The following data were collected from the patients' clinical history:

- Time of evolution of the disease
- Type and schedule of biologic treatment and DMARDs
- Adherence: percentage of the prescribed dosage of the drug that the patient withdraws from the hospital pharmacy.
- Disease activity: considering remission/low activity in patients with RA when they had a DAS28 (CRP) $\leq$ 3.2 and in patients with SpA a BASDAI $\leq$ 4 and ASDAS (CRP) $\leq$ 2.1. The activity indices were obtained from the consultation prior to the measurement of the levels.

With these data, a group of patients with RA and SpA was obtained and in each, subgroups with drug dosages according to the technical data sheet (standard dose) and others with dosages lower than those recommended (suboptimal dose), as well as patients with/without treatment with DMARDs.

Table 1
Summary of variables assessed, by rheumatic disease.

Variable	Rheumatoid arthritis N = 74	Spondyloarthritis N = 119	Total N = 193	*P* value
Age (years)[a]	59.8 (12.6)	54.7 (14.0)	56.7 (13.7)	.011
Women, N (%)	57 (77)	44 (36.9)	101 (52.3)	.000
Infliximab (g/mL)	2.10 (1.70–3.50)	2.9 (0.85–6.50)	2.3 (1.0–5.80)	.546
Adalimumab (g/mL)	2.80 (1.80–6.10)	5.40 (1.50–8.95)	3.80 (1.80–8.60)	.272
Etanercept (g/mL)	2.60 (1.20–4.00)	2.0 (.83–3.20)	2.40 (1.0–3.45)	.200
Biological therapy, N	74	119	193	.022
Infliximab, *N (%)*	16 (21.6)	34 (28.6)	50 (25.9)	
Adalimumab, *N (%)*	19 (25.7)	46 (38.6)	65 (33.7)	
Etanercept, *N (%)*	39 (52.7)	39 (32.8)	78 (40.4)	
Time to disease progression, (years)	12.6 (8.20–21.4)	13.1 (6.64–22.9)	12.9 (7.49–22.5)	.877
Time on biologic therapy, (years)	5.87 (2.05–9.53)	4.20 (1.80–9.14)	4.85 (1.82–9.26)	.386
BMI, (kg/m^2)	26.2 (22.6–29.1)	25.8 (23.3–29.8)	26.1 (23.1–29.6)	.325
CRP, (mg/dl)	.27 (.13–.70)	.24 (.11–.58)	.26 (.13–.61)	.555
DAS28, (CRP)	2.79 (2.27–3.62)	—	2,79 (2,27–3,62)	
BASDAIa	—	3.47 (2.2)	3.47 (2.2)	
ASDAS, (CRP)	—	1.70 (1.40–2.27)	1.70 (1.40–2.27)	
DMARDs, N (%)	50 (67.5)	27 (22.6)	77 (39.8)	.000
Methotrexate, N (%)	33 (44.5)	19 (15.9)	52 (26.9)	
Leflunomide, N (%)	16 (21.6)	5 (4.2)	21 (10.8)	
Sulphasalazine, N (%)	1 (1.63)	3 (2.53)	4 (2.1)	
Cases with suboptimal dose of anti-TNF, N (%)	26 (35.1)	39 (32.7)	65 (33.6)	.735
Infliximab, N (%)	5 (6.7)	9 (7.56)	14 (7.25)	
Adalimumab, N (%)	5 (6.7)	14 (11.7)	19 (9.84)	
Etanercept, N (%)	16 (21.6)	16 (13.4)	32 (16.5)	
Remission/low activity, N (%)	55 (74.3)	88 (77.8)	143 (76.5)	.575

ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BMI: Body Mass Index; CRP: C-reactive protein; DAS28: Disease Activity Score 28-joint counts; DMARDs: synthetic disease-modifying drugs.

[a] Data expressed as mean (standard deviation), other continuous quantitative variables expressed as median (interquartile range).

Table 2
Anti-TNF drug levels in standard-dose patients. A: Overall results. B: Anti-TNF drug levels according to rheumatic disease and according to remission/low disease activity vs. no remission/no low disease activity. C: Drug levels according to treatment with DMARDs and C1 according to rheumatic disease.

A	anti-TNFα levels (μg/mL), N = 128		
Infliximab	2.2 (1.4–5.25)		
Adalimumab	4.9 (.8–8.9)		
Etanercept	3.1 (2.3–4.4)		
B	Remission/LDA vs. no remission/no LDA		
	Rheumatoid arthritis N = 48		
	Remission/LDA N = 33	No remission/no LDA N = 15	*P* value
Infliximab	2.0 (1.5–2.8)	3.4 (3.4–3.4)	.427
Adalimumab	6.4 (2.8–8.0)	2.0 (0.23–3.4)	.128
Etanercept	2.7 (2.3–4.2)	4.0 (3.1–4.3)	.366
	Spondyloarthritis N = 80		
	Remission/LDA N = 55	No remission/no LDA N = 25	*P* value
Infliximab	4.4 (1.4–7.55)	2.4(1.0–6.2)	.563
Adalimumab	6.6 (0.45–9.95)	7.2 (1.85–8.9)	.999
Etanercept	2.8 (2.4–3.4)	4.2 (2.35–6.65)	.219
C	DMARDs N = 52	No DMARDs N = 76	*P* value
Infliximab	4.0 (2.2–6.0)	1.8 (1.0–2.4)	.035
Adalimumab	4.2 (.7–8.8)	4.9 (1.2–9.1)	.607
Etanercept	3.4 (2.6–4.7)	2.5 (1.8–3.7)	.039
C1	Rheumatoid arthritis N = 48		
	DMARDs N = 32	No DMARDs N = 16	*P* value
Infliximab	2.2 (1.8–5.2)	2.0 (1.55–2.75)	.520
Adalimumab	1.9 (0.7–7.45)	3.9 (3.55–4.8)	.539
Etanercept	3.2 (2.6–4.2)	3.2 (1.95–4.9)	.833
	Spondyloarthritis N = 80		
	DMARDs N = 20	No DMARDs N = 60	*P* value
Infliximab	5.4 (3.4–7.4)	2.1 (0.95–6.65)	.223
Adalimumab	9.3 (6.6–10.2)	6.3 (0.55–9.7)	.607
Etanercept	4.4 (3.3–6.1)	2.5 (1.95–3.25)	.008

LDA: low disease activity; DMARDs: synthetic disease-modifying drugs.
Results expressed as median (interquartile range).

Ethical aspects

All patients signed an informed consent form for this study and for the use of biological samples for biomedical research. This study was approved by the Research Ethics Committee of the Autonomous Community of Aragon.

Statistical method

Quantitative variables: distribution was determined with the Kolmogorov-Smirnov statistic (Lilliefors correction); in variables with N < 50, the Shapiro–Wilk statistic was applied; if the distribution was normal, the mean and standard deviation (SD) were determined; in variables with non-parametric distribution, the median and interquartile range (IQR) were determined. For differences between means and between medians: Student's t test and Mann–Whitney U test were used, respectively. For qualitative variables: 2 × 2 contingency tables with Pearson's Chi-square test. Statistical procedures were performed with the R statistical programme and calculated with a 95% confidence interval.

Results

A total of 53, 73, and 78 patients on treatment with infliximab, adalimumab, and etanercept, respectively, were studied. In all cases, a single sample extraction was performed. Eleven patients were excluded due to AFA and absence of drug levels: 3 (5.6%) treated with infliximab, all with SpA, none treated with DMARDs; 8 (11%) treated with adalimumab, 2 with RA on leflunomide, 6 patients with SpA, one treated with leflunomide, the remaining 5 without DMARDs. No anti-etanercept antibodies were detected.

No differences were found in drug levels according to disease type and disease activity. Patients with RA had a median DAS28: 2.79 (RI: 2.27−3.62) and those with SpA had a BASDAI of 3.47 (SD: 2.2) and an ASDAS of 1.70 (1.40−2.27). The variables studied are displayed in Table 1.

The percentage of remission/LDA in cases with RA and SpA was 74.3% and 77.8%, respectively. The time of disease progression was 12.9 years (RI: 7.49−22.5), with no differences between diseases (Table 1); adherence was ≥80% in 88.6% of cases.

Drug levels in patients on standard-dose anti-TNF were 2.2 g/mL (1.4–5.2), 4.9 g/mL (0.8−8.9), and 3.1 g/mL (2.3−4.4) for infliximab, adalimumab and etanercept, respectively (Table 2A), with no differences according to rheumatic disease (data not shown). We also found no differences in the group of cases with standard drug dosages, segmented by disease type and activity (Table 2B). When dividing patients with standard drug dosages according to treatment with/without DMARDs, we obtained significant differences in serum levels of infliximab and etanercept; adalimumab levels were similar in both groups (Table 2C), and subdividing these cases according to rheumatic disease, only etanercept levels exhibited differences in patients with SpA (Table 2C1).

Discussion

The drug level achieved after the standard treatment regimen may differ from one patient to another; however, the drug level required to achieve remission may not differ, hence the importance of evidence to support monitoring of anti-TNF6 levels.

The patients studied were fairly homogeneous, even between those in remission and non-remission; for instance, RA patients had generally low activity indices, which may have contributed to differences in drug levels not being conspicuous when comparing patient subgroups.

With respect to infliximab, the study by Jurado T et al. found that most RA patients in remission at week 54 after perfusion displayed levels of 4.4 g/mL at week[6,7] whereas in our study at week 12, we logically found lower levels of infliximab, with no differences in the remission/LDA vs. non-remission/non-LDA groups. Our results show no difference between infliximab levels between RA and SpA; nevertheless, Padilla-Martínez EM et al. detected different infliximab trough levels between the 2 diseases[8], but did not exclude cases with ADA from the analysis; similarly, they had a smaller sample size.

Sanmarti R et al. found adalimumab levels of 6.9 g/mL in patients with RA in remission[9]. Pouw MF et al. suggest that they should have levels of between 5−8 g/mL[10], similar to what was found in our study in patients in remission. Finally, Kneepkens EL et al. obtained an etanercept level of 3.8 g/mL (2.5–5.2) in SpA patients with ASDAS < 2.1[11] and Sanmarti R et al. obtained etanercept levels of 2.3 g/mL in RA patients in remission[9]. Our results were similar in both diseases excluding patients with suboptimal doses.

Anti-TNF levels can be affected by different factors such as comorbidity, route of drug administration, ADA formation, or the use of cSFs[12]. In our study, we detected differences in drug levels between patients with/without cAMP for infliximab and etanercept; nonetheless, we found no differences for adalimumab levels. However, Vogelzang EH et al. found higher levels of adalimumab in patients with RA or psoriatic arthritis treated with methotrexate[13].

In general, we did not find differences in drug levels according to disease activity, perhaps because of the homogeneity of the sample in this aspect, but if we add a cSF-MEF, then differences do emerge, mainly in SpA. Does this suggest the need to always use cSF-MEFs in association with anti-TNFs? Probably not routinely, albeit this opinion might be different if we assessed other biomarkers, such as the CXCL12 genotype or HLA-DQA1*05[14,15].

One of the limitations of our study is that as it is observational, retrospective, and conducted in clinical practice. As such, we do not aways have the results for all the variables studied. In addition, when the sample was subdivided, it was reduced, in some cases losing representativeness of the population under study.

In summary, we purport that anti-TNF drug levels will be modified by treatment with cAMP.

Funding

This research has not received any specific public or private funding.

Conflict of interest

None.

References

1. Chen DY, Chen YM, Tsai WC, Tseng JC, Chen YH, Hsieh CW, et al. Significant associations of antidrug antibody levels with serum drug trough levels and therapeutic response of adalimumab and etanercept treatment in rheumatoid arthritis. Ann Rheum Dis. 2015;74:1–10, http://dx.doi.org/10.1136/annrheumdis-2013-203893.
2. Pascual-Salcedo D, Plasencia C, Ramiro S, Nuño L, Bonilla G, Nagore D, et al. Influence of immunogenicity on the efficacy of long-term treatment with infliximab in rheumatoid arthritis. Rheumatology (Oxford). 2011;50:1445–52, http://dx.doi.org/10.1093/rheumatology/ker124.
3. Arstikyte I, Kapleryte G, Butrimiene I, Venalis A, Shi G. Influence of immunogenicity on the efficacy of long-term treatment with TNF α blockers in rheumatoid arthritis and spondyloarthritis patients. Biomed Res Int. 2015;2015:7–9, http://dx.doi.org/10.1155/2015/604872.
4. Terc M, Ogrič M, Terčelj M, Praprotnik S, Tomšič M, Božič B, et al. Detection of adalimumab and anti-adalimumab antibodies in patients with rheumatoid arthritis: a comprehensive overview of methodology pitfalls and benefits. Immunol Res. 2017;65:172–85, http://dx.doi.org/10.1007/s12026-016-8824-8.
5. Rosas J, Martín-López María, Otón T, Balsa A, Calvo-Alén J, Sanmartí R, et al. Aspectos prácticos de la medición de los niveles de fármacos biológicos y de

anticuerpos antifármaco en artritis reumatoide y espondiloartritis. Reumatol Clin. 2020;16:378–85, http://dx.doi.org/10.1016/j.reuma.2018.09.006.
6. den Broeder AA, van Herwaarden N, van den Bemt BJF. Therapeutic drug monitoring of biologicals in rheumatoid arthritis: a disconnect between beliefs and facts. Curr Opin Rheumatol. 2018;30:266–75, http://dx.doi.org/10.1097/BOR.0000000000000487.
7. Jurado T, Plasencia-Rodríguez C, Martínez-Feito A, Navarro-Compán V, Rispens T, Vries de A, et al. Predictive value of serum infliximab levels at induction phase in rheumatoid arthritis patients. Open Rheumatol J. 2017;11:75–87, http://dx.doi.org/10.2174/1874312901711010075.
8. Padilla-Martínez EM, Romero-Sánchez C, Bello-Gualtero JM, Mesa-Betancourt AM, Bautista Molano W, Valle OR. Drug levels and antibodies against TNF-blockers in spondyloarthritis and rheumatoid arthritis are associated with the activity but they do not predict it. Curr Rheumatol Rev. 2019;15:329–35, http://dx.doi.org/10.2174/1573397115666190708113601.
9. Sanmarti R, Inciarte-Mundo J, Estrada-Alarcon P, Garcia-Manrique M, Narvaez J, Rodriguez-Moreno J, et al. Towards optimal cut-off trough levels of adalimumab and etanercept for a good therapeutic response in rheumatoid arthritis. Results of the INMUNOREMAR study. Ann Rheum Dis. 2015;74:e42, http://dx.doi.org/10.1136/annrheumdis-2015-207530.
10. Pouw MF, Krieckaert CL, Nurmohamed MT, Van Der Kleij D, Aarden L, Rispens T, et al. Key findings towards optimising adalimumab treatment: the concentration-effect curve. Ann Rheum Dis. 2015;74:513–8, http://dx.doi.org/10.1136/annrheumdis-2013-204172.
11. Kneepkens EL, Krieckaert CLM, van Der Kleij D, Nurmohamed MT, van Der Horst-Bruinsma IE, Rispens T, et al. Lower etanercept levels are associated with high disease activity in ankylosing spondylitis patients at 24 weeks of follow-up. Ann Rheum Dis. 2015;74:1825–9, http://dx.doi.org/10.1136/annrheumdis-2014-205213.
12. Mould DR. The pharmacokinetics of biologics: a primer. Dig Dis. 2015;33 Suppl 1:61–9, http://dx.doi.org/10.1159/000437077.
13. Vogelzang EH, Pouw MF, Nurmohamed M, Kneepkens EL, Rispens T, Wolbink GJ, et al. Adalimumab trough concentrations in patients with rheumatoid arthritis and psoriatic arthritis treated with concomitant disease-modifying antirheumatic drugs. Ann Rheum Dis. 2015;74:474–5, http://dx.doi.org/10.1136/annrheumdis-2014-206588.
14. Ducourau E, Rispens T, Samain M, Dernis E, Le Guilchard F, Andras L, et al. Methotrexate effect on immunogenicity and long-term maintenance of adalimumab in axial spondyloarthritis: a multicentric randomised trial. RMD Open. 2020;6:6, http://dx.doi.org/10.1136/rmdopen-2019-001047.
15. Hässler S, Bachelet D, Duhaze J, Szely N, Gleizes A, Abina SHB, et al. Clinicogenomic factors of biotherapy immunogenicity in autoimmune disease: a prospective multicohort study of the ABIRISK consortium. PLoS Med. 2020;17:e1003348, http://dx.doi.org/10.1371/journal.pmed.1003348.