Quality of life and clinical outcomes in Polish patients with high activity rheumatoid arthritis treated with leflunomide (Arava®) in Therapeutic Program: A retrospective analysis of data from the PLUS study

Małgorzata Emilia Tłustochowicz[B,C,E,F], Bartłomiej Kisiel[C,D,F], Witold Tłustochowicz[A,C,E,F]

Department of Internal Diseases and Rheumatology, Military Institute of Medicine, Warszawa, Poland

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online) *Adv Clin Exp Med*. 2019;28(11):1545–1553

Address for correspondence
Małgorzata Tłustochowicz
E-mail: m.tlustochowicz@gmail.com

Funding sources
Sanofi-Aventis sp. z o.o.

Conflict of interest
Małgorzata Tłustochowicz has received a consulting fee, congress sponsoring and was a speaker for Sanofi-Aventis sp. z o.o. Witold Tłustochowicz has received congress sponsoring and was a speaker for Sanofi-Aventis sp. z o.o. Bartłomiej Kisiel declares no conflict of interest.

Acknowledgements
Language assistance was provided by Proper Medical Writing Sp. z o.o., Warszawa, Poland.

Received on June 6, 2018
Reviewed on June 29, 2018
Accepted on February 18, 2019

Published online on October 29, 2019

Cite as
Tłustochowicz ME, Kisiel B, Tłustochowicz W. Quality of life and clinical outcomes in Polish patients with high activity rheumatoid arthritis treated with leflunomide (Arava) in Therapeutic Program: A retrospective analysis of data from the PLUS study. *Adv Clin Exp Med*. 2019;28(11):1545–1553. doi:10.17219/acem/104548

DOI
10.17219/acem/104548

Abstract

Background. Rheumatoid arthritis (RA) is a chronic autoimmune disease. Therapy is based on disease-modifying agents. Methotrexate (MTX) is used in first-line therapy and, in the case of failure, its alternatives include leflunomide, which was recommended in Poland within the National Health Fund Therapeutic Program.

Objectives. The purpose of the study was to evaluate the parameters of quality of life of Polish patients with high RA activity during treatment with leflunomide. Additional aims were to evaluate the effectiveness and safety of treatment.

Material and methods. We performed a retrospective analysis of the data from the PLUS study. The PLUS study comprised 887 adult patients from 30 centers. During the study patients received leflunomide in a maintenance dose of 20 mg or 10 mg once daily. Before the study, 100 mg of leflunomide had been administered daily for 3 days, followed by a maintenance dose of 20 mg/day or 10 mg/day for at least a month before enrollment. The PLUS study observation time was up to 12 months with 1 control visit every 3 months. The patients' quality of life was assessed with Health Assessment Questionnaire Disability Index (HAQ-DI). Erythrocyte sedimentation rate (ESR), Disease Activity Score (DAS28) and CRP (C-reactive protein) concentration were used to assess the disease activity.

Results. Six hundred seventy-nine patients completed the study. The HAQ-DI decreased after 3 months of observation (mean value 1.46 vs baseline 1.63; $p = 0.001$) and remained stable. The percentage of patients with HAQ-DI less than 1 and greater than 2 increased from 12.2% to 17.8% and decreased from 33.2% to 20.3%, respectively ($p < 0.0001$); DAS28 progressively decreased on subsequent visits. C-reactive protein and ESR decreased after 3 months and remained stable. Adverse events were observed in 4.4% of patients.

Conclusions. Treatment with standard leflunomide doses is safe and allows for significant clinical improvement.

Key words: leflunomide, disease-modifying antirheumatic drugs, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune and systemic connective tissue disease characterized by symmetrical arthritis and the presence of extra-articular manifestations. Its prevalence in Poland is about 0.45% of the adult population, affecting approx. 131,000–157,000 patients.[1,2] Treatment is based on synthetic or biological disease-modifying anti-rheumatic drugs (DMARDs). According to the European League Against Rheumatism (EULAR) recommendations,[3] methotrexate (MTX) 25–30 mg/week is the first-line drug. In the case of contraindications, intolerance or ineffectiveness, other drugs are used, including leflunomide, which is considered an alternative to MTX according to American College of Rheumatology (ACR) recommendations.[4] Leflunomide at low doses is a reversible inhibitor of the dihydroorotate dehydrogenase enzyme resulting in decreased synthesis of pyrimidines. At higher concentrations, it also inhibits tyrosine kinases interfering with cell signal transduction. Finally, it exerts immunomodulatory, anti-inflammatory and possibly immunosuppressive and antiproliferative effects. Its effectiveness is similar to that resulting from low doses of MTX and its therapeutic effect is visible after 4–6 weeks. In the next 4–6 months, the patient's condition can be further improved.[5] In Poland, leflunomide was initially available in the Therapeutic Program, created and funded by the National Health Fund (NHF), which strictly defined patient's inclusion and exclusion criteria, and specified ways of monitoring treatment and disease activity, schedule of control visits, the type and timing of additional tests, and method of data recording. Analysis of these data makes it possible to obtain reliable and reproducible information collected on a large group of Polish patients.

We performed a retrospective analysis of the data from the PLUS study (the study was conducted between 2007 and 2009). The primary objective of the analysis was to evaluate the parameters of quality of life of Polish patients with high-activity RA during treatment with leflunomide (Arava®, Sanofi-Aventis Deutschland GmbH; Frankfurt am Main, Germany). Additional aims were to evaluate the effectiveness and safety of treatment.

Material and methods

The PLUS study was a multicenter, non-interventional, observational, and prospective study of RA patients enrolled in the Therapeutic Program of National Health Fund in Poland and treated with leflunomide (Arava®, Sanofi-Aventis). The PLUS study was conducted between 2007 and 2009. The study was composed exclusively of patients who were already enrolled in the Therapeutic Program (already treated with leflunomide). Each patient provided informed consent to participate in the Therapeutic Program. All procedures performed by the physicians were carried out according to the rules and requirements of the Therapeutic Program (no additional procedures were performed). The patients' data and outcomes were obtained from 30 of the 50 wards and outpatient rheumatology units in Poland which used leflunomide (Arava®) in 2007 under the Therapeutic Program in accordance with its rules, with the said patients agreeing to the data transfer. According to the Polish law at the time, the Ethics Committee approval was not necessary for the PLUS study (leflunomide was used in accordance with the Therapeutic Program guidelines and summary of product characteristics, patients already treated with leflunomide were enrolled in the study, no additional diagnostic and monitoring procedures were performed). The study protocol was sent to the Pharmacovigilance Department of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. We performed a retrospective analysis of the data from the PLUS study. This retrospective analysis was approved by the Military Institute of Medicine Ethics Committee.

Patient selection

Patients suffering from RA and treated with leflunomide as part of the Therapeutic Program at least a month prior to the inclusion were included into the PLUS study. The inclusion criteria of the Therapeutic Program were as follows: 1) RA diagnosed according to 1987 ACR criteria[6]; 2) age of 18 years or more; 3) presence of poor prognostic factors of the disease; 4) MTX (or other DMARD) treatment failure or contraindications to MTX; 5) high RA activity according to the Ritchie index score, morning stiffness >30 min, erythrocyte sedimentation rate (ESR) >28 mm/h, C-reactive protein (CRP) >2 mg/dL; 6) both complete blood count and alanine transaminase level within normal limits; 7) consent for appropriate contraception during the participation in the Therapeutic Program and 2 years after treatment cessation. The exclusion criteria from the Therapeutic Program were: 1) inadequate response after 6 months of therapy; 2) bone marrow failure (anemia, neutropenia, leukopenia, and thrombocytopenia); 3) presence of severe medical conditions, such as congestive heart failure, unstable coronary artery disease, chronic respiratory insufficiency, chronic renal insufficiency, or chronic liver failure; 4) presence of malignancy or premalignant state; 5) current or planned pregnancy and/or breastfeeding during the 2 years after the end of the treatment; 6) drug and/or alcohol abuse. Contraindications to leflunomide listed in Polish summary of product characteristics (SmPC) and participation in any other clinical trial were also considered as exclusion criteria.

Study medication protocol

During the study, leflunomide was used according to Therapeutic Program guidelines and SmPC. Patients who had already received leflunomide for at least 1 month

were qualified for the observational study. Such patients received leflunomide in maintenance doses of 20 mg or 10 mg once daily (depending on the activity of the disease, tolerance of the treatment and physician's decision). Some patients concurrently used other conventional synthetic DMARDs, corticosteroids and non-steroidal anti-inflammatory drugs.

Quality of life, efficacy and safety analyses

Observation time was 12 months with visits in months: 0 (visit V1), 3 (V2), 6 (V3), 9 (V4), and 12 (V5), or until the end of treatment because of ineffectiveness or adverse drug effects. During each visit, quality of life was assessed using Health Assessment Questionnaire Disability Index (HAQ-DI).[7,8] Disease activity was assessed based on the Disease Activity Score (DAS28), CRP concentration and ESR.[9] During each visit, a complete blood count (routine procedure required in the Therapeutic Program) was performed and an interview concerning a history of adverse reactions was conducted.

Statistical analysis

All statistical analyses were performed with Stata v. 10 software (StataCorp, College Station, USA). The analysis was performed for patients who completed the full study participation – this was ascribed to individuals for whom the V1 and V5 forms were submitted with the visit dates entered, and for whom the time between visit 1 (V1) and visit 5 (V5) exceeded 10 months. The distributions of frequencies of categorical variables, measured during subsequent visits, were compared with the use of marginal distribution testing. The existence of a linear relationship between the variables with ordered categories was assessed with linear trend testing. The generalized estimating equation for continuous variables was used to analyze the changes in the mean HAQ-DI, DAS28, ESR, and CRP. The result was expressed as a mean change (beta) in the studied parameter at each subsequent visit in relation to visit 1. On following visits, the observed changes were tested to determine whether the results had changed, and in the case of a statistically significant results, the changes between individual visits were compared. The generalized estimating equation for binary variables was used to evaluate a decrease in HAQ by at least 0.22 at subsequent visits. All performed tests were two-tailed.

Results

Eight hundred and eighty-seven patients (84% women) were enrolled in the PLUS study, of whom 679 (76.6%) completed the study (data from visits V1–V5 was available and the duration between visits was greater than 10 months). One hundred and eighty-six patients dropped out the study earlier. In the case of 22 patients, it was not possible to determine whether the study was completed due to the lack of dates of V1 or V5 in case report forms (CRFs).

Patients over 50 years old accounted for 66.5%, and 22.5% of patients were 40–49 years of age. Patients 30–39 years old comprised 7.8% and patients 18–29 years old 3.2% of the study population. The mean duration of RA was 9.4 ±7.2 years (range: 0.25–43.8 years). Rheumatoid arthritis lasted longer than 2 years in 92.7% of patients. High disease activity was reported in 57.5% of patients according to DAS28, moderate activity in 32.1% of patients, low activity in 4.7% of patients, and 5.6% of patients were in remission.

The majority of patients (74.4%) used at least 2 classical synthetic DMARDs before leflunomide therapy, including therapy with at least 3 DMARDs in 25% of patients. Only 1 drug was used in 25.6% of patients. The most commonly used drugs were MTX in 95.5% and sulfasalazine (SSZ) in 58.8% of patients. In 56% of patients, both MTX and SSZ were used in the past, while 1.4% of patients had never been treated with any of these drugs. The reason for changing the previous therapy to leflunomide was lack of efficacy of the previous treatment in 76% of patients, intolerance in 15%, and both inefficiency and intolerance to DMARDs in 9% of patients.

The average duration of treatment with leflunomide prior to enrollment was 1.43 ±0.92 years. At study entry leflunomide was used in a standard maintenance dose of 20 mg daily in 98.37% of patients, and 10 mg in 1.63% of patients. The reason for early termination of patient participation in the study was lack of efficacy in 32 patients (3.6%), intolerance to treatment in 11 patients (1.2%) and other reported causes in 8 patients (0.9%) (e.g., the decision of the patient). In the remaining 135 patients (15.2%), no reason was given for early discontinuation.

At the time of inclusion in the study, the mean value of the HAQ-DI was 1.63 ±0.62, and 54.6% of patients were characterized by moderate disability (HAQ-DI value 1–2), 33.2% by severe disability (HAQ-DI > 2) and 12.2% by mild disability (HAQ-DI < 1). The mean HAQ-DI decreased significantly during the first 3 months of observation (1.63 ±0.62 on V1 vs 1.46 ±0.64 on V2, $p < 0.001$). Afterwards, it remained stable (mean HAQ-DI on V3, V4 and V5 was 1.42 ±0.64, 1.40 ±0.63 and 1.38 ±0.61, respectively). The percentage of patients for whom HAQ-DI was less than 1 increased between V1 and V5 from 12.2% to 17.8%, while the percentage of patients with HAQ-DI > 2 decreased from 33.2% to 20.3%. The difference in the distribution of HAQ-DI between V5 and V1 was significant ($p < 0.0001$) (Table 1).

The proportion of patients with a reduction in HAQ-DI of at least 0.22 (difference considered significant in terms of treatment) was 39.5% on V2, 47% on V3, 50.7% on V4, and 50.3% on V5 (Table 2).

The likelihood of obtaining a reduction of at least 0.22 was significantly higher on V3, V4 and V5 as compared to V2 ($p \leq 0.001$). The decrease in HAQ-DI of at least

Table 1. Distribution of HAQ-DI on baseline and follow-up visits

HAQ-DI	V1 (baseline)[a]	V2 (3 months)[b]	V3 (6 months)[c]	V4 (9 months)[d]	V5 (12 months)[e]
<1	69 (12.2%)	109 (18.3%)	107 (18.0%)	111 (18.4%)	107 (17.8%)
1–2	309 (54.6%)	335 (56.4%)	351 (59.0%)	368 (61.1%)	371 (61.8%)
>2	188 (33.2%)	150 (25.5%)	137 (23.0%)	123 (20.4%)	122 (20.3%)

[a] Data available for 566 patients; [b] data available for 594 patients; [c] data available for 595 patients; [d] data available for 602 patients; [e] data available for 600 patients.

Table 2. Significant change in HAQ-DI on follow-up visits (as compared to baseline visit)

Variable	V2 (3 months)[a]	V3 (6 months)[b]	V4 (9 months)[c]	V5 (12 months)[d]
Decrease in HAQ-DI of at least 0.22	219 (39.5%)	258 (47%)	276 (50.7%)	272 (50.3%)
p-value for comparison vs V2	–	p = 0.001	p < 0.001	p < 0.001

[a] Data available for 554 patients; [b] data available for 549 patients; [c] data available for 544 patients; [d] data available for 541 patients.

Table 3. Clinically significant change in HAQ-DI (≥0.22) dependent on duration of leflunomide therapy prior to enrollment

Visit	Duration of leflunomide therapy prior to enrollment ≤6 months	Duration of leflunomide therapy prior to enrollment >6 months	p-value
V2[a] (3 months)	48/114 (42.1%)	114/322 (35.4%)	p = 0.2
V3[b] (6 months)	66/115 (57.4%)	124/317 (39.1%)	p < 0.001
V4[c] (9 months)	61/111 (55.0%)	135/316 (42.7%)	p = 0.026
V5[d] (12 months)	61/111 (55.0%)	138/316 (43.7%)	p = 0.04

[a] Data available for 436 patients; [b] data available for 432 patients; [c] data available for 427 patients; [d] data available for 427 patients.

Table 4. Distribution of DAS28 on subsequent visits

DAS28	V1 (baseline)[a]	V2 (3 months)[b]	V3 (6 months)[c]	V4 (9 months)[d]	V5 (12 months)[e]
<2.6	38 (5.6%)	42 (6.3%)	48 (7.2%)	47 (7.1%)	56 (8.4%)
2.6 ≤ DAS28 < 3.2	32 (4.7%)	64 (9.6%)	56 (8.5%)	72 (10.9%)	102 (15.4%)
3.2 ≤ DAS28 < 5.1	217 (32.1%)	316 (47.4%)	374 (56.5%)	373 (56.3%)	367 (55.2%)
≥5.1	389 (57.5%)	245 (36.7%)	184 (27.8%)	170 (25.7%)	140 (21.0%)

[a] Data available for 676 patients; [b] data available for 667 patients; [c] data available for 662 patients; [d] data available for 662 patients; [e] data available for 665 patients.

0.22 on V5 was not significantly associated with age, sex, duration of illness, or number of previously taken disease-modifying drugs. However, a significant difference in the frequency of a decrease of HAQ-DI of at least 0.22 was observed between patients treated with leflunomide ≤6 months and >6 months prior to enrollment beginning from V3 (Table 3).

At the time of inclusion in the study, the mean value of DAS28 was 5.27 ±1.51. High disease activity was observed in 57.5%, moderate in 32.1%, low in 4.7%, and remission in 5.6% of patients. The mean and median DAS28 decreased with increasing duration of observation and all the differences in comparison to V1 were statistically significant (p < 0.001). The mean value for V2, V3, V4, and V5 was 4.60 ±1.29, 4.44 ±1.22, 4.37 ±1.23, and 4.21 ±1.22, respectively. Changes in DAS28 after 6 and 12 months as compared to V1 were significant and were −0.83 (95% CI = −0.92–−0.74, p < 0.001) and −1.06 (95% CI = −1.15–−0.97, p < 0.001), respectively. Mean changes (beta) of DAS28 for subsequent visits compared to the preceding visit beginning with V2 were small and did not reach statistical significance (−0.16 for V3, −0.08 for V4 and −0.15 for V5).

The percentage of patients for whom DAS28 was <2.6 increased from 5.6% on V1 to 8.4% on V5, and of patients with low disease activity from 4.7% to 15.4%, respectively. At the same time, the proportion of patients with high disease activity (DAS28 > 5.1) decreased from 57.5% on V1 to 21% on V5 (Table 4) (p < 0.0001).

It was found that the shorter duration of therapy with leflunomide at the time of enrollment, the greater the percentage of patients with a decrease in DAS28 and the smaller percentage of patients with an increase in DAS28 (at each visit, the linear trend was statistically significant, p ≤ 0.001)

Table 5. Change in DAS28 (compared to baseline) depending on the duration of leflunomide therapy prior to enrollment

Visit	Test for linear trend	Change in DAS28	Duration of leflunomide therapy prior to enrollment			
			1–3 months	3–6 months	6–12 months	≥12 months
V2, n = 536	p = 0.001	decrease	65 (89.0%)	46 (72.0%)	46 (67.7%)	218 (65.9%)
		increase	7 (9.6%)	15 (23.4%)	19 (27.9%)	99 (30.0%)
V3, n = 532	p < 0.001	decrease	67 (92.0%)	45 (70.3%)	45 (68.2%)	212 (64.4%)
		increase	6 (8.2%)	16 (25.0%)	19 (28.8%)	112 (34.0%)
V4, n = 532	p < 0.001	decrease	66 (89.2%)	48 (73.9%)	45 (69.2%)	212 (64.6%)
		increase	8 (10.8%)	17 (26.2%)	20 (30.8%)	113 (34.4%)
V5, n = 537	p < 0.001	decrease	64 (86.5%)	50 (76.9%)	49 (72.1%)	218 (66.1%)
		increase	10 (13.5%)	14 (21.5%)	19 (27.9%)	110 (33.3%)

Table 6. Mean ESR and CRP on baseline and follow-up visits

Variable	V1 (baseline)	V2 (3 months)	V3 (6 months)	V4 (9 months)	V5 (12 months)
ESR [mm/h]	38.77 ±22.10	30.98 ±18.54	30.87 ±18.98	30.35 ±19.18	30.45 ±20.10
CRP [mg/L]	19.23 ±22.35	12.61 ±15.78	12.37 ±15.77	11.83 ±13.39	11.52 ±14.10

ESR – erythrocyte sedimentation rate; CRP – C-reactive protein.

(Table 5). Men more often than women experienced remission on V5 (OR = 3.7, 95% CI = 1.6–8.6, p = 0.002).

Patients with a history of ineffective combined therapy with MTX and SSZ (prior to treatment with leflunomide) obtained clinical improvement on V5 less often than other patients (OR = 0.56, 95% CI = 0.36–0.87, p = 0.01).

The mean ESR value on V1 visit was 38.77 ±22.1 mm/h and mean CRP concentration was 19.23 ±22.35 mg/L. Both ESR and CRP decreased on V2 and remained stable until the end of observation (Table 6). Changes in ESR after 6 and 12 months as compared to baseline were significant: −8.08, 95% CI = −9.52–−6.63, p < 0.001; and −7.34, 95% CI = −9.8, −6.9, p < 0.001, respectively. Similarly, changes in CRP levels on V3 and V5 compared to V1 were significant: −7.05, 95% CI = −8.5–−5.6, p < 0.001; and −8.0, 95% CI = −9.4–−6.6, p < 0.001, respectively.

A total of 45 adverse events occurred in 39 patients (4.4%). The most common complaints were gastrointestinal complications, including diarrhea, nausea, vomiting, and abdominal pain that occurred in 21 patients (46% of all reported adverse events), and skin lesions in 6 patients. Increased activity of serum transaminases occurred in 7 patients – it exceeded 3 times upper limit of normal (ULN) and was the reason for discontinuation of treatment in 4 patients. Four serious adverse events were reported, including an increase in transaminases activity over 3 times ULN in a patient with concomitant cholelithiasis, exacerbation of purulent skin lesions observed several years before treatment with leflunomide, an episode of severe hypertension after 9 months of treatment with leflunomide in a patient with previously well-controlled hypertension, and fatal myocardial infarction.

The most common therapeutic procedure in case of adverse events was the decision to stop treatment in 26 patients (67%). In 96% of these cases, it resulted in a resolution of symptoms, but no attempts were made to return to treatment. In 1 patient who discontinued treatment due to an increase in transaminases activity, the decision was made to re-introduce the drug and hypertransaminasemia did not recur. In 11 (28%) patients who experienced adverse events, a decision to change the dosage was elected, while full-dose treatment was continued in 2 patients (5%).

Discussion

Rheumatoid arthritis in its natural course inevitably leads to joint damage, organ involvement and premature death. It is well-known that the most important factor determining the outcome of the disease is its activity. Several indices may be used to assess the activity of RA, with DAS28 being widely used in Europe. Objective markers of joint damage are erosions and joint space narrowing on X-ray, with deformations and ankylosis in advanced cases. For the patient, however, the most important factors are physical impairment, life activity limitation and reduction of health-related quality of life. The method that allows for the measurement of physical disability is HAQ. According to ACR criteria, it is recommended as part of the assessment of improvement for use in all clinical trials. It includes 20 questions grouped into 8 categories, and the patient provides responses on a scale from 0 (performed without any difficulty) to 3 (cannot be performed at all). The need to use additional help is also taken into consideration. The answers are then summed, and their mean is called HAQ Disability Index (HAQ-DI). There are also other ways to express HAQ index, but this method,

as the most widely used in RA, was adopted for the present study.[7,8]

The assessment of the physical functioning of the patient is influenced by joint pain and range of motion. A reduction in range of motion, hand grip strength, a greater number of swollen joints, and an increase in pain intensity correlates with limited physical functioning. Therefore, HAQ comprises components that are both constant (irreversible) and variable (reversible). Joint damage manifested by erosions, joint space narrowing and radiographic ankylosis is irreversible and is a constant component. In contrast, active inflammation and accompanying pain are variable components of disability. Therefore, the baseline physical functioning of the patient assessed in clinical trials depends on the disease activity, severity and duration. Smaller HAQ improvement is observed in patients with long-lasting RA compared with patients with a shorter duration of RA and is a result of irreversible joint damage. According to Aletaha et al., each additional year of average duration of RA decreases the effect size of the HAQ by 0.02, which corresponds to a decrease in average HAQ improvement of 0.01.[10]

As shown in many randomized controlled trials, evaluating the efficacy of treatment in RA, a change in HAQ correlates well with other disease activity measures and the severity of the disease over time, distinguishes accurately active treatment from placebo, and aptly predicts long-term morbidity and mortality.[11] Improvement of HAQ correlates significantly with other indicators such as Short-Form Health Survey (SF-36) not only in the physical aspects, but also in the functioning in society, emotional life and general sense of health. In early RA, a deterioration in HAQ allows for the prediction of early job loss and death, and correlates with the progression of disability and increased costs of the disease. A decrease of 0.22 in HAQ-DI is considered a minimal clinically significant change and the effectiveness of treatment may be expressed with the percentage of patients who achieved it. Singh et al.[12] showed that an increase of 1 point in HAQ-DI in the first 2 years of the disease causes a 90% increase in disability and an 87% increase in the cost of treatment in the next 3 years along with a 75% increase in disability and 74% increase in costs in the next 8 years. Yelin and Wanke[13] demonstrated that RA patients in the top quartile of the disability generate an annual cost that is 2.55 times greater and a cost of hospitalization that is 6.97 times greater than that of patients in the lowest quartile. Therefore, it must be assumed that the stabilization of HAQ for 12 to 24 months can significantly reduce the medical and overall costs of treatment of these patients.[11,14]

In our large study, initially involving 887 patients, 66% were patients over 50 years old and the mean age was similar to that reported in randomized trials of leflunomide (53.3–58.8 years)[15–19] and in observational studies (46–65 years).[20–27] The mean duration of RA was 9.4 years, which was markedly longer than 3.5–7.6 years cited in randomized trials[15–19] but similar to most of the abovementioned observational studies (8.0–12.1 years)[20–22,24,25]; in 2 of the cited studies, the mean duration of RA was similar to that of the randomized trials (4.1–5.1 years),[23,27] while 1 study involved patients with early RA.[26] It is particularly important to note that only 7.3% of the patients had a disease duration <2 years compared to 37.6–45.2% of patients in randomized trials.[15–19] In this study, 74.4% of the patients previously experienced treatment failure with 2 DMARDs and 25% with 3 DMARDs, while in the randomized trials, patients received previously 0.7–1.1 DMARDs.[15–19] Almost all patients (95.5%) in this study received MTX in the past, but the dosage among patients is not known. The dose was probably 10–15 mg/week because this is apparent from other studies on the prescribing behavior of Polish physicians.[28–29] In 85% of patients, treatment with leflunomide was indicated in the case of of prior therapy failure, and only 15% experienced side effects. Therefore, this was a negatively selected group of patients in whom the efficacy of treatment with another DMARD was poor, but, in contrast to clinical trials, this accurately reflects the usual practice based on Polish recommendations modeled on EULAR recommendations. At baseline, 62% of patients were taking leflunomide ≥12 months (with an average of 1.43 years), which, in the context of a maximal therapeutic effect in the first 3 months,[15–18,27,30–32] also affects treatment outcome.

Final analysis included 679 patients who completed the survey with established endpoints. This large group of Polish patients were treated with leflunomide and the dosing regimen was similar to previously published studies of 63–501 patients observed in randomized trials and observational studies.[15,16,18,27,33] Baseline HAQ-DI was 1.63, which indicated moderate disability (55% had HAQ value 1–2, and 33% had >2), and was similar to that in randomized trials (1.3–1.7). However, it should be emphasized that the majority of patients in this study had already been treated with leflunomide for more than a year at that time, and considering that the NHF program required as an inclusion criterion disease activity expressed by DAS28 > 5.1, the actual value at the beginning of treatment was probably greater. Despite this, from the 3rd month (V2) significant improvement in HAQ-DI was observed (–0.17, $p < 0.001$). From the 6th month (V3) it reached the level of minimal clinical importance (–0.22, $p < 0.001$), and it was maintained throughout the 12th month (V5) at the same level (–0.26, $p < 0.001$). The percentage of patients with HAQ-DI < 1 increased from 12.0% to 17.4% while the percentage of patients with HAQ-DI > 2 decreased from 32.9% to 18.3%. These differences were highly significant ($p < 0.0001$). The percentage of patients in whom a decrease of at least 0.22 was reported increased from 39.5% on V2 to 50.3% on V5 ($p < 0.001$), but the differences between subsequent visits beyond V2 did not reach statistical significance. Thus, the biggest chance of improvement was observed during the first 3 months of observation; after

that time, there was further improvement, but to a much lesser degree. A significant difference in the frequency of a decrease of HAQ-DI of at least 0.22 was observed between patients treated with leflunomide ≤6 months and >6 months prior to enrollment (beginning from V3), it can be suggested that the observed improvement in HAQ-DI is mostly attributable to patients with short leflunomide therapy prior to enrollment. The frequency of change in HAQ-DI of at least 0.22 on V5 was not associated with age, sex, duration of RA, or number of previously taken DMARDs. The magnitude of HAQ-DI improvement in the present study is different from randomized trials, in which it ranged from −0.45 to −0.89 and was similar to values observed for low doses of MTX used as a control (from −0.26 to −0.37).[15–17] Similarly, clinically significant improvement in HAQ-DI was higher in randomized trials than in the current study (71–78% vs 50.3%). The observed differences can be explained by the previously discussed selection of patients treated in the present study (patients with a longer duration of disease and failure of treatment with 2 or more first-line drugs), and by the fact that they were already treated with leflunomide for an average of 1.4 years, i.e., after the time of its greatest effectiveness.

Evaluation of the effectiveness of treatment on subsequent visits with the use of the DAS28 index was a secondary objective of the study. Its baseline value of 5.27 was high and it significantly decreased to the final value of 4.21 after 1 year. The biggest change was observed during the first 3 months of observation. The proportion of patients in remission or with low disease activity (DAS28 < 3.2, target therapeutic effect recommended by EULAR) increased between V1 and V5 from 10.4% to 23.8%. At the same time, the proportion of patients with high disease activity (DAS28 > 5.1) decreased from 57.5% to 21% ($p < 0.0001$). It was also found that the shorter the duration of leflunomide therapy prior to enrollment, the greater the percentage of patients with improvement of DAS28 and the smaller ratio of patients with a worsening of DAS28. In previous randomized trials, 70% improvement was achieved in 20% of patients treated with leflunomide and 50% improvement in 33–34% of patients after 12 months of treatment.[16,18] The efficacy of treatment was better than placebo and small doses (7.5–15 mg/week) of MTX,[16,18] and significantly worse than the dose of 10–15 mg/week of MTX,[19] and comparable to SSZ.[18]

An important finding of our study is a persistent beneficial effect of the leflunomide treatment during long-term observation. The mean duration of leflunomide treatment before enrollment was 1.43 years. All parameters assessed in this study (i.e., HAQ-DI, DAS28, ESR, and CRP) decreased mainly in the first 3 months of observation and then remained stable or continued to decrease, but much more slowly. This strong effect of leflunomide on HAQ-DI and disease activity in the first period of observation seems to be attributed to patients with a shorter duration of leflunomide treatment. This finding is not surprising as the beneficial effect of leflunomide is visible mostly in the first few months of treatment. Our results are in agreement with the results of previous studies. In randomized trials, drug efficacy was maintained at month 24, with 26% sustaining 70% improvement and 56% sustaining 50% improvement. These results were better than those for low doses of MTX (mean: 12.5 mg/week) and SSZ.[15,17] Similarly, the effectiveness of the treatment at 4 and 5 years was maintained,[27] wherein the improvement of 70% was observed in 19.6% of patients and 50% improvement in 43% of patients. The efficacy of treatment decreased after the reduction of the maintenance dose from 20 mg/day to 10 mg/day.

The ESR and CRP levels, an objective indicator of improvement, were also analyzed in the current study. Mean and median ESR and CRP levels decreased after 3 months of observation and remained stable until the end of the follow-up. Erythrocyte sedimentation rate and CRP changes after 6 and 12 months as compared to the first visit were statistically significant and were −8.08 ($p < 0.001$) and −7.34 mm/h ($p < 0.001$) for ESR, and −7.05 ($p < 0.001$) and −8.0 mg/L ($p < 0.001$) for CRP. These changes were consistent with the data reported in the literature, where ESR decreased by 6.3 mm/h to 17.7 mm/h and CRP levels were reduced by 2.2 mg/L to 27 mg/L.[15–17,19,23,25,26]

Treatment ineffectiveness was the reason for the premature exclusion of 32 patients (3.6%) from the study. In randomized studies, treatment ineffectiveness was the cause for excluding 5–17% of patients treated with leflunomide, 3–22% of those treated with low doses of MTX, 3% of patients treated with SSZ, and 32–53% of those treated with placebo (after 6 months).[16,17,19] However, our results cannot be compared with those from clinical trials, as no reason of discontinuation is known in 135 of our patients.

Adverse events occurred in 39 patients (4.4%), mostly gastrointestinal complications. A significant increase of activity of transaminases was observed only in 7 patients, and in 4 patients it was the cause for treatment discontinuation. Discontinuation of therapy in 26 patients resulted in resolution of adverse events in 96% of patients.

The safety profile of leflunomide in this observational study is better than reported in many previous studies assessing the safety of the treatment for 2 years, and was similar to this observed in patients treated longer than 2 years.[15,17,19,27] This may suggest that many patients were excluded from treatment with leflunomide before enrollment in the current study. However, it should be emphasized that the number of adverse events may be underestimated in our study, as 135 patients discontinued the study without given reason. Types of observed adverse events were consistent with the known side effects of leflunomide.[15–27] According to the data in published studies, adverse events were the cause of discontinuation of treatment in 6.3–29% of patients.[16,18,20–22,24,26,27] In a study by Strand et al., the most common side effects were the following: gastrointestinal complications (in 60.4% of patients, and

in 5.5% they were the cause of therapy discontinuation), rash (in 22.4% of patients, and in 2.2% as the cause of withdrawal of treatment), exacerbated and new hypertension (in 13.1% of patients, and in 1.1% as the cause of withdrawal), and reversible alopecia (in 9.9% of patients).[16] Asymptomatic increase of activity of transaminases was observed in 11% of patients, and in 7.1% it was the cause of discontinuation of treatment.[16] During the current study, there were no toxic effects on bone marrow and maintenance of normal morphological values was observed during the entire follow-up period (data not shown). Similarly, no significant changes of these parameters were reported in other cited studies.[15–18]

According to data from previous studies, adverse events that led to treatment discontinuation were more frequent than after small doses of MTX (22% vs 10.4%)[16] and less frequent than after SSZ (14% vs 19%).[18] The number of adverse events did not increase in the 2nd year of treatment and was 18.9%; they also did not change in nature.[15] Similarly, their character did not change within 5 years of treatment.[27] However, the number of adverse events decreased over time because when they were observed, patients were excluded from treatment, and such a mechanism may explain the results of the presented work.

Conclusions

The results of our study, including a large group of patients, indicate that treatment with standard doses of leflunomide allows for significant clinical improvement as measured by HAQ-DI and DAS28 in most patients. The long-term treatment seems to be relatively safe.

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