Original paper

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Impact of comorbidities, diabetes, and smoking on sustained outcomes in rheumatoid arthritis: a retrospective study

Zhaklin Apostolova, Tanya Shivacheva, Tsvetoslav Georgiev ✉

First Department of Internal Medicine, Faculty of Medicine, University Hospital St. Marina, Medical University – Varna, Bulgaria

Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic autoimmune disease significantly impacting patients' quality of life (QoL) and necessitating complex, long-term treatment. This study aimed to assess the long-term therapeutic outcomes of biologic therapies in a real-world clinical setting, focusing on the achievement and maintenance of low disease activity (LDA) among RA patients, while also investigating factors influencing these outcomes.

Material and methods: A retrospective observational analysis was conducted on 190 RA patients receiving tumor necrosis factor α (TNF-α) or interleukin (IL)-6 inhibitors. Disease activity was evaluated using the Disease Activity Score 28 (DAS28) at baseline, 6 months, and 12 months. Based on the DAS28 with C-reactive protein (DAS28-CRP) values, the disease was categorized into 2 main groups: remission/low activity (target achieved) when the DAS28-CRP value was less than 3.2, and insufficient therapeutic response when the value exceeded 3.2.

Results: The study group consisted of 190 RA patients, predominantly women (85.8%), with a mean age of 58.7 years and a disease duration of 12.5 years. We found that 45.8% of patients achieved single-point LDA, with 39.5% sustaining this response after 12 months. Notably, comorbidities such as diabetes and smoking negatively affected the likelihood of maintaining LDA. Statistical analysis revealed that patients without diabetes had a significantly higher chance of retaining sustained LDA (OR = 0.100; $p = 0.014$).

Conclusions: These findings emphasize the need for personalized treatment approaches that consider comorbidities and lifestyle factors to enhance long-term therapeutic efficacy in RA management. Consequently, this study highlights the critical importance of ongoing monitoring and individualized strategies to improve outcomes and QoL for patients with RA.

Key words: rheumatoid arthritis, biological therapy, comorbidity, smoking.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease with a profound impact on quality of life (QoL), necessitating complex, long-term treatment strategies [1]. Functional disability and chronic pain are key contributors to diminished QoL, often leading to reduced work capacity, absenteeism, and productivity loss. These challenges, compounded by prolonged disease duration, frequently contribute to comorbidities, including a number of cardiovascular conditions and depression [2]. On the other hand, pain and disability are the strongest predictors of work instability [3]. Sick leave represents a significant source of financial burden, which can be mitigated through early diagnosis and prompt initiation of disease-modifying antirheumatic drugs (DMARDs).

The treat-to-target strategy (T2T), emphasizing early DMARD use, is associated with improved QoL and reduced disability [4, 5]. Achieving and maintaining low disease activity (LDA) or remission is a primary therapeutic goal, offering better long-term outcomes and enhanced health-related QoL [6, 7]. Advances in biological therapies

Address for correspondence:
Tsvetoslav Georgiev, University Hospital St. Marina, 1, Hristo Smirnenski blvd., Varna 9010, Bulgaria, e-mail: tsetso@medfaculty.org
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targeting key inflammatory mediators such as tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) have significantly reduced disease activity, alleviating pain and disability while improving overall QoL for many patients [8].

The long-term outcomes of these therapies in real-world settings remain insufficiently studied, regarding both the achievement and maintenance of the therapeutic response. In clinical practice, a significant portion of patients with RA suffer from comorbid conditions that may impact the sustainability of the therapeutic response to biological therapy, especially concerning various comorbidities [9]. Clinical registries have been established and are continuously evolving to monitor patient characteristics, disease activity, and the effectiveness and safety of new therapeutic agents [10].

Preliminary evidence suggests that comorbidities, such as diabetes and overweight/obesity, may significantly hinder the achievement of favorable long-term therapeutic outcomes with both synthetic and biologic DMARDs in RA patients, and may notably impact the retention of the therapeutic response [11]. The need for further investigation into these factors is crucial to optimize long-term treatment efficacy and to develop personalized therapeutic approaches.

The present study aimed to determine the proportion of patients receiving biologic therapies in real-world clinical practice who adequately respond to treatment and achieve LDA, as well as the proportion of patients who maintain this response after 12 months. A secondary objective was to identify factors and comorbidities related to therapeutic outcomes and the ability to maintain LDA or remission.

Material and methods

Study design and setting

The study was conducted as a retrospective, observational, single-center study that included patients with RA undergoing long-term biologic therapy.

The study was conducted at the Rheumatology Clinic at St. Marina University Hospital, Varna, Bulgaria in RA patients who received outpatient biological therapy (TNF-α inhibitors and IL-6 inhibitors) and visited the committee for continuation of treatment every 6 months. One hundred and ninety patients with RA who received outpatient biologic therapy were included.

The study included the entire period of exposure to biological therapy (until September–October 2018). The long-term therapeutic outcomes of the patients were assessed in detail using their follow-up data for a 12-month period (3 visits) from June 2017 until October 2018. In September–October 2024, all necessary data for the analysis were extracted.

Eligibility criteria

The study included patients with RA who met the following criteria:

- over 18 years of age,
- confirmed diagnosis of RA (American Rheumatism Association [ARA] 1987 criteria) [12],
- treatment with biological therapy with TNF-α inhibitors or IL-6 inhibitors,
- long-term treatment with biological therapy,
  – for a total of at least 18 months:
    - 6 months before the active analysis period,
    - 12 months during the study analysis,
- complete active medical records were available.

Patients were excluded from the analysis if they met any of the following criteria: 1) having an additional diagnosis that made them eligible for biological therapy, such as ankylosing spondylitis or psoriatic arthritis; 2) having received biological therapy for a duration shorter than 6 months prior to study entry; 3) dropping out of biological therapy during the 12-month analysis period for any reason; 4) having incomplete medical records, including missing baseline demographic and lifestyle data, comorbidities of interest, or laboratory and clinical results necessary to assess long-term treatment outcomes. These exclusion criteria were implemented to ensure that the study population was homogeneous and that long-term therapeutic effects could be accurately evaluated.

Sources and methods for selecting participants

Patients were selected through a systematic review of clinic records to ensure data relevance.

The medical records of patients undergoing biological therapy were used. Each patient on biological therapy has a medical record in the Rheumatology Clinic, which is part of the registry of patients at the clinic. It contains medical documents with initial data on the diagnosis of RA, data on concomitant diseases, and initial treatment, and usually includes the initial discharge/outpatient list, as well as subsequent outpatient lists and discharges, which contain data on the course of the disease and therapeutic interventions.

The participants were selected among RA patients according to the order of presentation to the committee for continuation of treatment between June and October 2017.

Follow-up methods

Follow-up of therapeutic efficacy and long-term treatment outcomes was performed through in-depth analysis of data from outpatient examination notes, laboratory

tests, and therapeutic regimens from follow-up examinations in the period from June 2017 to October 2018 (12 months – 3 visits for each patient) every 6 months (active analysis period).

Outcomes

Long-term therapeutic outcomes of RA patients proposed for biological therapy were assessed by the complex Disease Activity Score 28 (DAS28) based on C-reactive protein (CRP) at 3 time points: at the beginning of the active analysis period, and at 6 and 12 months. Based on the DAS28-CRP values, the disease was categorized into 2 main groups: remission/low activity (favorable long-term outcome) when the DAS28-CRP value was less than 3.2, and unsatisfactory therapeutic response (unfavorable long-term outcome) when the value exceeded 3.2.

The primary endpoint was to determine the proportion of patients with a single-point LDA who maintained a therapeutic response (sustained LDA), as well as those who lost a favorable outcome over the next 6 and 12 months.

Long-term outcomes of biological therapy were assessed over the entire treatment period, overall for the entire group, and by type according to the biological therapy (e.g., TNF-α inhibitors, IL-6 inhibitors), as monotherapy or in combination with methotrexate (MTX) and concomitant use of glucocorticosteroids (GCs) and nonsteroidal anti-inflammatory drugs (NSAIDs).

Predictors of a favorable, sustained therapeutic outcome in long-term biological therapy were investigated: age, body mass index (BMI) < 25 kg/m^2, non-smoking, duration of RA, X-ray stage, functional disability [13], duration of biological therapy, type of biological drug (TNF-α inhibitor or IL-6 inhibitor), combination with MTX, absence of concomitant diseases.

The need for daily use of NSAIDs and GCs were initially included as potential confounding effects/modifying factors.

Bias

To reduce potential sources of bias, the study strictly adhered to clear criteria for: participant selection, clearly defined analysis and treatment periods, and complete medical records available with data for calculating composite measures of disease activity.

Statistical analysis

Statistical methods employed in the study included the χ^2 test to analyze categorical data and assess associations between various demographic and clinical characteristics. Student's *t*-test was used for comparison of continuous variables to determine significant differences between groups. Multiple binomial logistic regression analysis was conducted to examine the relationship between therapeutic response, as measured by the level of LDA, and to identify factors significantly associated with a successful therapeutic outcome and its retention. A significance level of $p < 0.05$ was accepted for the entire study. The results are presented using both tabular and graphical methods.

Bioethical standards

The study was approved by the Research Ethics Committee of the Medical University of Varna, Bulgaria, approval number 2 dated 04/07/2024.

Results

In the study group of 190 patients with RA, the mean age was 58.7 ±11.2 years, with 85.8% of participants being women. The average weight was 73.2 ±16.3 kg, and 55.3% of patients were classified as overweight (BMI > 25 kg/m^2), while 23.2% were obese (BMI > 30 kg/m^2); 30.5% of patients were smokers.

Disease characteristics

The mean duration of RA was 12.5 ±9.2 years. The distribution by disease duration was as follows: 15.8% of patients had RA for 1 to 5 years, 36.8% for 5 to 10 years, and 47.3% for more than 10 years ($p < 0.001$). The radiographic stage of the disease was stage II in 34.2%, stage III in 28.9%, and stage IV in 36.8% of the patients. A significant proportion of them exhibited structural damage associated with radiographic stage III/IV ($p < 0.001$). The functional class was evenly distributed among the participants, with 54.2% in functional class II and 45.8% in class III ($p > 0.05$). Table I shows clinical and demographic characteristics of RA patients.

The median time from RA diagnosis to initiation of biologic therapy was 9 years (range 2–44 years). The median duration of biologic therapy prior to data analysis was 3.4 years, with a range of 1–13 years, and there was no significant difference between the 2 groups (anti-TNF: median 3.4 years, range 1–13; anti-IL-6: median 3.4 years, range 1–10, $p > 0.05$).

Altogether, 45.8% of patients achieved LDA by 1 point (95% CI: 38.57–53.17, $p = 0.246$) using biologic therapy over 3.4 years. Out of this group, 8% lost this therapeutic outcome at 6 months, and an additional 5.7% lost LDA in the following 6 months. After 12 months, sustained LDA was present in 39.5% of all patients, while the re-

Table I. Clinical and demographic characteristics of patients with RA (*N* = 190)

Indicators	Mean ±SD	*n* (%)
Age [years]	58.7 ±11.2	
Sex: female		163 (85.8)
Weight [kg]	73.2 ±16.3	
Overweight or obese [BMI > 25 kg/m²]		105 (55.3)
Smoking		58 (30.5)
Duration of RA (median, range) [years]	12.5 ±9.2	
Duration of RA [years]		
1 to 5 years		30 (15.8)
5 to 10 years		70 (36.8)
> 10 years		90 (47.3)
X-ray stage		
II		65 (34.2)
III		55 (28.9)
IV		70 (36.84)
Functional class		
II		103 (54.2)
III		87 (45.0)
HTN		112 (58.9)
DM		29 (15.3)

BMI – body mass index, DM – diabetes mellitus, FC – functional class, HTN – arterial hypertension, RA – rheumatoid arthritis, SD – standard deviation.

maining 6.3% showed an unstable therapeutic response (Table II).

Out of all 87 patients who achieved single-point LDA, 86.2% sustained LDA for 12 months. The difference between patients who achieved single-point LDA and patients who sustained LDA is 13.8% (95% CI: 6.42–23.38, $p < 0.001$).

Factors influencing the sustainability of therapeutic outcomes in rheumatoid arthritis treated with tumor necrosis factor and interleukin-6 inhibitors

The likelihood of maintaining sustained LDA is significantly higher in patients without diabetes. The results indicate that patients with diabetes have a substantially lower chance of maintaining persistent LDA (odds ratio [OR] = 0.100, 95% CI: 0.016–0.628, $p = 0.014$) compared to those without diabetes. Furthermore, smoking has been identified as a poor prognostic factor for maintaining sustained LDA (OR = 0.265, 95% CI: 0.067–1.048, $p = 0.058$; Table III).

Table II. Therapeutic characteristics and long-term results in RA patients on biological therapy

Indicators	Total	
	Median (range)	*n* (%)
NSAIDs		82 (43.2)
Methylprednisolone (use)		109 (57.4)
Methotrexate (use)		117 (61.6)
Time to bDMARDs [years]	9.0 (2–44)	
Duration of bDMARDs [years]	3.4 (1–13)	
Type of biological medication		
Anti-IL-6		85 (44.7)
Anti-TNF-α		105 (55.3)
One-point LDA		87 (45.8)
Sustained LDA		
6-month		80 (42.1)
12-month		75 (39.5)

IL-6 – interleukin-6, TNF-α – tumor necrosis factor α, bDMARDs – biological disease-modifying anti-rheumatic drugs, LDA – low disease activity, NSAIDs – nonsteroidal anti-inflammatory drugs.

Table III. Analysis of factors associated with long-term therapeutic response (sustained LDA)

Factor	Adj. OR*	95% CI	*p*
For all treated patients			
RA and DM	0.100	0.016–0.628	0.014
Smoking	0.265	0.067–1.048	0.058
For TNF-α inhibitor treated patients			
RA and DM	0.064	0.005–0.841	0.036
For IL-6 inhibitor treated patients			
Smoking	0.046	0.004–0.556	0.015
RA and DM	0.069	0.003–1.562	0.093

** Adjusted odds ratios (adj. OR) are corrected for age, sex, BMI > 30 kg/m², duration of RA, duration of biological treatment, X-ray stage, functional class, combination with methotrexate, NSAIDs and GCs used, HTN.*
DM – diabetes mellitus, IL-6 – interleukin-6, RA – rheumatoid arthritis, TNF-α – tumor necrosis factor α.

Several covariates considered in the analysis, including age, sex, BMI > 30 kg/m², duration of RA, duration of biological treatment, X-ray stage, functional class, combination with MTX, NSAID and GC use, and hypertension, were not found to be significant predictors of sustained LDA. These variables did not meet the threshold for statistical significance ($p > 0.05$) and thus were not included in the final model. Consequently, they were not recognized

as significant predictors for achieving and maintaining persistent LDA.

For patients receiving TNF-α inhibitor treatment, the presence of RA and DM was found to significantly influence the likelihood of maintaining sustained LDA, with an OR of 0.064 (95% CI: 0.005–0.841, $p = 0.036$), indicating a significantly lower chance of achieving persistent LDA in patients with both RA and DM compared to those without.

For patients receiving IL-6 inhibitors, smoking was identified as a significant negative prognostic factor, with an odds ratio of 0.046 (95% CI: 0.004–0.556, $p = 0.015$), suggesting that smokers have a considerably lower chance of maintaining sustained LDA.

Additionally, while there was weak evidence for the presence of RA and DM influencing outcomes for IL-6 inhibitors patients, the association was not statistically significant, with an OR of 0.069 (95% CI: 0.003–1.562, $p = 0.093$).

Discussion

Long-standing RA is often associated with unhealthy lifestyle factors and health challenges, such as overweight/obesity, diabetes, and arterial hypertension. Smoking, obesity and poor physical activity are associated with a worse treatment outcome [14]. Clear guidelines recommend treatment strategies targeting disease control through synthetic, biologic, and targeted synthetic therapies [15]. Achieving and maintaining clinical remission/LDA is associated with several clinical and QoL benefits for patients. Patients in remission/LDA have improved radiographic outcomes, physical functioning, no progression of disability, and lower mortality [16]. These benefits were observed in clinical remission/LDA, regardless of how early or late it was achieved [17].

The primary target of modern therapies for treating RA is to achieve LDA in long-standing RA or remission in those with early disease. Once LDA has been reached, the next target is to sustain this effect for at least 12 months, after which a gradual tapering of medication may be attempted, with the goal of reaching a drug-free status [18].

In practice, however, reaching these targets remains challenging for the majority of patients, for whom composite and index assessments do not indicate values determining disease activity as remission/LDA. Available data are controversial. Some biologic registers show in the 3rd year 45% remission with TNF-α inhibitors, while others show significantly higher figures [7, 19–21]. On the other hand, real-life studies continue to demonstrate significant superiority of TNF-α inhibitors compared to conventional DMARD therapy. A recent study showed that achievement of short-term and long-term remission at 1 and 2 years, respectively, after the start of TNF-α inhibitor therapy compared to triple synthetic therapy had significant superiority [22].

Complex individual patient characteristics, as well as sociodemographic factors, behavioral habits, and comorbidities, are discussed as being associated with differences in long-term responses [23]. A wealth of data suggests that RA, especially in long-standing disease with highly active inflammation, is often associated with behavioral risks and comorbid conditions, including metabolic disorders such as obesity and diabetes [9, 24]. Both RA alone and its combination with these comorbidities lead to increased cardiovascular morbidity and mortality [25].

The present study was conducted in patients with long-standing RA (mean duration of RA 12.5 years) in which biologic treatment started late after diagnosis (mean 9 years). The median duration of biologic therapy prior to data analysis was 3.4 years, and it lasted a mean of 44.9 months until assessment of the therapeutic response. Point LDA was detected in 46.8% of all patients, which is consistent with data reported from other biological registries [26].

The ratio of patients with a sustained therapeutic response to those with loss of response was significantly in favor of the former (39.4% vs. 6.3%). These data indicate that some patients with DAS28-CRP LDA lose the therapeutic response during long-term treatment with TNF-α and IL-6 inhibitors. In these cases, the therapeutic effect cannot be sustained with unchanged treatment regimens.

Loss of the therapeutic response in patients treated with TNF-α and IL-6 inhibitors is associated with several factors. One primary cause is the development of anti-drug antibodies (ADAs), which can neutralize the biologic agents or increase their clearance, leading to reduced drug efficacy and suboptimal therapeutic outcomes [27]. Additionally, poor adherence to treatment regimens in outpatient settings may further contribute to the diminished long-term effectiveness of biologics [28]. Furthermore, both subjective (pain) and objective (CRP levels) components of the DAS28 score can fluctuate due to various factors, complicating the assessment of the therapeutic response [29].

This highlights the critical importance of considering key patient lifestyle factors and comorbidities that may influence individual components of the DAS28-CRP score, potentially affecting the overall value. Such influences could lead to misclassification of the therapeutic response, resulting in inappropriate adjustments to treatment regimens. Cardiovascular issues and diabetes mellitus are amongst the most common comorbidities in patients with rheumatic diseases [30, 31].

Our data suggest that patients with and without sustained LDA for 12 months share similar characteris-

tics, including age, sex, X-ray stages, functional class, RA duration, and the use of NSAIDs, GCs, and biological therapies (either as monotherapy or in combination with MTX). These findings underscore the homogeneity of factors influencing the long-term therapeutic response in this patient group.

Patients with RA and DM have a lower chance of maintaining LDA, with a high likelihood of it worsening in the following months, both in patients treated with TNF-α inhibitors and in those treated with IL-6 inhibitors, indicating that these comorbidities impair long-term therapeutic outcomes.

Smokers have a lower chance of maintaining LDA, with a high likelihood of it worsening in the following months. This is observed in the entire patient group, but smoking is particularly associated with poorer outcomes in patients treated with IL-6 inhibitors, indicating that this comorbidity impairs long-term therapeutic results in this subgroup.

Study strengths and limitations

The strengths of the study include the comprehensive overview and understanding of RA and its impact on patients' QoL. Focusing on comorbidities such as diabetes offers a deeper understanding of factors influencing treatment success, which are often overlooked in similar studies. Limitations of the study include the retrospective design, which may introduce biases related to data collection and patient self-reporting, potentially affecting the results' reliability. The study involved 190 patients from a single clinic in Bulgaria, which may limit the generalizability of the findings to other populations or countries. The analysis span is only 12 months, which may not capture the long-term sustainability of treatment responses and the potential evolution of patient conditions.

Conclusions

The results of this study highlight that personalized medicine in the treatment of RA, including consideration of individual patient characteristics, comorbidities, and lifestyle factors, is key to improving long-term therapeutic outcomes with biologic therapy. Although a significant number of patients achieve the desired therapeutic response with long-term biologic therapy, maintaining this response over a 12-month period remains a challenge, requiring attention to factors such as smoking and diabetes.

Disclosures

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Data availability: The data that support the findings of this study are available on request from the corresponding author (T.G.).

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