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ORIGINAL ARTICLE

Factors Predicting Early Failure of Etanercept in Rheumatoid Arthritis: An Analysis From the Gruppo Italiano di Studio sulla Early Arthritis (Italian Group for the Study of Early Arthritis) Registry

Marco SEBASTIANI[1], Andreina MANFREDI[1], Florenzo IANNONE[2], Elisa GREMESE[3], Alessandra BORTOLUZZI[4], Ennio FAVALLI[5], Chaira BAZZANI[6], Fausto SALAFFI[7], Enrico FUSARO[8], Rosario FOTI[9], Chiara GIANNITTI[10], Roberto CAPORALI[11], Alberto CAULI[12], Giulia CASSONE[13], Giuseppe LOPALCO[2], Luca PETRICCA[3], Gianfranco FERRACCIOLI[3], Giovanni LAPADULA[2]

[1]*Azienda Ospedaliera Policlinico Di Modena, University of Modena and Reggio Emilia, Rheumatology Unit, Modena, Italy*
[2]*Department of Medicine, Rheumatology Unit, University of Bari, Interdisciplinary Bari, Italy*
[3]*Policlinico Gemelli Foundation, Catholic University of the Sacred Heart, Rheumatology Unit, Rome, Italy*
[4]*Department of Clinical and Experimental Medicine, Rheumatology Unit, Sant'anna Hospital, University of Ferrara, Ferrara, Italy*
[5]*Department of Rheumatology, Gaetano Pini Institute, Milan, Italy*
[6]*Spedali Civili Di Brescia, Rheumatology and Clinical Immunology Unit, Brescia, Italy*
[7]*Università Politecnica Delle Marche, Rheumatology Unit, Jesi, Italy*
[8]*Città Della Salute E Della Scienza Hospital, Rheumatology Unit, Turin, Italy*
[9]*A.o.u. Policlinico Vittorio Emanuele, Rheumatology Unit, Catania, Italy*
[10]*University of Siena, Rheumatology Unit, Siena, Italy*
[11]*Irccs Policlinico San Matteo Foundation, University of Pavia, Rheumatology Unit, Pavia, Italy*
[12]*Department of Medical Sciences, Rheumatology Unit, Policlinico of the University of Cagliari, Cagliari, Italy*
[13]*Department of Clinical and Experimental Medicine, University of Modena and Raggio Emilia, Modena, Italy*

ABSTRACT

Objectives: This study aims to investigate the factors associated with early discontinuation (within one year) of etanercept (ETA) in rheumatoid arthritis (RA) patients who began ETA as first biologic disease-modifying antirheumatic drug (bDMARD) and who were entered into the Gruppo Italiano di Studio sulla Early Arthritis (Italian Group for the Study of Early Arthritis; GISEA) registry.

Patients and methods: This registry-based cohort study included 477 RA patients (95 males, 382 females; median age 53 years; range 18 to 83 years) who began ETA as first bDMARD. Patient demographics, disease features and drugs were re-evaluated after 12 months. Baseline predictors of ETA discontinuation were estimated by univariate and multivariate analyses using Cox regression model.

Results: Seventy patients (14.7%) discontinued ETA during the first year (for inefficacy in 55.8%, adverse events in 28.6%, and other reasons in 6.5%). Concurrent conventional synthetic DMARDs (csDMARDs) were reported in 54.3% of patients, mainly methotrexate (MTX), while 52.4% of subjects took low doses of glucocorticoids. Patients stopping ETA more frequently showed one or more comorbidities, mainly cardiovascular diseases (28.6% vs. 15.7% in patients stopping and continuing ETA, respectively, p=0.009). The presence of comorbidities and a combination therapy with csDMARDs other than MTX were independent factors associated with early discontinuation of ETA at multivariate Cox analysis.

Conclusion: Although ETA demonstrated a high persistence in biologic-naïve RA patients, about 15% of patients discontinued the treatment within 12 months. The presence of comorbidities and a combination therapy with csDMARDs other than MTX were the main factors for an early withdrawal of the drug.

Keywords: Etanercept, predictive factors, rheumatoid arthritis, treatment failure.

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Correspondence: Marco Sebastiani, MD. Azienda Ospedaliera Policlinico Di Modena, University of Modena and Reggio Emilia, Rheumatology Unit, 41124 Modena, Italy. Tel: +390594222595 e-mail: marco.sebastiani@unimore.it

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Tumor necrosis factor-alpha inhibitors (TNFi) are usually the first biologic drugs employed for the treatment of rheumatoid arthritis (RA) after the failure of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).[1] Among them, etanercept (ETA), a recombinant soluble TNF-alpha receptor, was one of the first TNFi to become commercially available, along with adalimumab and infliximab, with almost 20 years of experience in clinical practice.[2]

Adalimumab, ETA, and infliximab have shown similar high response rates in randomized controlled trials in terms of clinical efficacy and effect on joint damage progression;[3-5] however, the non-selected patients encountered in everyday clinical practice often have more complex features than those enrolled in randomized controlled trials because of concomitant therapies, comorbidities, personal habits, and poor adherence, all of which may affect treatment success.[1,2]

Although many registry studies investigated the predictors of efficacy and persistence in TNFi therapy, such as age, clinical response to prior treatments with a TNFi, concomitant therapy with methotrexate (MTX), and the presence of comorbidities, few studies have evaluated the causes of early failure of these drugs.[6-8] Some analyses have focused on the causes of discontinuation of biologic DMARDs (bDMARDs) in long-term treatment,[9,10] while, to our knowledge, no studies have searched for the factors associated to the failure of ETA in RA patients within the first year of therapy.

Given the recent introduction onto the market of new biologic and targeted synthetic drugs with different mechanisms of action, the profiling of patients with RA is strategic to identify patients with a lower possibility of response to therapy. Therefore, in this study, we aimed to investigate the factors associated with early discontinuation (within one year) of ETA in RA patients who began ETA as first bDMARD and who were entered into the Gruppo Italiano di Studio sulla Early Arthritis (Italian Group for the Study of Early Arthritis; GISEA) registry.

PATIENTS AND METHODS

The GISEA has developed and maintained a nationwide registry to promote the study of patients with rheumatic diseases who are being treated with biological drugs according to standard of care criteria.[11] The registry involves 21 hospitals and community-based rheumatology units throughout Italy and enrolls patients aged >18 years. The registry-based study was approved by the Hospital Ethics Committee of Modena (protocol number 2270, June 10th, 2015). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in Brazil 2013) and European and local rules of good clinical practice. In the GISEA registry, patient data are recorded at baseline, on prescribing of the bDMARD, and every six months thereafter (ClinicalTrials.gov identifier NCT01543594).

Rheumatoid arthritis was classified on the basis of the 1987 or 2010 American College of Rheumatology criteria.[12] The data collected include age, sex, ethnicity, disease duration, time from diagnosis to beginning of treatment with a biological drug (latency), concurrent use of glucocorticoids and DMARD (namely MTX, leflunomide, sulphasalazine, hydroxychloroquine, cyclosporin A), smoking status, body mass index (BMI), the 28-joint disease activity score (DAS28), C-reactive protein levels, anti-citrullinated peptide antibodies (ACPAs), rheumatoid factor (RF), side effects and erythrocyte sedimentation rate (ESR; mm/hour). Comorbidities were recorded, including anemia, anxiety/depression, cardiovascular diseases (coronary artery diseases, chronic heart failure, arrhythmias), hypertension, cerebrovascular diseases, gastropathies, liver diseases, nephropathy, and peripheral vasculopathy, diabetes, chronic obstructive pulmonary diseases, and cancer. Information on extra-articular manifestations of patients' rheumatic disease (Raynaud's phenomenon, rheumatoid nodules, lung involvement, and sicca syndrome) was also collected.

The study included 477 RA patients (95 males, 382 females; median age 53 years; range 18 to 83 years) who began ETA as first bDMARD between 01 January 2001 and 31 December 2016. Patients' demographic, clinical and serological data, the intake of glucocorticoids and csDMARDs, extra-articular manifestations and comorbidities were recorded. Patients' clinical status was re-evaluated after 12 months, with

a focus on disease activity and persistence with ETA therapy. When ETA was discontinued, the time and the cause of discontinuation were also recorded (i.e. lack or loss of efficacy, or adverse events). Time to discontinuation was defined as the time span between ETA initiation and the last administration plus one dispensation interval.

Statistical analysis

The differences between patients who stopped or continued ETA treatment within the first year of therapy were analyzed using the Mann-Whitney nonparametric test for continuous variables (median and interquartile ranges [IQRs]. The chi-squared test was used for categorical variables (absolute numbers and percentages) regarding baseline characteristics. The univariate and multivariate analyses were performed using Cox regression model. Cox regression analysis was performed to analyze the effect of the baseline features of the patients on ETA discontinuation.

The baseline variables taken into account were sex, disease duration, comorbidities, DAS28, ESR, concurrent use of glucocorticoids and DMARDs, BMI, extra-articular manifestations, and smoking habit. Analyses were performed using the SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA), with a p value <0.05 considered to be statistically significant. Unless otherwise indicated, the data are expressed as percentages or median (IQR).[13]

RESULTS

Four hundred and seventy-seven RA patients were included in the study [95 males, 382 females; median age 53 years (IQR: 18); range 18 to 83 years; median disease duration of 5.4 years (IQR: 8.1), median DAS28 of 5.56 (IQR: 1.69), median swollen joints of 5 (IQR: 8) and median tender joints of 9 (IQR: 11)] (the other serological and clinical features were reported in Table 1). RF and ACPAs were positive in 66% and 62.3% of patients, respectively. Comorbidities were observed in 17.6% of patients, mainly cardiovascular diseases (9.6% of patients), arterial hypertension (11.6%), diabetes (1.9%), and chronic pulmonary obstructive diseases (2.1%), while extra-articular RA manifestations were recorded in 6.3%. Concurrent csDMARDs therapies were reported in 54.3% of patients, mainly MTX [40.5%, median dosage 10 (IQR 5) mg weekly], while 52.4% of patients took low doses of steroids. One hundred and twenty-nine patients (27%) took ETA alone, without csDMARDs or steroids.

Seventy patients (14.7%) discontinued ETA during the first year (for ineffectiveness in 43 patients, adverse events in 22, and other reasons in five). ETA was stopped after a median of 23 weeks (range, 1-51 weeks).

The most frequent adverse events were represented by intolerance to the drug (skin reactions, fever after the injection, or malaise) in 21 patients, increase of liver enzymes in 12 patients, and infections in 16; only two

Table 1. Demographic, clinical and serological features of RA patients treated with etanercept as first-line biologic therapy (n=477)

	n	%
Gender		
Female	382	80.1
Current smoker	113	23.7
Ex smoker	82	17.2
ACPA-positive	297	62.3
RF	315	66
ACPA + RF-positive	257	53.9
RF positive alone	58	12.2
ACPA-positive alone	40	8.4
None	122	25.6
Erythrocyte sedimentation rate	28	25
C-reactive protein >5 mg/L	323	67.7
Comorbidities	84	17.6
Cardiovascular diseases	46	9.6
Lung diseases	10	2.1
Liver diseases	5	1
Diabetes mellitus	9	1.9
Extra-articular manifestations	30	6.3
Rheumatoid nodules	11	2.3
Interstitial lung disease	2	0.4
Sjögren's syndrome	8	1.7
Other	9	1.9
DMARDs	259	54.3
Methotrexate	193	40.5
Leflunomide	40	8.4
Hydroxycloroquine	16	3.3
Sulphasalazine	6	1.3
Cyclosporin A	4	0.8
Steroid therapy	250	52.4

RA: Rheumatoid arthritis; ACPA: Anti-citrullinated peptide antibody; RF: Rheumatoid factor; DMARDs: Disease-modifying anti-rheumatic drugs.

Table 2. Features of rheumatoid arthritis patients that continued or stopped etanercept within first year of therapy

	Continuing etanercept (n=407)				Stopping etanercept (n=70)				
	n	%	Median	IQR	n	%	Median	IQR	*p*
Age (years)			53	17			51	15	NS
Disease duration (years)			5.4	8.2			5.6	8	NS
Body mass index			24.5	5.8			25.4	6.3	NS
Erythrocyte sedimentation rate			28	23.2			28	35	NS
Tender joints 28			9	11			8	16	NS
Swollen joints 28			5	9			5	9	NS
Disease activity score in 28-joint			5.5	1.7			5.9	2.1	NS
Mean dosage of MTX (mg/week)			15	5			10	5	NS
Gender									
Female	323	79.4			59	84.3			NS
Current smoker	98	24.2			15	21.8			NS
Rheumatoid factor positive	268	65.8			47	67.1			NS
ACPA positive	249	61.2			48	68.6			NS
ACPA-RF positive	219	53.8			38	54.3			NS
RF positive alone	49	12			9	12.9			NS
ACPA-positive alone	30	7.4			10	14.3			NS
None	109	26.8			13	18.6			NS
Co-morbidities	64	15.7			20	28.6			0.009
Cardiovascular diseases	38	9.3			8	11.4			NS
Extra-articular manifestations	23	5.7			7	10			NS
Steroid therapy	210	51.6			40	57.1			NS
Etanercept monotherapy	194	47.7			24	34.3			0.038
DMARDs									
Methotrexate	164	40.3			29	41.4			NS
Other DMARDs	49	12			17	24.3			0.006
C-Reactive protein (>5 mg/L)	277	68			46	65.7			NS

IQR: Interquartile range; MTX: Methotrexate; ACPA: Anti-citrullinated peptide antibody; RF: Rheumatoid factor; DMARD: Disease-modifying antirheumatic drug; NS: Not significant.

patients had a major cardiovascular event (an acute myocardial infarction and a stroke).

Patients that discontinued ETA were more frequently treated with combination therapy (65.7% vs. 52.3%, p=0.038). In detail, the association with MTX did not increase maintenance in therapy, while patients treated with csDMARDs different from MTX discontinued ETA more frequently (24.3% vs. 12% in patients discontinuing or not discontinuing ETA, p=0.006) (Table 2). ETA monotherapy was more frequently recorded in patients that continued treatment (47.7% vs. 34.3%, p=0.038). No differences were observed

Table 3. Cause of failure of etanercept according to associated therapy

	Inefficacy	Adverse events	Other
	%	%	%
Methotrexate	72.4	20.7	6.9
Other csDMARDs	58.9	40.0	1.1
Etanercept monotherapy	50.0	37.5	12.5

csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs; For every therapeutic strategy, table reports percentage of causes of discontinuation.

Table 4. Factors associated with early discontinuation of etanercept according to multivariate Cox regression analysis

	Standard error	Odds ratio	95% CI	*p*
Comorbidities	0.28	1.86	1.07-3.25	0.029
DMARDs other than MTX	0.35	2.01	1.014-3.982	0.045
ETA monotherapy	0.297	0.701	0.392-1.256	0.232

CI: Confidence interval; DMARD: Disease-modifying antirheumatic drug; MTX: Methotrexate; ETA: Etanercept.

in the median dosage of MTX in patients that continued or failed ETA.

Poor treatment efficacy was the main cause of discontinuation of ETA independently by the associated DMARD: 72.4% when associated with MTX, 58.9% with other csDMARDs, and 50% with monotherapy (Table 3).

Comparing patients that failed ETA according to the type of associated therapy, we observed higher rates of adverse events as the cause of discontinuation in patients treated with csDMARDs other than MTX and in monotherapy (40% and 37.5%, respectively), while only 20.7% of failure was due to side effects in patients treated with MTX (Table 3). No significant associations were observed with glucocorticoids, the presence of RF or ACPA or disease activity at baseline.

At multivariate Cox regression, the presence of comorbidities and a combination therapy with csDMARDs different from MTX were confirmed as independent factors associated with early discontinuation of ETA (Table 4).

DISCUSSION

The primary endpoint of our study was the analysis of the causes of early discontinuation (within the first year) of ETA in a real-world setting, observing a discontinuation rate of 14.7% during the first year of treatment.

The profiling of patients with RA is strategic in order to identify the correct therapeutic strategy. In this regard, the identification of patients with a lower possibility to respond to a single mechanism of action is relevant in the selection of the first-line therapy, to reduce switches to other drugs and to minimize the possibility of adverse events.

Several studies have analyzed the retention rate and the causes of discontinuation of bDMARDs during long-term treatment; however, to our knowledge, no studies have assessed the predictive factors related to the discontinuation of ETA in the first year of therapy, and only indirect data are available on this topic.[7,8,10,14]

In 2016, Chen et al.[15] showed a discontinuation rate of 26.1% for ETA in the first year of therapy, with a lower risk compared to adalimumab, but without analyzing the causes of this finding. Chen et al.[15] observed a higher rate of discontinuation compared to our data. In either study, the percentage of patients in combination therapy with MTX was about 40%, while in the population described by Chen et al.,[15] a higher proportion of patients were treated with csDMARDs other than MTX, a possible factor associated with early discontinuation in our cohort.

Our data do not provide an explanation for the higher risk of ETA discontinuation in patients treated with csDMARDs other than MTX (i.e., lower efficacy, higher side effects, or reduced compliance) and only a few studies have explored this point.[16] However, we cannot exclude that the low percentage of discontinuation for side effects in patients taking MTX could be due to a challenging bias, with a lower prescribing of MTX in patients with comorbidities.[17]

Several studies have shown contradictory results due to different methodologies, the study populations, and primary aims, namely long-term retention rate rather than causes of early discontinuation.[6,7,18-21]

Of interest, monotherapy did not seem to be associated with a higher risk of discontinuation, nor did combination treatment with steroids modify the maintenance of ETA therapy. In this

regard, Favalli et al.[7] in 2016 showed a higher retention rate in patients in combination therapy with ETA and MTX, but only in long-term treatments. Moreover, in our cohort, the presence of comorbidities was a significant factor associated with an early failure of ETA, similar to other Italian studies;[18,19] however, other studies have described contradictory results, where the presence of associated diseases and the coadministration of csDMARDs (particularly MTX) were the best predictors of drug continuation in RA patients treated with TNFi.[20] However, this study analyzed all TNFi together (ADA, ETA, INF), without sub-analysis for individual drugs.[20]

Comorbidities were also associated with greater discontinuation rates in a Brazilian cohort of TNFi (±DMARD) users. On the other hand, in that study, the medication persistence rate at first year was 55.6% for ETA,[20] much lower than in our Italian population.

Also, the role of BMI in the failure of TNFi is debated. Our study confirms previous observations showing that obesity does not reduce the maintenance of ETA therapy in RA patients. Similarly, in another cohort from the GISEA registry, a higher BMI was associated with a reduction of remission rate after one year in RA for patients treated with infliximab, but not with ETA or adalimumab.[21] In contrast, in another Italian study, concomitant diseases positively predicted long-term TNFi continuation [odds ratio (OR) 0.6, $p<0.01$], even though no significant correlation with a single comorbidity was found.[6] However, when multiple regression analysis was applied, the only baseline variable that significantly predicted drug survival at four years was DMARD intake (OR 0.64, $p<0.05$), with MTX having the highest significance (OR 0.58, $p<0.01$).[6]

Kristensen et al.[22] observed a one-year persistence on therapy of 89% for ETA when associated with MTX, while, when ETA was administered as monotherapy, the levels of adherence to therapy at one year was 74%. No significant differences were found when ETA was combined with other concomitant csDMARDs other than MTX. In the ETA group, total persistence in therapy was significantly higher for the subgroup receiving concomitant csDMARDs compared with ETA alone ($p=0.015$). Moreover, patients receiving ETA showed no differences in withdrawals because of adverse events when comparing combination therapy with monotherapy.

This study has some limitations. In particular, some comorbidities, such as cardiovascular diseases, include more conditions, namely coronary artery diseases, chronic heart failure, and arrhythmias that were not available individually. Moreover, functional damage and other conditions associated with pain (such as fibromyalgia) were not evaluated in this study, possibly influencing the efficacy of the treatment.

In conclusion, the identification of conditions associated with early failure of biologic or csDMARDs could assist in personalizing the therapeutic choice and reducing the frequency of switches of biologic drugs, decreasing the costs of the treatments for the national health services and the frequency of flare for the patients. Our results suggest that in clinical practice, careful attention should be paid to RA patients with comorbidities, in particular when a csDMARD other than MTX is associated with ETA. In these cases, a different biologic or targeting synthetic DMARD should be considered.

Declaration of conflicting interests

EGF has served as a consultant and/or speaker for BMS, Lilly, Celgene, MSD, UCB, Pfizer, Janssen, Novartis, Sanofi, and Abbvie. RC has provided expert advice to and/or had speaking engagements for Abbvie, BMS, Celgene, Lilly, MSD, Novartis-Sandoz, Pfizer, Roche, Sanofi, UCB. FI has received consultancy fees and/or speaker honoraria for less than Euro 10,000 from Pfizer, AbbVie, MSD, BMS, UCB, Roche, Sanofi, Celgene, Novartis, Lilly outside this work. The other authors declare no conflict of interest.

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REFERENCES

1. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960-77.
2. Wells AF, Curtis JR, Betts KA, Douglas K, Du EX, Ganguli A. Systematic literature review and meta-analysis of tumor necrosis factor-alpha experienced rheumatoid arthritis. Clin Ther 2017;39:1680-94.
3. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363:675-81.
4. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 2003;48:35-45.
5. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000;343:1594-602.
6. Iannone F, Gremese E, Atzeni F, Biasi D, Botsios C, Cipriani P, et al. Longterm retention of tumor necrosis factor-α inhibitor therapy in a large italian cohort of patients with rheumatoid arthritis from the GISEA registry: an appraisal of predictors. J Rheumatol 2012;39:1179-84.
7. Favalli EG, Pregnolato F, Biggioggero M, Becciolini A, Penatti AE, Marchesoni A, et al. Twelve-Year Retention Rate of First-Line Tumor Necrosis Factor Inhibitors in Rheumatoid Arthritis: Real-Life Data From a Local Registry. Arthritis Care Res (Hoboken) 2016:68:432-9.
8. Wijbrandts CA, Tak PP. Prediction of Response to Targeted Treatment in Rheumatoid Arthritis. Mayo Clin Proc 2017;92:1129-43.
9. Markenson JA, Gibofsky A, Palmer WR, Keystone EC, Schiff MH, Feng J, et al. Persistence with anti-tumor necrosis factor therapies in patients with rheumatoid arthritis: observations from the RADIUS registry. J Rheumatol 2011;38:1273-81.
10. Fisher A, Bassett K, Wright JM, Brookhart MA, Freeman H, Dormuth CR. Comparative persistence of the TNF antagonists in rheumatoid arthritis--a population-based cohort study. PLoS One 2014;9:e105193.
11. Lapadula G, Ferraccioli G, Ferri C, Punzi L, Trotta F. GISEA: an Italian biological agents registry in rheumatology. Reumatismo 2011;63:155-64.
12. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81.
13. Altman DG. Practical Statistics for Medical Research. London: Chapman and Hall/CRC Press; 1990.
14. Hyrich KL, Watson KD, Silman AJ, Symmons DP. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 2006;45:1558-65.
15. Chen HH, Chen DY, Chen YM, Tang CH. Is drug discontinuation risk of adalimumab compared with etanercept affected by concomitant methotrexate dose in patients with rheumatoid arthritis? Patient Prefer Adherence 2016;10:123-34.
16. Soliman MM, Ashcroft DM, Watson KD, Lunt M, Symmons DP, Hyrich KL. Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2011;70:583-9.
17. Monti S, Klersy C, Gorla R, Sarzi-Puttini P, Atzeni F, Pellerito R, et al. Factors influencing the choice of first- and second-line biologic therapy for the treatment of rheumatoid arthritis: real-life data from the Italian LORHEN Registry. Clin Rheumatol 2017;36:753-61.
18. Iannone F, Salaffi F, Fornaro M, Di Carlo M, Gentileschi S, Cantarini L, et al. Influence of baseline modified Rheumatic Disease Comorbidity Index (mRDCI) on drug survival and effectiveness of biological treatment in patients affected with Rheumatoid arthritis, Spondyloarthritis and Psoriatic arthritis in real-world settings. Eur J Clin Invest 2018;48:e13013.
19. Salaffi F, Carotti M, Di Carlo M, Farah S, Gutierrez M. Adherence to Anti-Tumor Necrosis Factor Therapy Administered Subcutaneously and Associated Factors in Patients With Rheumatoid Arthritis. J Clin Rheumatol 2015;21:419-25.
20. Acurcio FA, Machado MA, Moura CS, Ferre F, Guerra AA Jr, Andrade EI, et al. Medication Persistence of Disease-Modifying Antirheumatic Drugs and Anti-Tumor Necrosis Factor Agents in a Cohort of Patients With Rheumatoid Arthritis in Brazil. Arthritis Care Res (Hoboken) 2016;68:1489-96.
21. Gremese E, Carletto A, Padovan M, Atzeni F, Raffeiner B, Giardina AR, et al. Obesity and reduction of the response rate to anti-tumor necrosis factor α in rheumatoid arthritis: an approach to a personalized medicine. Arthritis Care Res (Hoboken) 2013;65:94-100.
22. Kristensen LE, Saxne T, Nilsson JA, Geborek P. Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. Arthritis Res Ther 2006;8:174.