https://doi.org/10.31925/farmacia.2022.4.19 **ORIGINAL ARTICLE**

EVALUATION OF TAPERING BIOLOGICAL THERAPY IN RHEUMATOID ARTHRITIS

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Abstract

While it has been seen as a disease with a positive prognosis in the past, currently rheumatoid arthritis (RA) is labelled as a debilitating, progressive disease that causes substantial and crippling osteoarticular damage linked to increased premature mortality. Remission is increasingly faced with queries about the effective management of therapy due to newer generations of RA drugs (biological therapies), and the idea of minimizing or even halting their administration is a present and complex concept. Throughout this study, the objective was to assess the possibility of spacing biological therapy while maintaining the disease under control to ensure that patients benefit as completely as possible from a clinical outcome with less medication.
The method used was pursuing by age distribution and the variation of activity scores of the disease DAS 28, respectively SDAI throughout 12 months, with 3 assessments: initially, at 6 and 12 months. After 12 months, the outcome of the two targeted therapies on the DAS 28 and SDAI score were statistically significant in both tapered and non-tapered groups.

Rezumat

Deși a fost văzută ca o patologie cu prognostic pozitiv în trecut, actualmente poliartrita reumatoidă (PAR) este etichetată ca o boală debilitantă, progresivă, care provoacă leziuni osteoarticulare substanțiale și ireversibile, cu o incidență crescută a mortalității premature. Starea remisivă prezintă din ce în ce mai mult interes din perspectiva gestionării terapeutice eficiente, datorate apariției noilor generații de medicamente anti-reumatice (terapiile biologice), iar ideea de a reduce administrarea acestora este un concept complex și de actualitate. Pe parcursul acestui studiu, obiectivul a fost de a evalua posibilitatea distanțării terapiei biologice, menținând în același timp boala sub control, pentru a se asigura că pacienții beneficiază cât mai complet posibil de un rezultat clinic favorabil utilizând doza minimă eficace. Metoda utilizată a urmărit distribuția în funcție de vârstă și variația scorurilor de activitate al bolii DAS 28, respectiv SDAI, pe parcursul a 12 luni, cu 3 evaluări: inițială, la 6 și 12 luni. După 12 luni, rezultatele celor două grupuri cu terapii vizate în ceea ce privește scorurile DAS 28 și SDAI au fost semnificative statistic atât în grupul cu terapie distanțată, cât și în cel cu terapie non-distanțată.

Keywords: RA, remission, DMARD, successful dose tapering

Introduction

Rheumatoid arthritis (RA) is an arthropathy that is incurable, progressive, debilitating and deforming, most frequently followed by various systemic manifestations [5].
The most severe form of inflammatory rheumatism is represented by RA, affecting about 1% of the general population. The prevalence of this disease is observed in most cases in women, mainly between the ages of 25 - 50 years, according to advanced studies [7]. As remission or even low disease activity (LDA) is carry out for the majority of patients with established RA, medical approach like tapering and withdrawal of disease modifying antirheumatic drugs (DMARDs) are cross-examined. Modern treatments, dynamic or intrusive, such as step-up and treat-to-target schemes (recommended by the EULAR – European League Against Rheumatism) built on therapy adjustment until LDA or remission is gained, are feasible and consensual objective for RA patients [3].
It is well known that DMARD therapy is begun as soon as the diagnosis is confirmed [1]. The body of evidence has grown in the last decade, particularly for the targeted synthetic (ts) DMARDs inhibiting Janus Kinase inhibitor (JAKi), novel biological (b) DMARDs aiming acknowledged pathways and trials comparing bDMARDs to other bDMARDs or tsDMARDs. Studies on tapering and stopping treatment, how to optimally

treat patients to target or even comparing the efficacy and safety of biosimilars (bs) DMARDs with those of their bio-originators (bo) trials have shown that the progression of the disease is halting, along with the suppression of joint destruction, therefore decreasing both the pathological effect and the financial and social costs of the disease [18].

The RA inflammatory pathway itself, involving the activation of pro-inflammatory cytokines (TNF, IL-6, IL-1) along with other cells involved in the immune – inflammatory response [8, 10], has assisted the development of current highly selective biological therapy [11].

The pharmacotherapeutic strategy of RA patients has changed radically over time, in a positive direction, once biological therapy has been introduced. However, the side effects encountered in the case of biological treatment with anti-TNF alpha [15] cannot be over-looked. From normal discomfort due to administration to increased risk of infection, risk of malignancy, aggravation of congestive heart disease, positive anti-nuclear antibody (ANA) or demyelinating disease [6, 9, 12, 16, 22]. Frequently, the biological treatment is associated with anti-inflammatory medication [17] such as non-steroidal anti-inflammatory drugs (ibuprofen, diclofenac, nimesulide, ketoprofen) or corticosteroids (prednisone, methylprednisolone and dexamethasone) [2, 20].

Throughout this study, we aimed to combine the ideal treatment responses from various approved therapeutical tactics, while simultaneously attempting to maintain a low activity of the disease to ensure that patients benefit from a favourable clinical outcome by tapering the dosage of biological therapy.

In terms of clinical management, delaying the development of joint destruction or even reaching remission, preserving, or even enhancing the quality of patient's joint function and autonomy, focusing on reducing the occurrence of adverse drug effects by spacing prolonged therapy were beneficial. All these aspects are of significance in this research.

Materials and Methods

Study design

In the current research, we glanced at the probability of tapering doses and, respectively, widening the span of administration in patients undergoing biological therapy with a favourable evolution. 44 patients diagnosed with rheumatoid arthritis and monitored by a rheumatologist were evaluated in Oradea, Bihor County, Romania between 2015 and 2017. The patient's informed permission for data collection was secured for the study. Adults' patients with RA, with disease characterized by the Disease Activity Score of 28 joints (DAS 28) > 3,2 and a Swollen Joint Count (SJC) > 5 at two consecutive time points within a 3-months interval, using a combination of csDMARD (conventional synthetic DMARD) and TNFi were included. At the start of the study, the patients were requested to refrain from glucocorticoids (GCs). There were no restrictions of using NSAIDs drugs.

The research encountered a 12-month enrolment, follow-up, evaluation and assessment of 44 patients with RA undergoing combined therapy with methotrexate 10 - 20 mg/week and biologic therapy (etanercept 50 mg/week, adalimumab 40 mg every 2 weeks, or infliximab 200 - 300 mg every 8 weeks). The csDMARD as well as the TNF inhibitor were gradually tapered to discontinuation in three steps. Tapering csDMARDs was realized by cutting the dose into half, a quarter and thereafter stopped. TNF inhibitors were tapered by doubling the dose interval, followed by cutting the dosage into half and then stopped.

Patients were divided into two groups to measure the outcome of spacing the TNFα treatment: G1 (group 1) – Non-tapered treatment; G2 (group 2) – Tapered treatment.

Table I

Patients characteristics at the start of the study

	Non-tapered group	**Tapered group**
Mean age in years (± SD)	58 (12)	57 (13)
Female gender in %	86	87
RF positive in %	90	86
Presence of erosions in %	68	70
Mean disease duration in years (IQR)	4 (1-12)	4 (2-11)
Mean DAS28 (± SD)	6.71 (1.6)	6.77 (1.9)
Mean DSAI (± SD)	17.4 (1.7)	17.8 (1.8)
Median MTX dose in mg (IQR)		
10	0	0
10 - 17.5	46.3	41.4
17.5 = 20	53.7	58.6
Type of TNFi in % (n)		
Etanercept	68.1 (15)	59 (13)
Adalimumab	22.7 (5)	27.2 (6)
Infliximab	9 (2)	13.6 (3)

RF - rheumatoid factor; IQR - interquartile range

The first group (G1) included patients undergoing initial treatment regimens during the study (12 months) – 22 cases (non-tapered group). The second group (G2) included patients whose dosage of biological therapy was lowered after 6 months – 22 cases (tapered group). The patients' characteristics are presented in Table I.
In the study, we followed the age distribution, the DAS 28 for RA and simple disease activity index (SDAI). The research protocol included: initial assessment, re-evaluation after 6 months and 12 months, followed by data analysis and interpretation of results. We decide to succeed the "effect size" (ES) statistical computation technique in order to assess change sensitivity. The ES approach standardizes the amount of variation in a variable across time. It is the average change in a variable represented in standard deviation units.
The interpretation is as follows: 0.2 – minor variation; 0.2 - 0.49 – slight variation; 0.5 - 0.8 – moderate variation; 0.8 or above – significant variation.

Statistical analysis

The Excel 2019 ANOVA data analysis, including standard deviations, median values, and effect size, were used for data interpretation. The statistical significance level was set at 0.05.

Results and Discussion

As far as age distribution, G1 included patients from 41 years of age to 77 years of age and G2 patients between 40 and 75 years old.
Therefore, the average age in the non-tapered treatment group was slightly higher than in the non-tapered treatment group with an average age of 58.32 ± 4.96 years in the non-tapered group *vs.* 57.27 ± 5.09 years in the tapered group. The difference of average age does not present statistical difference between the two groups (p > 0.05) (Figure 1).

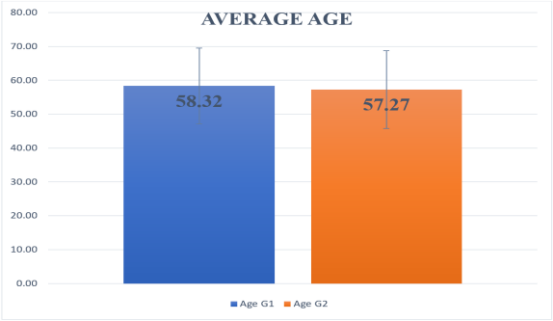

Figure 1.
Age distribution

From DAS 28 disease activity score perspective, according to our study, there are no substantial variations between the two groups in all three assessments (initial p = 0.074, 6 months p = 0.919, 12 months p = 0.063) (p > 0.05) (Figure 2).
In the non-tapered group, the DAS 28 score significantly decreased at 6 months (from 6.71 to 4.81, p = 0.007) and gradually decreased in the next 6 months (from 4.81 to 4.13, p = 0.106). The decline in the DAS 28 score at 12 months is important relative to the original rating (from 6.71 to 4.13, p = 0.004).

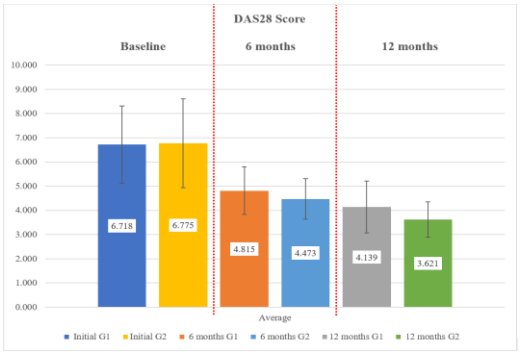

Figure 2.
DAS 28 score variations in initial, 6 months and 12 months assessments

In the tapered group, the DAS 28 score decreased substantially at 6 months (from 6.77 to 4.47, p = 0.033) and continued to slightly decrease over the next 6 months (from 4.47 to 3.62, p = 0.146). The downward trend in the DAS 28 score at 12 months is important relative to the original value (from 6.77 to 3.62, p = 0.002).
In terms of effect size the non-tapered therapy group, the DAS score of 28 was mild at 6 months (ES = 1.01) and 12 months was major (ES = 1.35).
In the tapered group, the occurrence at 6- and 12-months was statistically significant (ES = 1.05, ES = 1.41, respectively).
In all three evaluations, there are no major variations between the two groups in terms of SDAI score (p > 0.05).
SDAI values in the non-tapered G1 group decreased substantially at 6 months (from 17.419 to 8.745, p = 0.0194), but then decreased insignificantly (from 8.745 to 5.044, p = 0.194). The SDAI score at 12 months decreased significantly as compared to the initial value (from 17.419 to 5.044, p = 0.001).
SDAI values in the tapered G2 treatment group decreased significantly at 6 months (from 17.829 to 8.058, p = 0.0123), but then decreased insignificantly (from 8.058 to 5.594, p = 0.510). The SDAI score at 12 months declined substantially as compared to the initial value (from 17.829 to 5.594, p = 0.0014).
The effect on the SDAI score at 6 months was moderate (ES = 0.721) in the non-tapered treatment group, and statistically relevant (ES = 1.029) at 12 months. The effect at 6 and 12 months was statistically significant in the tapered treatment group (ES = 0.807, respectively ES = 1.011) (Figure 3).
We have taken into consideration the fact that patients treated with anti-TNFα have been diagnosed with RA for at least 3 years on the basis of current guidelines at the start of biological therapy [6, 12, 14].

The objective of this research was to determine the probability of achieving a favourable therapeutic effectiveness profile while maintaining a low activity of the disease, by distancing the treatment of patients with a successful clinical response or even by achieving remission of the disease. Our goal was premised on the idea that by lowering the dosage of biological therapy, the incidence of adverse effects would be diminished as well. The assessment of adverse effects evolution, on the other hand, requires a long-term study. The 6-month tapered treatment group was clinically significant in terms of the disease activity score. Both DAS 28 score and SDAI score, registered no substantial variations between the two groups in all three assessments ($p > 0.05$). The downward trend in the DAS 28 score at 12 months (from 6.71 to 4.13, $p = 0.004$) is notable in the non-tapered group especially compared to the original value. There is a substantial reduction in the DAS 28 score at 12 months (from 6.77 to 3.62, $p = 0.002$) in the tapered treatment group relative to the original value as well. These findings show that the improvements made to the therapy by spacing it in G2 were as successful as in the non-tapered G1 group, which followed the classical method in terms of treatment dosing regimen during the 12-month study. In the non-tapered therapy group, the DAS 28 score registered moderate impact effect at 6 months (ES = 1.01) and at 12 months was substantial (ES = 1.35). In the tapered treatment group, the occurrence at 6 and 12 months was statistically relevant (ES = 1.05 and ES = 1.41, respectively).

The SDAI score at 12 months is significantly lower in the group receiving non-tapered G1 therapy as compared to the initial value (from 17.419 to 5.044, $p = 0.001$). Provided the initial value, the decline in SDAI score at 12 months in the tapered treatment G2 group is substantial (from 17.829 to 5.594, $p = 0.0014$). At 6 months, the effect size of non-tapered therapy on SDAI score was moderate (ES = 0.721), but statistically significant (ES = 1.029) at 12 months. The tapered treatment group had a statistically significant effect at 6 and 12 months (ES = 0.807, respectively ES = 1.011) (Figure 3).

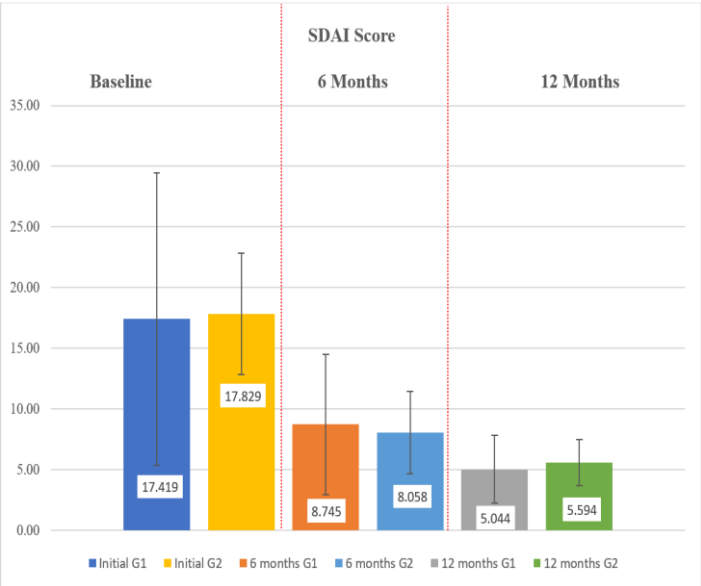

Figure 3.
SDAI score variations in initial, 6 months and 12 months assessments

In the view of the "effect size" statistical significance regarding DAS 28 disease activity score and SDAI score, we can acknowledge two main aspects: the upward trend of ES values throughout the 12-month research in both groups, which showed the efficacy of treatment and decrease of disease activity, and on the other hand, we can observe that the ES values in both groups are comparable, even if separate treatment regimens have been pursued, that emphasizes the fact that spacing therapy after 6 months is achievable without a detrimental impact on the patient's activity score and well-being, on the contrary, this treatment strategy may reduce the side effects of long-term TNF-α medication by lowering the dosage. Our findings add to previous research on the prospect of tapering biological therapy. A 2014 research looked at the prospect of spacing DMARDs and TNF inhibitor antirheumatic treatment for a year by steadily reducing doses to absolute discontinuation. According to the findings of this review, there are no significant variations in the outcomes achieved by DMARDs and TNF inhibitors, however, owing to the costs and the possibility of adverse effects, TNF inhibitors are favoured for distancing in the end [13]. Another one-year research sought to investigate the viability of DMARD tapering in preserving clinical disease management for RA

patients with chronic LDA or remission. Their results indicate that bDMARDs spacing may be a viable treatment option: few patients clinically relapsed within the first months of follow-up. Risk-to-benefit issues should include long-term health, functional, and institutional results, as well as safety and financial concerns, for a full assessment [21]. An 18-months study regarding biological therapy tapering (etanercept and adalimumab) compares the outcome of gradually spacing TNF-blocker to their preservation in patients with RA in remission. Patients were randomly assigned to one of two groups: maintenance or tapered treatment by half every three months until complete cessation. Tapering was not similar to a maintenance strategy, resulting in further relapses without affecting structural injury development. In this direction, more research is required to classify patients who may benefit from such approach [4]. In our research, we tapered biological therapy after 6 months by extending the time between administrations without completely discontinuing it for patients with low-moderate DAS 28 and SDAI scores.

The data obtained thus far regarding the disease's activity motivate us to conduct additional research focused on the safety profile.

Conclusions

There were no significant differences in age between the two groups with biological therapy (non-tapered and tapered), with an average age of 58.32, 57.27 years, respectively. In aspects of the DAS 28 score and SDAI score, there are no significant difference between the two groups, independent of the assessment, the effects after 12 months, of the two targeted therapies on the DAS 28 score and SDAI score were statistically significant in both tapered and non-tapered groups. These findings show that the improvements made to the therapy by spacing it in G2 were as successful as in the non-tapered G1 group, which followed the classical method in terms of treatment dosing regimen during the 12-month study. The dosage of biological therapy may be tapered after 6-months without having a detrimental effect on the 12-month parameters tested. This therapeutic method of spacing biological therapy doses has a positive impact on the disease activity score and may lessen the negative effects of long-term TNF-α medication by reducing the dosage, an aspect that will be studied further in the future.

Conflict of interest

The authors declare no conflict of interest.

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