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The Efficacy and Safety of Leflunomide in Patients with Active Rheumatoid Arthritis

Skuteczność i bezpieczeństwo stosowania leflunomidu u pacjentów chorych na aktywne reumatoidalne zapalenie stawów

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Abstract

Objectives. The aim of this study was to evaluate the efficacy and safety of leflunomide in patients with active rheumatoid arthritis (RA).
Material and Methods. The study included 100 patients (88 women and 12 men) with rheumatoid arthritis (RA). The mean age was 46.5 years and the mean duration of the disease was 10.3 years. The inclusion criteria were a Disease Activity Score (DAS28) of over 3.2, and contraindications to methotrexate or failure of treatment with methotrexate for at least 3 months. The patients that were enrolled in the study had developed lesions of various grades according to the Steinbrocker Radiological Classification. Leflunomide was administered at a dose of 20 mg per day for the whole observation period. During the monitoring appointments the duration of morning stiffness, pain and disease activity were evaluated on a visual analogue scale (VAS), as well as the number of tender and swollen joints and the DAS28 score. In compliance with the leflunomide therapy protocol, the following control tests were performed: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hematology, creatinine and liver function tests. Safety assessment included monitoring of adverse events and laboratory test results.
Results. During the one-year monitoring period significant improvements were noted in 68% of the patients, expressed as a decrease of 1.2 or more in their DAS28 scores. DAS28 > 0 < 1.2 was achieved in a further 18% of the patients. No improvement was reported by 14% of the subjects. In one year of treatment leflunomide was effective in 74% of the patients with active RA. The most marked clinical improvement in the DAS28 index was noted between the third and sixth months of treatment. In the next six months ESR, CRP and DAS28 scores continued to decline steadily, but the differences were not as clear as those recorded in the previous time period.
Conclusions. The most commonly observed adverse events were related to the gastrointestinal tract (i.e. diarrhea and periodic increases in liver function tests), and reported hair loss. Mild to moderate adverse events were observed in 19% of the patients; they resolved spontaneously or in response to medication, and were not a reason for discontinuing therapy in any of the cases (**Adv Clin Exp Med 2012, 21, 3, 337–342**).

Key words: leflunomide, active rheumatoid arthritis, disease activity score (DAS28).

Streszczenie

Cel pracy. Ocena skuteczności i bezpieczeństwa leflunomidu podczas rocznej obserwacji pacjentów chorych na aktywne reumatoidalne zapalenie stawów (r.z.s.), spełniających kryteria zarówno ACR z 1987 r., jak i Narodowego Funduszu Zdrowia przed włączeniem do programu terapeutycznego.
Materiał i metody. Do badania włączono 100 pacjentów (88 kobiet i 12 mężczyzn) chorych na r.z.s. Średni wiek wynosił 46,5 lat, a średni czas trwania choroby wyniósł 10,3 lat. Kryteria włączenia były następujące: aktywność choroby wyrażona za pomocą DAS28 > 3,2; przeciwwskazania do metotreksatu lub niepowodzenie leczenia metotreksatem przez co najmniej 3 miesiące. Pacjenci uczestniczący w badaniu, którzy zostali zakwalifikowani, byli w różnych okresach choroby ze względu na kryteria Steinbrockera. Leflunomid był podawany w dawce 20 mg/dobę przez cały okres obserwacji. Podczas badań kontrolnych oceniano: czas trwania sztywności porannej, ból i aktywność choroby według wizualnej skali analogowej (VAS), liczba bolesnych i obrzękniętych stawów

oraz DAS28. Według programu NFZ przeprowadzono następujące badania kontrolne: OB, CRP, hematologii, kreatyniny i prób wątrobowych. Przeprowadzono również ocenę bezpieczeństwa, w tym monitorowanie zdarzeń niepożądanych oraz wyników badań laboratoryjnych.
Wyniki. Podczas jednego roku obserwacji nastąpiła znaczna poprawa wyrażona przez DAS28 > 1,2; odnotowano ją u 68% pacjentów. Ponadto zmianę w DAS28 > 0 < 1,2 uzyskano również u 18% pacjentów. W przypadku 14% badanych nie odnotowano poprawy. Leflunomid był skuteczny podczas jednego roku leczenia u 74% pacjentów z aktywną postacią r.z.s. Najbardziej widoczną poprawę kliniczną mierzoną wskaźnikiem DAS28 odnotowano między 3. a 6. miesiącem leczenia. W ciągu kolejnych 6 miesięcy OB, CRP i wartości wskaźnika DAS28 systematycznie spadały, różnice nie były jednak tak widoczne jak w poprzednim okresie.
Wnioski. Do najczęściej obserwowanych działań niepożądanych należały te związane z przewodem pokarmowym, np. biegunka, okresowe zwiększenie aktywności enzymów wątrobowych, zgłoszono również wypadanie włosów. Działania niepożądane (łagodne i umiarkowane) zaobserwowano u 19% pacjentów, ustępowały samoistnie lub po zastosowaniu leków i nigdy nie były powodem przerwania leczenia (**Adv Clin Exp Med 2012, 21, 3, 337–342**).

Słowa kluczowe: leflunomid, aktywne reumatoidalne zapalenie stawów, wskaźnik aktywności choroby (DAS28).

Leflunomide is one of the classic disease modifying antirheumatic drugs (DMARDs). The active metabolite of leflunomide inhibits the enzyme dihydroorotate dehydrogenase and has antiproliferative properties. The dihydroorotate dehydrogenase pathway is particularly important for activated T lymphocytes. Leflunomide also inhibits tumor necrosis factor (TNF) activity. As an immunosuppressive drug, leflunomide inhibits inflammation, thus delaying the destruction of the joints and leads to improved quality of life.

The aim of this study was to evaluate the efficacy and safety of leflunomide during the annual observation of patients who met the criteria for active rheumatoid arthritis (RA) established in 1987 by the American College of Rheumatology (ACR – formerly the American Rheumatism Association) and the protocol for leflunomide therapy before being included in the study.

Material and Methods

The study included 100 patients (88 women and 12 men) with RA, diagnosed according to ACR criteria. The mean age was 46.5 years and mean disease duration was 10.3 years.

The inclusion criteria were a Disease Activity Score (DAS28) exceeding 3.2, failure of therapy with use of at least one conventional disease-modifying drug, including methotrexate therapy at a dose of 20 to 25 mg/week for at least 3 months, or contraindications to methotrexate.

The patients that were enrolled in the study had developed lesions of various grades according to the Steinbrocker Radiological Classification. Leflunomide was administered at a dose of 20 mg/day for the whole observation period. During the monitoring appointments, the following were assessed: the duration of morning stiffness and disease activity, on a visual analog scale (VAS); the number of tender and swollen joints; erythrocyte sedimentation rate (ESR); C-reactive protein (CRP); DAS 28 index; blood counts; and creatinine and liver function tests. Safety assessment included monitoring of adverse events and laboratory test results.

All the patients underwent physical examination, and medical histories were taken, including questions about their use of DMARDs and steroids. The use of cigarettes, coffee and alcohol was also noted.

Laboratory testing was conducted in the laboratory of Dr. J. Biziel's 2nd University Hospital in Bydgoszcz (Poland).

Results

The results of the study are shown in the accompanying tables and figures.

A significant decrease in DAS28 index value after one year of therapy (i.e. a decline equal to

Table 1. The correlation coefficient of ESR and CRP with the DAS28 in patients with rheumatoid arthritis. The arithmetic mean for these parameters was calculated

Tabela 1. Współczynnik korelacji parametrów krwi, takich jak OB i CRP z DAS 28 u pacjentów chorych na reumatoidalne zapalenie stawów. Obliczono średnią arytmetyczną dla wyżej wymienionych parametrów

Output parameter (Wskaźnik wyjściowy)	DAS 28 – average (DAS 28 – średnie)	ESR after 1 hour – average (ESR po godzinie – średnie)	CRP – average (CRP – średnie)
Women (Kobiety)	4.68	38.3	16.08
Men (Mężczyźni)	4.46	36.8	15.12

Table 2. The correlation coefficient of ESR and CRP with DAS28 values in patients with rheumatoid arthritis, after 3, 6 and 12 months of treatment. The arithmetic mean for these parameters was calculated

Tabela 2. Współczynnik korelacji parametrów krwi, takich jak OB i CRP z DAS 28 u pacjentów chorych na reumatoidalne zapalenie stawów. Obliczono średnią arytmetyczną dla wyżej wymienionych parametrów po 3, 6 i 12 miesiącach leczenia

Women (Kobiety)	DAS28	ESR	CRP
After 3 months (Po 3 miesiącach)	4.24	36.00	15.07
After 6 months (Po 6 miesiącach)	3.39	27.5	12.87
After 12 months (Po 12 miesiącach)	3.35	23.5	12.75
Men (Mężczyźni)			
After 3 months (Po 3 miesiącach)	4.05	31.9	14.25
After 6 months (Po 6 miesiącach)	3.42	27.7	12.95
After 12 months (Po 12 miesiącach)	3.28	24.85	12.83

Table 3. VAS variability in relation to gender and the duration of treatment. The visual analogue scale was used for the patients' own assessment of pain. The tables show the arithmetic mean of the VAS in relation to gender

Tabela 3. Zmienność VAS w zależności od czasu trwania leczenia i płci. Zastosowano analogową skalę VAS do oceny bólu przez pacjenta. W tabeli przedstawiono średnią arytmetyczną VAS w zależności od płci

	Women (Kobiety)	Men (Mężczyźni)
Baseline (Stan początkowy)	78	64
After 3 months (Po 3 miesiącach)	70	53
After 6 months (Po 6 miesiącach)	65	54
After 12 months (Po 12 miesiącach)	64	51

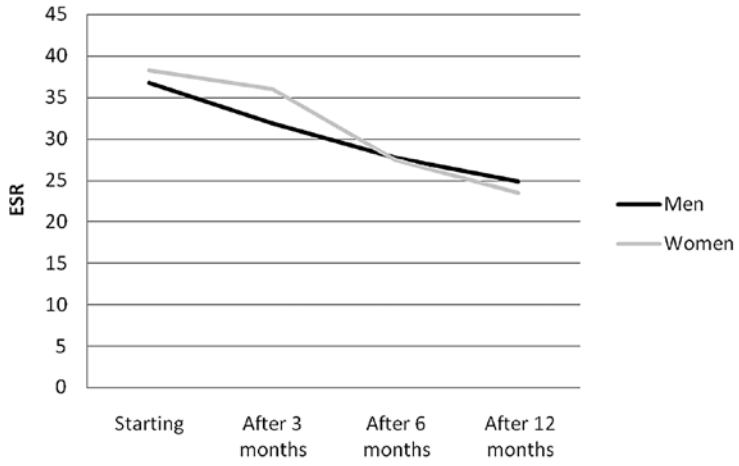

Fig. 1. Mean ESR

Ryc. 1. Średnie wartości OB

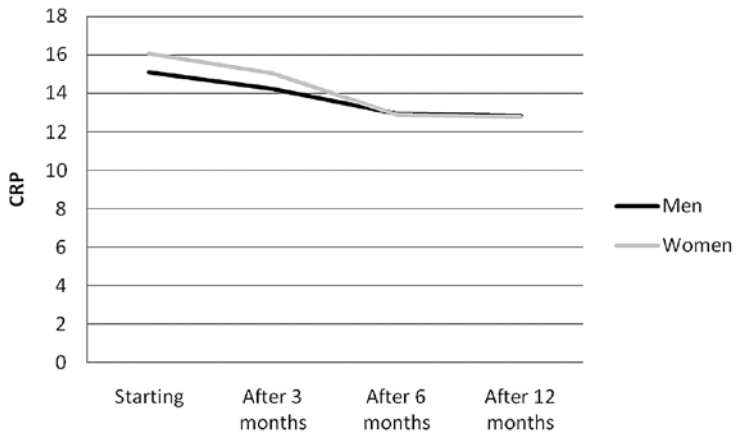

Fig. 2. Mean CRP

Ryc. 2. Średnie wartości CRP

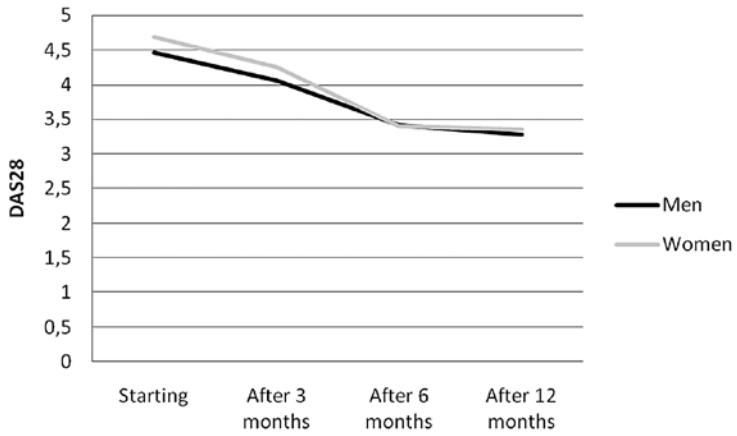

Fig. 3. Mean DAS28

Ryc. 3. Średnie wartości DAS28

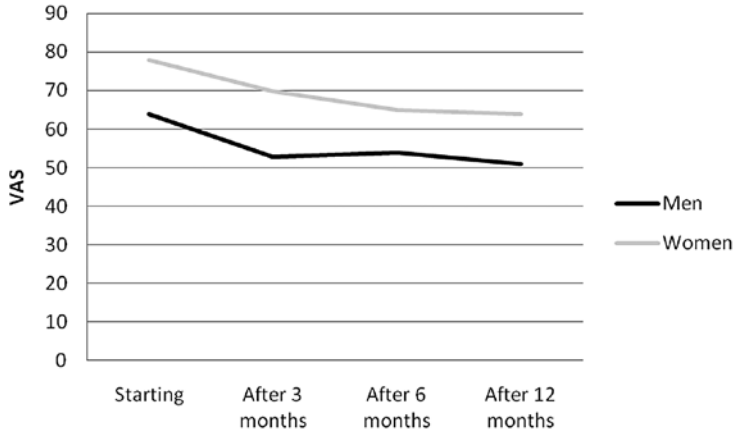

Fig. 4. Mean VAS

Ryc. 4. Średnie wartości VAS

or greater than 1.2) was observed in 68% of the patients. Clinical improvement was most marked between the third and sixth months of treatment. In the second six-month period ESR, CRP and DAS28 index values continued to decline steadily; however, the differences were smaller.

A decrease in DAS28 less than 1.2 was achieved in another 18% of the patients during the year. In total, the one-year leflunomide therapy resulted in a decline in DAS28 in 86% of the patients.

A reduction of morning stiffness was noted, especially after the first 6 months of treatment.

The subjective VAS self-assessment showed improvement in the patients' well-being, but with no significant correlation with DAS28 scores.

No significant difference based on gender was observed.

The most common observed side effects related to the gastrointestinal tract (such as diarrhea and temporary increases in liver enzymes activity) and reported hair loss. Mild or moderate adverse events were observed in 19% of the patients. They resolved spontaneously or in response to medication and did not cause discontinuation of the therapy.

Discussion

The efficacy and safety of leflunomide in the treatment of rheumatoid arthritis has been the subject of numerous studies, both in Poland and elsewhere. Some difficulties in comparing these studies are related to differences in the principles of patient selection (the duration of the disease, previous therapy, the presence of cardiovascular disease, metabolic, disorders, diet, habits, age, etc.).

This article reports on a study involving 100 patients who were qualified for leflunomide treatment, with no additional burden caused by diseases or disorders, and not using prescription drugs that are considered to affect leflunomide tolerance.

During the year-long study, disease activity was assessed after 1, 3, 6 and 12 months of therapy on the basis of parameters such as ESR, CRP, a VAS and DAS28 index value. A decrease of > 1.2 in DAS28 score after one year of treatment was regarded as a good therapeutic response. This was achieved in about 68% of the patients; in nearly half of the patients this was achieved during the first six months of treatment. Average and

mediocre improvement, expressed by a decrease in DAS28 value of < 1.2, was reported in 18% of respondents. In total, during the year-long treatment 86% of patients responded as expected to treatment with leflunomide.

Rell-Bakalarska et al. evaluated a population of 158 patients with active RA over a six-month period. A good therapeutic response (a DAS28 reduction > 1.2) was observed in about 65% of the patients, and an average response (a DAS28 reduction > 0.6 and < 1.2) was observed in about 12% [1].

Targońska-Stepniak et al. conducted a study on the impact of leflunomide treatment on indices of inflammation in patients with rheumatoid arthritis. The study took into account the activity and indicators of inflammation within the first six months of treatment in 37 patients. Nearly 84% of the patients responded well to the treatment, but almost 16% stopped the treatment due to a lack of therapeutic effect or to adverse events [2].

Zoń-Giebel et al. evaluated a group of 87 patients. A good therapeutic response during the 30 months (a decrease in DAS28 > 1.2) was observed in 57%. A response sufficient to warrant maintaining leflunomide treatment for two years of observation was noted in 87% of the participants [3].

Raczkiewicz-Papierska et al. assessed leflunomide as a second choice in treating patients with rheumatoid arthritis. This group comprised 81 patients that responded well to treatment. After five months of treatment, clinical improvement and a decrease in DAS28 > 1.2 were recorded in 54% of the patients; a decrease between 0.6 and 1.2 was noted in about 30%; in approximately 16% no improvement was observed [4].

Agarwal et al. reported on the use of leflunomide in standard doses in 121 patients, of whom 102 achieved a good therapeutic response and could continue treatment. Within a short (16-week) follow-up DAS28 decreases were noted in 74% of the patients [5].

The efficacy of leflunomide was confirmed in a study by Balabanov et al. observing 200 patients from four clinical centers in Moscow. The authors evaluated its effectiveness based on DAS28 over 16 weeks, and found clinical improvement in 129 patients (65%); high activity of RA remained in only 17% [6].

A study by Dougados et al. showed the efficacy of leflunomide monotherapy. In a 24-week study on 968 patients qualified for the first phase, 17% of the participants were withdrawn due to side effects. However, 672 persons responded well to monotherapy. There were also 106 patients whose poor responsive to leflunomide led to their being qualified for combination therapy with sulphasalazine or with concomitant sulphasalazine and placebo [7].

Nguyen et al. reported on 378 people qualified for leflunomide therapy (out of an initial group of 407 patients). Based on DAS28 scores, in six months good efficacy was achieved in 21.8% of the participants and average efficacy in 61.8%. Side effects were observed in 15.9% of the patients. Serious adverse events affected 2.4% of those surveyed [8].

An analysis of the incidence of adverse events is as follows. In the present study involving 100 patients, side effects were observed in 19% of patients during the one-year observation period, but did not lead to discontinuation of therapy in any of the cases. Rell-Bakalarska et al. reported adverse reactions in 8.86% of the participants in their six-month clinical trial involving 158 people; in 3.79% therapeutic effect was not achieved and treatment was discontinued [1]. Targońska-Stepniak et al. reported that after six months treatment was discontinued in 37 (16.2%) due to adverse events or a lack of therapeutic effect [2]. At the end of a two-year study with 87 participants, Zoń-Giebel et al. found that further treatment with leflunomide was not indicated in 13% of the patients [3]. In the study by Raczkiewicz-Papierski et al. on 81 patients over a five- month period, adverse reactions were noted in 44.4% of the people, but it was necessary to interrupt therapy with leflunomide in only 7.4% [4]. Nguyen et al. reported adverse events in 15.9% of 407 patients, of whom 2.4% were withdrawn from therapy [8]. In the study by Agarwal et al. involving a group of 121 patients, side effects or a lack of response to treatment were reported in 19 patients (about 16%); three persons died of unrelated causes before the end of the study [5].

As this analysis presented above shows, the efficacy of leflunomide observed in this study was similar to what has been reported in the available literature.

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