

# Rheumatoid arthritis treatment with TNF inhibitors and alternative procedures in case of its failure – results of the Polish survey in the context of EULAR recommendations

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## Abstract

**Introduction:** According to the European League Against Rheumatism (EULAR), rheumatoid arthritis (RA) treatment aims to achieve remission or low disease activity (LDA) within 6 months. In Poland, despite the existence of the National Health Fund Drug Program (NHF-DP), data on the effects of treatment with biological agents in patients with RA are not publicly available. Also we cannot compare registers from other countries with the Polish results because the rules of the therapeutic program in Poland impose restrictions that do not exist in other countries. For this reason, the data will not be comparable, but the results of the currently used regimen for biological treatment in Poland should be analyzed and compared with the recommendations of the European EULAR as a contribution to further discussion.

**Objectives:** To determine the tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) inhibitor treatment patterns in RA patients in Poland, to evaluate the frequency and causes of treatment failure as well as post-failure recommendations, and to compare Polish clinical practice enforced by the therapeutic program with the EULAR recommendations.

**Material and methods:** The data on 895 RA patients were retrospectively collected from routine medical records. A questionnaire was completed only once for each patient.

**Results:** After 3 months of treatment with a TNF- $\alpha$  inhibitor, the therapeutic target was achieved in 72% of patients: 4% in remission, 8% LDA, and 60% with moderate disease activity (MDA); after 9 months, 46% had reached the target: 16% in remission, 30% with LDA. An average of 49% of patients presented with MDA or high disease activity (HDA), thus requiring treatment modification. Treatment failure was confirmed in 14% of patients and a modified therapy administered: rituximab (72%) or adalimumab (20%). The most common cause of failure was inefficacy of treatment (70%).

**Conclusions:** In the Polish therapeutic program, despite the persistence of MDA or HDA, the treatment with TNF inhibitors rarely qualifies as ineffective and therefore is seldom modified by switching to another biologic drug. As long as the initiation of treatment and its modifications are enforced by the NHF-DP and not the recommendations of EULAR, treatment may be less effective and paradoxically cost-intensive. Therefore, it seems obvious that it is necessary to change and adapt the NHF-DP requirements to European standards.

**Key words:** rheumatoid arthritis, TNF inhibitors, treatment failure, treatment modification.

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## Introduction

Biological drugs used in rheumatoid arthritis (RA) increase the chance of achieving both clinical remission and low disease activity (LDA), as well as giving individual patients physical independence. The most important predictor of remission and LDA after 1 year of treatment is treatment efficacy in the first 3 months [1]. The individual response to tumor necrosis factor (TNF) inhibitor treatment varies, but generally one-third of RA patients responded to treatment very well, another one-third responded well, and in the remaining patients treatment did not improve patients' health status [2]. In available registries of biological treatment, the percentage of patients for whom treatment failure with a TNF inhibitor was reported ranges from 21% (DANBIO registry) to 38% (LOHREN registry) [3]. According to the 'treat to target' concept promoted by the European League Against Rheumatism (EULAR) [4] and developed further in therapeutic recommendations [5], the objective of each therapy, including using biological drugs, is to achieve remission or at least LDA after 6 months of treatment. It should also be noted that in accordance with the 2013 EULAR recommendations, after 3 months of treatment, at least moderate disease activity (MDA) should be achieved in patients who began their RA treatment in a stage of high activity. In all other cases, treatment failure is defined as requiring modification of the current procedure by adjusting the dose of a disease-modifying anti-rheumatic drug (DMARD) or replacement of one biological drug for another.

In Poland, the biological treatment of RA was carried out within the framework of the National Health Fund Drug Program (NHF-DP), until the end of 2012. During this period in the treatment of RA in Poland the following biological drugs were available: TNF inhibitors (infliximab, etanercept, adalimumab) and rituximab (a chimeric anti-CD20 monoclonal antibody) [6]. According to the NHF-DP, TNF inhibitors have been used in the first-line therapy in all patients. In the case of failure, rituximab was administered. In Poland, no data have been published on the effectiveness of TNF inhibitor treatment regulated by a program, and the data from the register of biological treatment of RA conducted by the National Health Fund are also not available.

The objective of this study was to determine TNF inhibitor treatment patterns in RA patients in Poland, to evaluate the frequency and causes of treatment failure as well as post-failure recommendations. Also the aim of the study was to draw attention to the need to compare and to adapt the current NHF program to the standards set out by EULAR.

## Material and methods

The study involved 36 centers, which treated RA patients with biological drugs under the NHF-DP and agreed to participate. One of the NHF-DP eligibility criteria is an aggressive course of RA and high activity of the disease, defined as a Disease Activity Score 28 (DAS28) above 5.1. Data were collected retrospectively from available medical records, using an electronic questionnaire. The study covered all patients treated with TNF inhibitors, who between January and June 2012 had a follow-up visit after 3 or any subsequent 6 months of treatment. For each patient, the questionnaire was completed only once. The following data were collected during the follow-up: age, sex, duration of RA, previously and currently used TNF inhibitors (including monotherapy in combination with methotrexate), treatment duration, DAS28-OB, calculated using the EULAR recommendations, C-reactive protein (CRP) concentration and ESR (erythrocyte sedimentation rate) [7, 8]. Additionally, in the case of treatment failure, as defined by the NHF-DP, data on the cause and type of recommended procedure were collected.

Statistical analyses were performed using SPSS software, version 10. Duration of disease, duration of previous and current TNF- $\alpha$  inhibitor treatment, CRP concentration, ESR level, and DAS28 indicators were presented as means  $\pm$  standard deviation (SD), with minimum and maximum. For independent comparison, Student's *t* test was used, and for non-normally distributed variables the Mann-Whitney *U* test was used. One-way ANOVA was used to test significant differences in the average time of drug admission and the average values of CRP, OB and DAS28 in patients treated with different drugs. The *p*-value < 0.05 was considered statistically significant.

## Results

Data were collected on 895 [736 women (82%)] patients with RA treated with TNF inhibitors (65.5% of all patients treated with TNF inhibitors at this time). Average disease duration was 10.6  $\pm$  7.5 years (range: 1.16–32.52 years); 46% of patients had suffered from RA for more than 10 years. Patients were treated with etanercept (*n* = 564; 63%), adalimumab (*n* = 278; 31%), and infliximab (*n* = 53; 6%). In 771 patients (86%), a TNF inhibitor had been used as first-line therapy, and in 14% of patients (*n* = 124) as second-line biological therapy; in the latter group, 82% used adalimumab, which resulted from the previous NHF-DP recommendations. In 694 (78%), a TNF inhibitor was used in combination with methotrexate (in different doses – 7.5–25 mg/week), and in 199 (22%) as monotherapy.

Duration of biological drug administration was  $18.5 \pm 13.3$  months (2.6–127.6 months). The number of patients treated with a TNF inhibitor in 6-month intervals is shown in Fig. 1. The majority of patients ( $n = 760$ ) took the medication for up to 2.5 years (Fig. 1).

Nearly half of the patients ( $n = 439$ ; 49%) suffered from MDA or high disease activity (HDA) (Fig. 2).

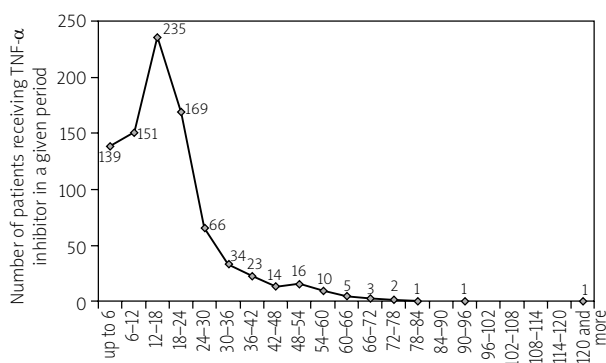
Of 179 patients for whom data were collected after 3 months of treatment (the first follow-up visit), remission was reported in 7 (4%), LDA in 14 (8%), MDA in 108 (60%), and HDA in 50 (28%) (Table I). During the second follow-up, which according to the NHF-DP was after 9 months of treatment, data were collected for 161 patients. Twenty-six of these (16%) were in remission,

49 (30%) had LDA, and 86 (54%) presented as having no therapeutic effect, as they had MDA or HDA (Table I). Different, but high, numbers of patients evaluated during the third and subsequent follow-up visits had MDA and HDA (26–63%) (Table I).

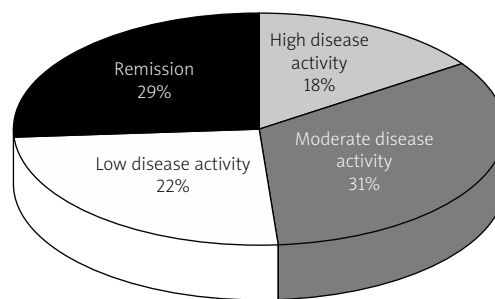
Mean DAS28 values for patients receiving different TNF inhibitors in a given time period are shown in Fig. 3.

During the follow-up, the average CRP level was 9.49 mg/l, and ESR 22.36 mm/h. Differences between average levels of CRP and ESR for patients receiving various TNF inhibitors were not significant statistically.

During the follow-up, treatment failure according to NHF-DP definitions was confirmed in 128 (14%) patients, in whom treatment modification was implemented.



**Fig. 1.** Duration of currently used TNF inhibitors (6-month intervals).



**Fig. 2.** Distribution of DAS28-OB ( $n = 895$ ).

**Table I.** Profile of disease activity according to the DAS28-OB during the follow-up. Data shown as number of patients ( $n$ ) and proportion (%)

Follow-up visits (according to the time of drug administration)	Disease activity according to the DAS28								
	Remission		Low activity of RA		Moderate activity of RA		High activity of RA		Total $n$
	$n$	%	$n$	%	$n$	%	$n$	%	
Visit 1 (3 months)	7	4	14	8	108	60	50	28	179
Visit 2 (9 months)	26	16	49	30	62	39	24	15	161
Visit 3 (15 months)	106	43	76	31	44	18	20	8	246
Visit 4 (21 months)	72	51	26	18	23	16	20	14	141
Visit 5 (27 months)	18	33	16	30	11	20	9	17	54
Visit 6 (33 months)	7	29	3	13	10	42	4	17	24
Visit 7 (39 months)	4	20	6	30	5	25	5	25	20
Visit 8 (45 months)	7	54	1	8	2	15	3	23	13
Visit 9 (51 months)	1	6	5	31	6	38	4	25	16
Visit 10 (57 months)	2	40	1	20		0	2	40	5
Visit 11 (63 months)	4	67	2	33		0		0	6
Visit 12 and later ( $\leq 69$ months)	1	3	2	7	7	23	20	67	30

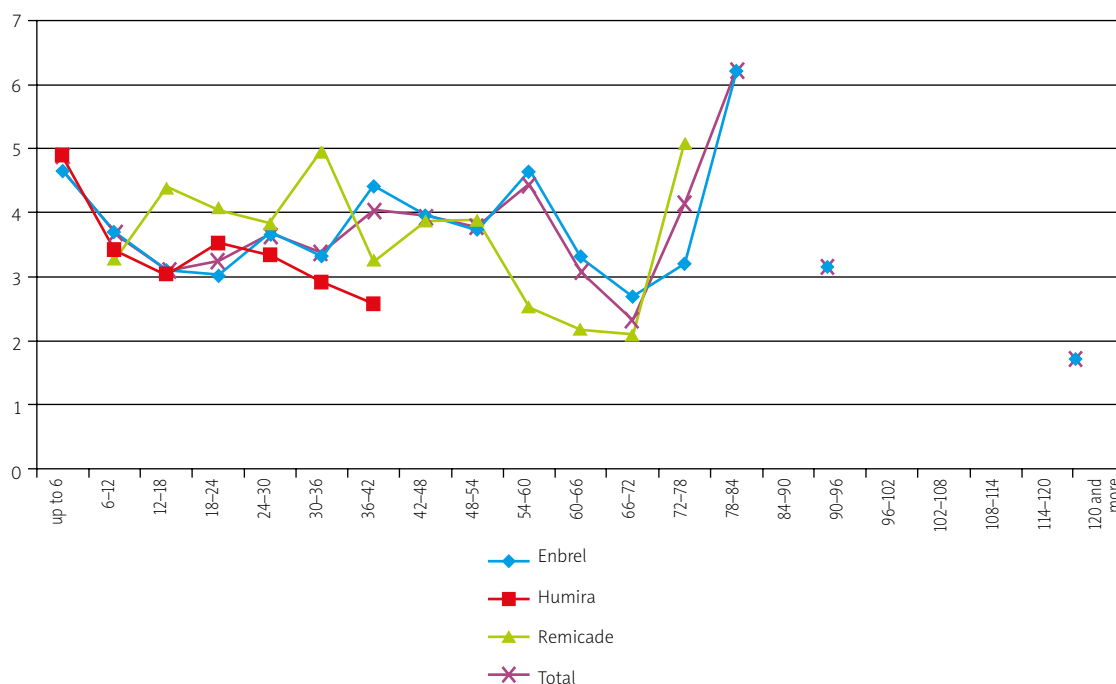


Fig. 3. Duration of treatment with TNF inhibitors by drug and DAS28.

Almost 25% of these patients were previously treated with another TNF inhibitor: etanercept (58%), infliximab (36%), and adalimumab (6%). The reason for treatment failure of TNF inhibitors are presented in Fig. 4. The most frequent reasons for treatment failure were loss of efficacy ( $n = 90$ ; 70%) or initial lack of efficacy ( $n = 26$ ; 20%); adverse events (AEs) ( $n = 12$ ; 9%) and other causes ( $n = 5$ ; 4%) were less frequent. The duration of treatment with a TNF inhibitor did not differ between patients in whom treatment failure was observed and those who continued treatment; in both groups, the reported mean duration of treatment was 1.5 years. In contrast, patients with treatment failure were characterized by higher DAS28, CRP concentration, and ESR level ( $p < 0.001$ ). The treatment with TNF inhibitor was interrupted in 110 patients. Another biological treatment was administered in 98 (77%), most commonly with rituximab ( $n = 70$ ; 71%) or another TNF inhibitor ( $n = 28$ ; 29%). In 13%, the glucocorticoid dose was increased, and DMARDs were modified in 8% of patients; sometimes more than one measure was used (Fig. 5).

### Discussion

Joint damage, physical disability and reduction in quality of life (QoL) are the main complications of the inflammatory process in RA. Premature mortality is also observed in patients with RA. A good predictive factor of

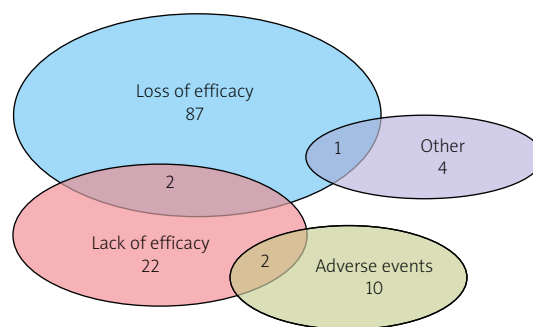


Fig. 4. Reasons for treatment failure with TNF inhibitor.

the above is the disease activity expressed by the number of swollen joints, as well as reactive indicators or complex indicators of disease activity such as DAS28. In many patients, in daily practice, remission is an achievable goal, and its rapid achievement can stop joint damage, regardless of the type of treatment – by synthetic or biological drugs. Low activity of the disease (LDA), particularly in a stable form that lasts for many years, may be an alternative goal. In our study population, the average duration of RA was 10.6 years and, therefore, as a measure of treatment effectiveness, achieving LDA was also considered. The Polish therapeutic program defines remission as  $DAS28 < 2.6$ , and LDA as  $DAS28$  be-

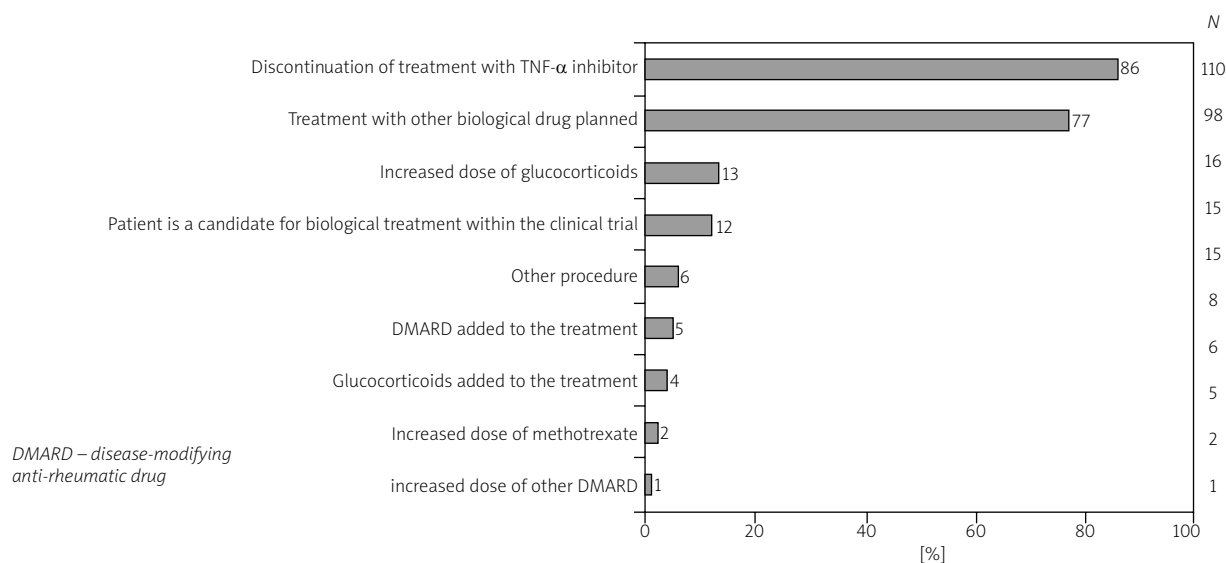


Fig. 5. Treatment modifications after confirmed treatment failure (multiple choices allowed).

tween 2.6 and 3.2. Only patients with HDA (DAS28 > 5.1) are enrolled in the therapeutic program. Starting treatment with biological agents only when patients reach such high disease activity may be one of the reasons for lower efficacy of therapy in this group.

In the EULAR recommendations, if a patient does not achieve an improvement in health status after 3 months, such as a reduction from HDA to MDA, and after 6 months at least LDA, treatment should be modified by changing the medication to another biologic drug. On the other hand, the recommendations assume the continued use of biological drugs despite the achievement of LDA or remission, taking into account dose reduction or increasing the intervals between doses.

In the Polish NHF program a reduction in DAS28 of 1.2, which does not exclude the persistence of HDA (DAS28 > 5.1), is important. According to EULAR recommendations the patient, at any stage of treatment, cannot have HAD [4]. Thus, the goal of treatment should be achieved within a maximum of 6 months [5]. In patients treated with TNF- $\alpha$  inhibitors in the Polish therapeutic program, the target in the third month of treatment, according to EULAR, was achieved by more than 70% of patients, and after 9 months, when LDA or remission is considered as a therapeutic effect, this rate was estimated at 46%. In the Polish therapeutic program, the second follow-up is at the ninth month of treatment; thus, how many patients achieved the therapeutic target after 6 months of treatment cannot be assessed. Of note, more than half of the patients evaluated at the ninth month had MDA or HDA. According to EULAR recommendations, in the case of treatment failure, treatment should be modified

after 6 months [5]. In our study, although treatment failure was formally, according to NHF definition, confirmed in only 14% of patients, the proportion of patients with MDA and HDA during the follow-up indicates that treatment failure with a TNF- $\alpha$  inhibitor occurred much more frequently.

Based on the published registry data, treatment failure using TNF inhibitors is estimated at 21.4–38.1% [3]. The most common causes of treatment failure are inefficacy of treatment (16.9–46.4%) and AE (18.2–30.6%) [3, 9, 10]. Our results confirmed inefficacy as the most common cause of failure; AEs were less frequently reported. The higher level of AE reporting in countries with routine biological treatment registries [1] may explain this difference. Rituximab was used more often than any other TNF- $\alpha$  inhibitor as post-failure treatment modification. EULAR recommends another TNF inhibitor or other biological drug with a different mechanism of action (abatacept, rituximab or tocilizumab), after confirmation of TNF- $\alpha$  inhibitor treatment failure [5, 11]. One TNF inhibitor is replaced by another in approximately 38% of patients [12]; in our study, nearly 25% of patients were given another TNF- $\alpha$  inhibitor in the past. No clinical trial data on the effectiveness of such changes are available, and recommendations are based solely on observational studies [5, 13–15]. No conclusions in this regard can be drawn from the GO-AFTER study with golimumab [16]. In this study, LDA was achieved in 12% of patients in the twenty-fourth week after replacing one TNF- $\alpha$  inhibitor with another; however, the majority of patients had previously been effectively treated with a TNF- $\alpha$  inhibitor, and that treatment was interrupted

not because of treatment failure but because of side effects or other administrative reasons [15, 16]. Administration of rituximab after the initial failure of a TNF inhibitor could be more beneficial than changing one TNF inhibitor for another [17–19]. It has been shown that patients in whom treatment failure using a TNF inhibitor was observed responded better (in terms of DAS28) when rituximab was introduced compared with other TNF inhibitors [20]. The efficacy of rituximab in such cases was the highest in seropositive patients (RF present or anti-CCP antibodies) and among those who had not previously received more than one biological drug [21, 22]. Another treatment modification reported after confirmed treatment failure was an increase in the dose of glucocorticoids. It should be noted, however, that such a procedure does not always improve treatment effects and often leads to treatment failure, with a considerable increase in the incidence of AEs; therefore, it should not be recommended [5, 23]. In contrast, dose adjustments of DMARDs, particularly methotrexate, were rarely reported, although as shown by other studies, in Poland it was often used in non-therapeutic doses, as shown by research in previous years, although now significant improvement is observed [24, 25]. In the context of the presented results, it appears that introducing biological drugs into rheumatological practice in Poland has not considerably changed the patient's situation, as described by Sokka et al. in 2007 [26]. It is necessary to underline the fact that in Poland there are much fewer biologically treated patients than in other countries according to e.g. the Quest–RA study, and the treatment starts at a very high activity of the disease [26]. Such a classification of patients may have an impact on the effectiveness of treatment. There is no doubt that the originally created and subsequently insufficiently modified NHF program standards of RA treatment with biological agents in Poland did not reflect, and still do not reflect, the EULAR recommendations.

## Conclusions

The results of the study in Poland indicate that TNF- $\alpha$  inhibitor treatment failure defined by the therapeutic program has been confirmed less frequently in comparison with data from global registries of biological treatment. Based on the distribution of patients with MDA and HAD in Polish/our data, it should be considered that treatment failure occurs in a larger number of patients than actually reported. This situation is enforced by the rules of the therapeutic program, the fear of withdrawal of treatment with the patient and reduced decisions of doctors, who should also decide whether to continue or change therapy.

The data presented here relate to the period from 2012. Despite attempts to change the program, there are still significant differences between the international/EULAR recommendations and permitted (paid by the payer) treatment available.

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### Conflict of interest:

*Grażyna Dębowska and Joanna Spytek are permanent employees of Roche Polska Sp. z o.o.*

*Witold Tlustochowicz – National Consultant in Rheumatology, Chief of Department of Internal Medicine and Rheumatology, Military Institute of Medicine, Warsaw, Poland, cooperates with Roche Polska Sp. z o.o. on the basis of fee-for-service contracts, e.g. delivering the lectures during Roche sponsored events.*

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