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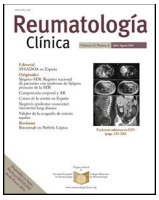

Original Article

Can we predict the risk factors for switching due to ineffectiveness in the first year of therapy with bDMARD in patients with rheumatoid arthritis?

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ABSTRACT

Introduction: Biological disease-modifying antirheumatic drugs (bDMARD) have improved the clinical course and quality of life of patients with rheumatoid arthritis (RA). However, some patients failed to respond or have an insufficient response to bDMARD early in the course of the treatment.
Objectives: To determine the percentage of RA patients who need to switch due to ineffectiveness in the first year of treatment and to identify specific baseline features as possible predictors of switch due to ineffectiveness in the first year of treatment.
Materials and methods: An observational retrospective study was conducted with patients with RA that started their first bDMARD. Demographic data, disease characteristics, disease activity data scores, laboratory parameters and treatment at baseline were collected. The proportion of patients who failed to respond and who switched to another bDMARD in the first year of treatment was calculated.
Results: A total of 437 (364 females, 83.3%) patients with RA were included. The majority of these patients started an anti-TNF-α agent ($n = 315$, 72.1%). Forty-eight (11.0%) patients failed to respond to the bDMARD in the first year of treatment. There were significantly more current or former smokers ($p = 0.030$), with a history of depression ($p = 0.003$) and positive for RF at baseline ($p = 0.014$) in the switch group.
In the multivariate analysis, anti-TNF-α agents use (OR 8.3, 95% CI 2.4–28.8, $p = 0.001$), tobacco exposure (OR 2.3, 95% CI 1.1–4.8, $p = 0.02$) and history of depression (OR 3.1, 95% CI 1.3–7.7) seem to predict the need to switch in the first year of treatment due to ineffectiveness.
Discussion and conclusion: In our study, tobacco exposure and depression appear to be modifiable risk factors associated with early switching due to ineffectiveness. Addressing these factors in daily clinical practice is crucial to enhance the overall response to therapy and improve the well-being of patients.

¿Cuáles son los factores de riesgo para el cambio de bDMARD en el primer año de terapia debido a la falta de eficacia en pacientes con artritis reumatoide?

Palabras clave:
Artritis reumatoide
Cambio en el primer año de tratamiento
Falta de eficacia
Fármacos antirreumáticos modificadores de la enfermedad biológicos
Factores de riesgo

RESUMEN

Introducción: Los fármacos antirreumáticos modificadores de la enfermedad biológicos (FAMEb) han mejorado la evolución clínica y la calidad de vida de los pacientes con artritis reumatoide (AR). No obstante, algunos pacientes no responden adecuadamente o muestran una respuesta insuficiente a los FAMEb en las primeras etapas del tratamiento.

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Objetivos: Determinar el porcentaje de pacientes con AR que necesitan cambiar de FAMEb en el primer año debido a la falta de eficacia, e identificar características específicas en el inicio del tratamiento como posibles predictores del cambio por falta de eficacia en el primer año de tratamiento.
Materiales y métodos: Estudio observacional retrospectivo que incluyó pacientes con AR y que iniciaron su primer FAMEb. Se recopilaron datos clínicos y demográficos, así como datos de actividad de la enfermedad, parámetros de laboratorio y tratamiento en el momento de la inclusión. Se calculó la proporción de pacientes que no respondieron y que cambiaron a otro FAMEb en el primer año de tratamiento.
Resultados: Se incluyeron un total de 437 pacientes con AR (364 mujeres, 83,3%). La mayoría de estos pacientes comenzaron un agente anti-TNF-α (n = 315, 72,1%). De estos pacientes, 48 (11,0%) no respondieron al FAMEb en el primer año de tratamiento. En el grupo de cambio, hubo significativamente más fumadores actuales o antiguos (p = 0,030), con antecedentes de depresión (p = 0,003) y positivos para el factor reumatoide (p = 0,014).
En el análisis multivariado, el uso de agentes anti-TNF-α (OR 8,3, IC 95% 2,4-28,8, p = 0,001), la exposición al tabaco (OR 2,3, IC 95% 1,1-4,8, p = 0,02) y antecedentes de depresión (OR 3,1, IC 95% 1,3-7,7) parecen predecir la necesidad de cambiar en el primer año de tratamiento debido a la falta de eficacia.
Discusión y conclusión: En nuestro estudio, la exposición al tabaco y la depresión parecen ser factores de riesgo modificables asociados con el cambio temprano debido a la falta de eficacia. Abordar estos factores en la práctica clínica diaria es crucial para mejorar la respuesta general al tratamiento y el bienestar de los pacientes.

Introduction

Biological disease-modifying antirheumatic drugs (bDMARDs) have revolutionized the treatment of chronic inflammatory rheumatic diseases, such as rheumatoid arthritis (RA), over the past two decades.[1] These drugs have significantly improved the clinical and functional outcomes of RA, changed the disease course and enhanced the quality of life of patients.

The bDMARDs are indicated for those who responded inadequately to conventional synthetic DMARDs (csDMARD) or experienced side effects with these drugs. They are highly effective, enabling a high percentage of patients to achieve sustained remission or low disease activity.[1–4] However, a significant number of patients treated with bDMARD failed to respond adequately or had an insufficient response, some of them within the few first months of treatment. The underlying reasons for these outcomes and the specific characteristics of such patients have yet to be fully investigated and understood.

While many studies have investigated the predictors of effectiveness and persistence in anti-TNF-α therapy, there has been a notable scarcity of studies that have evaluated the causes of early failure of these drugs.[5–7] Some studies have primarily focused on the causes of discontinuation of bDMARDs in long-term treatment, however the factors linked to the early failure of bDMARDs in the first year of therapy have been poorly investigated.[8–10]

Given the limited knowledge in this area and the importance of identifying potentially modifiable risk factors for early bDMARD failure in patients with RA, this study was conducted. The study aimed to determine the percentage of RA patients who need to switch due to ineffectiveness in the first year of treatment and to investigate the risk factors associated with switching during the first year of bDMARD therapy in a cohort of Portuguese patients with RA.

Methods

Study design and population

A retrospective cohort study was conducted at the Department of Rheumatology of a University Hospital and included patients with RA (according to the 2010 ACR/EULAR criteria).[11] All the patients were registered in the Portuguese Rheumatic Diseases Register (Reuma.pt), started their first bDMARD between June 2000 and December 2021 and had a minimum follow-up of 12 months.

Patient selection

Patients aged 18 years or older who were diagnosed with RA according to 2010 ACR/EULAR criteria that started treatment with a bDMARD and were registered in the Reuma.pt database were included. Patients with psychiatric or cognitive disorders that could interfere with data collection and who were physically or psychologically unable to communicate were excluded. Patients with significant missing data and with a follow-up of bDMARD treatment less than a one year were also excluded.

The Guideline for Good Clinical Practice of the International Conference on Harmonization and the ethical principles of the Declaration of Helsinki were followed. All patients signed informed consent and data were anonymized in accordance with the Portuguese Data Protection Law and the General Data Protection Regulation.

Data collection

Sociodemographic, clinical characteristics and laboratory parameters

Data were mainly collected from the Reuma.pt database and additional information was obtained from local medical records. Sociodemographic characteristics at baseline, such as age and gender, along with disease characteristics including age at onset, disease duration, presence of specific manifestations, such as rheumatoid vasculitis, smoking and alcohol drinking habits, history of depression (based on a previous diagnosis by a psychiatrist) and body mass index (BMI) were collected. Details on concomitant immunosuppressive therapies at baseline (systemic corticosteroids and csDMARD), and type of bDMARD administered were also fully detailed. Laboratory parameters including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), presence of rheumatoid factor (RF), anti-citrullinated peptide antibodies (ACPA) and antinuclear antibodies (ANA) were collected in all patients.

Disease activity measurements

At baseline, disease activity score for 28 joints with C-reactive protein (DAS-28-CRP),[12] Clinical Disease Activity Index (CDAI)[13] and Simplified Disease Activity Index (SDAI)[14] were collected.

Table 1
Description of the switching rates due to ineffectiveness in the first year for each biological disease-modifying antirheumatic drug (bDMARD).

	Switching rate due to ineffectiveness in the first year (number of patients that switch/total number of treated patients), %
Anti-TNF-α	14.3 (45/315)
Adalimumab	9.4 (10/106)
Etanercept	12.9 (17/132)
Infliximab	3.3 (1/30)
Certolizumab	25.0 (2/8)
Golimumab	38.5 (15/39)
Tocilizumab	2.0 (1/51)
Rituximab	3.0 (2/66)
Abatacept	0.0 (0/5)
All bDMARDs	11.0 (48/437)

Physical function was assessed through the Health Assessment Questionnaire (HAQ).[15]

Evaluation of switching in the first year

The patients were reevaluated during the first year of treatment with bDMARD. This included anamnesis, physical examination, laboratory analysis and assessment of disease activity. The number of patients who switched to another bDMARD due to ineffectiveness were collected. Those patients who did not achieve remission or low disease activity[16] in the first year of treatment discontinued their current treatment and switched to a different bDMARD. Patients who discontinued treatment in the first year due to adverse events were excluded. Switch and non-switch groups were compared regarding several variables.

Statistical analysis

Descriptive statistics for continuous variables with normal distribution were presented with mean and standard deviation. Categorical variables were presented with absolute and relative (percentage) frequencies. Chi-square test, for categorical variables, *t*-test, for normally distributed continuous variables, and Mann–Whitney *U* test, for not normally distributed continuous data were conducted. Moreover, a multivariate logistic regression analysis was performed. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A p-value <0.05 was considered statistically significant. Data analysis was performed using IBM SPSS for Windows (version 26, IBM Corporation Software Group, New York, NY, USA).

Results

A total of 437 (364 females, 83.3%) patients with RA were included. The mean age was 52.4 ± 11.4 years and the disease duration was 11.8 ± 8.8 years. The majority of these patients started an anti-TNF-α agent as first bDMARD (n = 315, 72.1%). The remaining patients started rituximab (n = 66, 15.1%), tocilizumab (n = 51, 11.7%) and abatacept (n = 5, 1.1%).

Forty-eight (11.0%) patients failed to respond to the bDMARD in the first year of treatment and needed to switch to another bDMARD. The mean duration of first bDMARD treatment in patients that needed to switch was 0.75 ± 0.3 years. The switching rate was higher among the anti-TNF-α agents, as described in Table 1.

Demographic characteristics were similar in the group of patients that switch due to ineffectiveness and patients that did not switch in the first year. Gender, disease duration, age at onset, disease activity scores (DAS-28-CPR, CDAI, SDAI), functional scores (HAQ) and inflammatory parameters at baseline were also similar in the two groups. There were significantly more current or former smokers in the group of patients that needed to switch in the first year of therapy (p = 0.030). Moreover, depression was significantly more frequent in the switch group (p = 0.003). Positivity for RF at baseline was also significantly more frequent in the switch group (p = 0.014).

Regarding the type of bDMARD, patients in the switch group were more frequently treated with anti-TNF-α agents (p < 0.001). Table 2 describes demographic and disease characteristics, laboratory parameters, disease activity at baseline and treatment at baseline of the included patients.

In the multivariate analysis adjusted for gender and age, anti-TNF-α agents use (versus non-anti-TNF-α agents) (OR 8.3, 95% CI 2.4–28.8, p = 0.001), tobacco exposure (OR 2.3, 95% CI 1.1–4.8, p = 0.02) and history of depression (OR 3.1, 95% CI 1.3–7.7) seem to predict the need to switch due to ineffectiveness in the first year of treatment, as shown in Table 3.

Discussion

In this study, the switching rate due to ineffectiveness was 11.0% for all bDMARDs. Specifically, it was 14.3% (with a range between 3.3% and 38.5% depending on the subtype of anti-TNF-α agent) for anti-TNF-α agents, 2% for tocilizumab and 3% for rituximab. A previous systematic review found a bDMARD discontinuation rate due to ineffectiveness in the first year of 14%, ranging from 10% to 19%.[17] Furthermore, a study that analyzed the discontinuation rate of etanercept during the first year of treatment also reported a similar rate of 14.7%.[10] In this study, anti-TNF-α agents exhibited a higher discontinuation rate compared to non-anti-TNF-α agents, specifically tocilizumab, rituximab, and abatacept. This finding is consistent with previous literature. Previous studies indicated that abatacept and tocilizumab had lower discontinuation rate due to inefficacy than anti-TNF-α within the first 36 months, with this difference being already observed at 12 months of therapy.[18] Additionally, research suggests that patients on abatacept switched less frequently than those on anti-TNF-α in the first 12 months of treatment.[19,20] Rituximab also appeared to have lower discontinuation rate due to inefficacy compared to anti-TNF-α, which is consistent with the findings of this study.[20,21]

In this study, current and former smokers, patients with depression and those with positive RF and history of rheumatoid vasculitis had a higher rate of switching due to ineffectiveness. This analysis identified tobacco exposure, history of depression and the use of anti-TNF-α agents as predictive factors for switching due to ineffectiveness in the first year of treatment.

Seropositivity for RF and ACPA has been linked to a more aggressive and active form of RA.[22,23] This increased disease aggressiveness may explain why RF-positive patients more frequently required to switch the treatment within the first year. However, we observed an association only with RF and not with ACPA. Interestingly, Santos-Moreno et al. reported similar findings in their study. They noted that remission was less frequent among RF-positive patients treated with anti-TNF-α agents compared to RF-negative patients, with no differences being reported in the remission rates of ACPA-positive and ACPA-negative patients.[24] Other studies have suggested that positive RF and ACPA titers can predict an inadequate response to anti-TNF-α therapy,[25,26] whereas others reported inconsistent and contradictory conclusions.[27–29]

Rheumatoid vasculitis is an uncommon but severe manifestation of RA that represents a more aggressive form of the disease and influences the treatment approach. A previous study found that patients who were refractory to at least three bDMARDs or two bDMARDs with different mechanism of action had a higher prevalence of extra-articular manifestations, including vasculitis.[30] This corroborates the findings of this study, supporting the idea that

Table 2
Demographic and disease characteristics, laboratory parameters, disease activity at baseline and treatment at baseline of patients with rheumatoid arthritis.

	Switch due to ineffectiveness in the first year (n = 48)	No switch in the first year (n = 389)	p-Value
Demographic characteristics			
Gender (female), n (%)	40 (83.3)	324 (83.3)	0.994
BMI, median (IQR)	26.6 (23.8–31.2)	26.0 (23.4–29.7)	0.340
Smoking habits, n (%)			**0.030**
Former/current smoker	20 (41.7)	104 (26.7)	
Non smoker	28 (58.3)	285 (73.3)	
Drinking habits, n (%)	8 (17.4)	50 (14.8)	0.307
Depression, n (%)	9 (19.1)	25 (6.7)	**0.003**
Disease characteristics			
Age at onset, years, mean ± ST	44.1 ± 11.6	42.5 ± 12.7	0.413
Disease duration, years, mean ± ST	10.6 ± 7.7	11.9 ± 9.0	0.337
Presence of vasculitis, n (%)	2 (4.3)	3 (0.8)	**0.039**
Laboratory parameters at baseline			
ESR, mean ± ST	36.7 ± 25.6	38.0 ± 22.3	0.72
CRP, mean ± ST	2.0 ± 2.1	1.9 ± 2.8	0.85
Positivity of RF, n (%)	44 (91.7)	296 (76.1)	**0.014**
Positivity of ACPA, n (%)	41 (85.4)	322 (82.8)	0.645
Positivity of ANA, n (%)	17 (35.4)	132 (33.9)	0.894
Disease activity at baseline			
CDAI, mean ± ST	31.1 ± 11.6	27.8 ± 11.6	0.133
SDAI, mean ± ST	33.0 ± 12.5	29.7 ± 12.3	0.158
DAS-28-CRP, mean ± ST	5.3 ± 1.0	5.2 ± 1.2	0.42
HAQ, mean ± ST	1.79 ± 0.62	1.67 ± 0.64	0.249
Treatment at baseline, *n* (%)			
bDMARD agent			**<0.001**
Anti-TNF-α	45 (93.7)	270 (69.4)	
Non-anti-TNF-α	3 (6.3)	119 (30.6)	
Concomitant csDMARD	42 (87.5)	320 (82.3)	0.364
Hydroxychloroquine	3 (6.3)	19 (2.3)	
Methotrexate	18 (37.5)	150 (38.5)	
Leflunomide	11 (22.9)	108 (27.8)	
Sulfasalazine	4 (8.3)	6 (1.5)	
Methotrexate + sulfasalazine	6 (12.5)	37 (9.5)	
Concomitant corticotherapy	41 (85.4)	348 (89.5)	0.398
Prednisolone			

ANA: anti-nuclear antibodies; ACPA: anti-citrullinated peptide antibodies; bDMARD: biological disease-modifying antirheumatic drugs; BMI: body mass index: CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IQR: interquartile range; HAQ: Health Assessment Questionnaire; RF: rheumatoid factor; ST: standard deviation.

Table 3
Multivariate regression model analysis used to identify variables associated with switch due to ineffectiveness in the first year.

	β	OR (95% CI)	p-Value
Gender (female)	0.31	1.36 (0.53–3.52)	0.519
Age at first bDMARD	0.02	1.02 (0.99–1.05)	0.157
Tobacco exposure	0.84	**2.32** ((1.13–4.75)	**0.022**
History of depression	1.13	**3.10** ((1.25–7.67)	**0.015**
Anti-TNF-α agents use (versus non-anti-TNF-α agents)	2.11	**8.28** ((2.38–28.80)	**0.001**
Presence of rheumatoid factor	0.97	2.64 (0.90–7.79)	0.078
Presence of vasculitis	1.75	5.73 (0.69–47.80)	0.107

bDMARD: biological disease-modifying antirheumatic drugs: TNF: tumor necrosis factor.

vasculitis can be associated with a higher switch rate of bDMARDs. However, it is important to note that the number of patients with rheumatoid vasculitis in this study is small, and therefore, conclusions draw from these results should be interpreted with caution.

Smoking has long been recognized as one of the most important extrinsic risk factors for the development and severity of RA.[31,32] Previous literature suggests that patients treated with anti-TNF-α agents who are smokers tend to experience poorer treatment response and drug survival.[33–36] One the other hand, smokers treated with rituximab and tocilizumab did not seem to have a worse response to therapy.[37,38]

Furthermore, a prior study involving patients with RA who started their first bDMARD revealed a significantly higher rate of switching in the first year of treatment among those with a history of depression.[39] Additionally, other study that included patients with RA, psoriatic arthritis and axial spondyloarthritis who received bDMARDs over a 2-year period found that the switching was associated with the use of antidepressant and anxiolytic medications.[40]

Tobacco exposure and depression appear to be modifiable risk factors associated with early switching due to ineffectiveness in patients with RA. These findings underscore the importance of addressing these factors in daily clinical practice to enhance the overall response to therapy and the well-being of patients.

To optimize treatment outcomes, it is imperative to reinforce the importance of smoking cessation in patients with RA. Healthcare providers should engage patients in discussions about quitting smoking and offer effective interventions and support to facilitate smoking cessation.

Depression, another factor linked to early switching due to ineffectiveness in this study, is often underdiagnosed and undertreated

in patients with RA.[41] To improve patient outcomes, routine screening for depression should be integrated into daily clinical practice of RA management. Identifying and addressing depression early on can have a positive impact not only on the patient's emotional well-being, but also on their ability to manage their illness and on the treatment response.

Some limitations of this study should be acknowledged. Major limitations are related to the single-center retrospective nature of the study and the extended study duration that may interfered with the outcome. Additionally, the small number of patients treated with abatacept may limit the conclusions about the switching rate due to ineffectiveness of this drug.

To our knowledge, this is the first study that identifies specific baseline features as possible predictors of switching due to ineffectiveness in the first year of treatment in a Portuguese cohort of RA patients.

Conflict of interests

None to declare.

References

1. Nam JL, Takase-Minegishi K, Ramiro S, Chatzidionysiou K, Smolen JS, van der Heijde D, et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2017;76:1113–36, http://dx.doi.org/10.1136/annrheumdis-2016-210713.
2. Smolen JS, Landewe RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79:685–99, http://dx.doi.org/10.1136/annrheumdis-2019-216655.
3. Fraenkel L, Bathon JM, England BR, St Clair EW, Arayssi T, Carandang K, et al. 2021 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2021;73:1108–23, http://dx.doi.org/10.1002/art.41752.
4. Ostergaard M, Unkerskov J, Linde L, Krogh NS, Ravn T, Ringsdal VS, et al. Low remission rates but long drug survival in rheumatoid arthritis patients treated with infliximab or etanercept: results from the nationwide Danish DANBIO database. Scand J Rheumatol. 2007;36:151–4, http://dx.doi.org/10.1080/03009740601089267.
5. Iannone F, Gremese E, Atzeni F, Biasi D, Botsios C, Cipriani P, et al. Longterm retention of tumor necrosis factor-alpha 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, http://dx.doi.org/10.3899/jrheum.111125.
6. 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, http://dx.doi.org/10.1002/acr.22788.
7. Wijbrandts CA, Tak PP. Prediction of response to targeted treatment in rheumatoid arthritis. Mayo Clin Proc. 2017;92:1129–43, http://dx.doi.org/10.1016/j.mayocp.2017.05.009.
8. 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, http://dx.doi.org/10.3899/jrheum.101142.
9. 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, http://dx.doi.org/10.1371/journal.pone.0105193.
10. Sebastiani M, Manfredi A, Iannone F, Gremese E, Bortoluzzi A, Favalli E, et al. 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. Arch Rheumatol. 2020;35:163–9, http://dx.doi.org/10.46497/ArchRheumatol.2020.7499.
11. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69:1580–8, http://dx.doi.org/10.1136/ard.2010.138461.
12. Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis. 2009;68:954–60, http://dx.doi.org/10.1136/ard.2007.084459.
13. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther. 2005;7:R796–806, http://dx.doi.org/10.1186/ar1740.
14. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford). 2003;42:244–57, http://dx.doi.org/10.1093/rheumatology/keg072.
15. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23:137–45, http://dx.doi.org/10.1002/art.1780230202.
16. Smolen JS, Landewe RBM, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023;82:3–18, http://dx.doi.org/10.1136/ard-2022-223356.
17. Souto A, Maneiro JR, Gomez-Reino JJ. Rate of discontinuation and drug survival of biologic therapies in rheumatoid arthritis: a systematic review and meta-analysis of drug registries and health care databases. Rheumatology (Oxford). 2016;55:523–34, http://dx.doi.org/10.1093/rheumatology/kev374.
18. Ebina K, Hashimoto M, Yamamoto W, Ohnishi A, Kabata D, Hirano T, et al. Drug retention and discontinuation reasons between seven biologics in patients with rheumatoid arthritis – the ANSWER cohort study. PLoS One. 2018;13:e0194130, http://dx.doi.org/10.1371/journal.pone.0194130.
19. Meissner B, Trivedi D, You M, Rosenblatt L. Switching of biologic disease modifying anti-rheumatic drugs in patients with rheumatoid arthritis in a real world setting. J Med Econ. 2014;17:259–65, http://dx.doi.org/10.3111/13696998.2014.893241.
20. Aronova ES, Lukina GV, Glukhova SI, Gridneva GI, Kudryavtseva AV. Survival of bDMARDs in bionaive patients with rheumatoid arthritis: data from a retrospective 12-month follow-up. Ter Arkh. 2020;92:39–45, http://dx.doi.org/10.26442/00403660.2020.05.000630.
21. Brodszky V, Biro A, Szekanecz Z, Soos B, Baji P, Rencz F, et al. Determinants of biological drug survival in rheumatoid arthritis: evidence from a Hungarian rheumatology center over 8 years of retrospective data. Clinicoecon Outcomes Res. 2017;9:139–47, http://dx.doi.org/10.2147/CEOR.S124381.
22. Young A, van der Heijde DM. Can we predict aggressive disease? Baillieres Clin Rheumatol. 1997;11, http://dx.doi.org/10.1016/s0950-3579(97)80031-3.
23. Jilani AA, Mackworth-Young CG. The role of citrullinated protein antibodies in predicting erosive disease in rheumatoid arthritis: a systematic literature review and meta-analysis. Int J Rheumatol. 2015;2015:728610, http://dx.doi.org/10.1155/2015/728610.
24. Santos-Moreno P, Sanchez G, Castro C. Rheumatoid factor as predictor of response to treatment with anti-TNF alpha drugs in patients with rheumatoid arthritis: results of a cohort study. Medicine (Baltimore). 2019;98:e14181, http://dx.doi.org/10.1097/MD.0000000000014181.
25. Potter C, Hyrich KL, Tracey A, Lunt M, Plant D, Symmons DP, et al. Association of rheumatoid factor and anti-cyclic citrullinated peptide positivity, but not carriage of shared epitope or PTPN22 susceptibility variants, with anti-tumour necrosis factor response in rheumatoid arthritis. Ann Rheum Dis. 2009;68:69–74, http://dx.doi.org/10.1136/ard.2007.084715.
26. Tanaka Y, Takeuchi T, Inoue E, Saito K, Sekiguchi N, Sato E, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year clinical outcomes (RECONFIRM-2). Mod Rheumatol. 2008;18:146–52, http://dx.doi.org/10.1007/s10165-008-0026-3.
27. Soto L, Sabugo F, Catalan D, Wurmann P, Cermenatti T, Gatica H, et al. The presence of anti-citrullinated protein antibodies (ACPA) does not affect the clinical response to adalimumab in a group of RA patients with the tumor necrosis factor (TNF) alpha-308 G/G promoter polymorphism. Clin Rheumatol. 2011;30:391–5, http://dx.doi.org/10.1007/s10067-011-1679-4.
28. Canhao H, Rodrigues AM, Mourao AF, Martins F, Santos MJ, Canas-Silva J, et al. Comparative effectiveness and predictors of response to tumour necrosis factor inhibitor therapies in rheumatoid arthritis. Rheumatology (Oxford). 2012;51:2020–6, http://dx.doi.org/10.1093/rheumatology/kes184.
29. Cuchacovich M, Catalan D, Wainstein E, Gatica H, Soto L, Aravena O, et al. Basal anti-cyclic citrullinated peptide (anti-CCP) antibody levels and a decrease in anti-CCP titres are associated with clinical response to adalimumab in rheumatoid arthritis. Clin Exp Rheumatol. 2008;26:1067–73.
30. Novella-Navarro M, Plasencia C, Tornero C, Navarro-Compan V, Cabrera-Alarcon JL, Peiteado-Lopez D, et al. Clinical predictors of multiple failure to biological therapy in patients with rheumatoid arthritis. Arthritis Res Ther. 2020;22:284, http://dx.doi.org/10.1186/s13075-020-02354-1.
31. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis. 2010;69:70–81, http://dx.doi.org/10.1136/ard.2008.096487.
32. Heliovaara M, Aho K, Aromaa A, Knekt P, Reunanen A. Smoking and risk of rheumatoid arthritis. J Rheumatol. 1993;20:1830–5.
33. Hyrich KL, Watson KD, Silman AJ, Symmons DP, British Society for Rheumatology Biologics Register. 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, http://dx.doi.org/10.1093/rheumatology/kel149.
34. Soderlin MK, Petersson IF, Geborek P. The effect of smoking on response and drug survival in rheumatoid arthritis patients treated with their first anti-TNF drug. Scand J Rheumatol. 2012;41:1–9, http://dx.doi.org/10.3109/03009742.2011.599073.

35. Mattey DL, Brownfield A, Dawes PT. Relationship between pack-year history of smoking and response to tumor necrosis factor antagonists in patients with rheumatoid arthritis. J Rheumatol. 2009;36:1180–7, http://dx.doi.org/10.3899/jrheum.081096.
36. Abhishek A, Butt S, Gadsby K, Zhang W, Deighton CM. Anti-TNF-alpha agents are less effective for the treatment of rheumatoid arthritis in current smokers. J Clin Rheumatol. 2010;16:15–8, http://dx.doi.org/10.1097/RHU.0b013e3181ca4a2a.
37. Chatzidionysiou K, Lukina G, Gabay C, Hetland ML, Hauge EM, Pavelka K, et al. Smoking and response to rituximab in rheumatoid arthritis: results from an international European collaboration. Scand J Rheumatol. 2019;48:17–23, http://dx.doi.org/10.1080/03009742.2018.1466363.
38. Theander E, Proven A, Fallang A, Svelander L, Trollmo T. FRI0163 smoking status does not seem to affect tocilizumab efficacy in RA patients. Ann Rheum Dis. 2015;74:482.
39. Matcham F, Davies R, Hotopf M, Hyrich KL, Norton S, Steer S, et al. The relationship between depression and biologic treatment response in rheumatoid arthritis: an analysis of the British Society for Rheumatology Biologics Register. Rheumatology (Oxford). 2018;57:835–43, http://dx.doi.org/10.1093/rheumatology/kex528.
40. Bournia VK, Tektonidou MG, Vassilopoulos D, Laskari K, Panopoulos S, Fragiadaki K, et al. Introduction and switching of biologic agents are associated with antidepressant and anxiolytic medication use: data on 42 815 real-world patients with inflammatory rheumatic disease. RMD Open. 2020;6, http://dx.doi.org/10.1136/rmdopen-2020-001303.
41. Nagyova I, Stewart RE, Macejova Z, van Dijk JP, van den Heuvel WJ. The impact of pain on psychological well-being in rheumatoid arthritis: the mediating effects of self-esteem and adjustment to disease. Patient Educ Couns. 2005;58:55–62, http://dx.doi.org/10.1016/j.pec.2004.06.011.