МЕДИЦИНА

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USE OF THE DISEASE-MODIFYING DRUG LEFLUNOMIDE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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This paper is dedicated to an urgent problem of modern medicine, namely the treatment of rheumatoid arthritis. According to the literature, the activation and proliferation of the T-cell and macrophage pool with the involvement of synoviocytes/chondrocytes plays an important role in the pathoge. It is known that the mechanism of action of the active metabolite leflunomide (A771726) blocks dihydroorotate dehydrogenase, which in turn inhibits pyrimidine synthesis in rapidly dividing cells (activated T-lymphocytes, macrophages). As a result, leflunomide blocks the main link in the pathogenetic mechanism of rheumatoid arthritis development and progression.nesis of rheumatoid arthritis, which in turn leads to the destruction of articular cartilage.

The study involved 52 patients with rheumatoid arthritis. This group of patients was represented predominantly by women (46 patients); the majority were seropositive for rheumatoid factor (RF) – (42 patients). The drug was prescribed according to the standard scheme: 100 mg/day for the first 3 days, then 20 mg/day. The dose was temporarily reduced in some patients to 10 mg/day in case of intolerance reactions.

The effectiveness of leflunomide was evaluated in relation to the effect on indicators of RA activity and progression. In 30% of patients, the duration of rheumatoid arthritis at the time of leflunomide prescription was less than 3 years, in 46% – 4–10 years, and in 24% – more than ten years. Radiological stages III–IV were recorded in 70% of patients. With the exception of 2 patients with rheumatoid arthritis activity of grade II–III, and according to the criteria of the European Anti-Rheumatic League using the Disease activity score (DAS), all patients had moderate to high RA activity. In 35 patients (70%), arthritic manifestations were detected before the start of therapy. The rapid effect of action of Leflunomide is certain with the reliable decline of indexes of arthritis syndrome and laboratory indexes of activity of inflammation in 1 month of treatment.

Key words: *rheumatoid arthritis, arthritis syndrome, T-cells, extraarticular displays, morning constraint.*

Олена Руснак-Каушанська, Альона Антонів, Зоряна Коцюбійчук. Застосування хворобомодифікуючого препарату Лефлуномід у пацієнтів з ревматоїдним артритом

За даними літератури відомо, що в патогенезі ревматоїдного артриту важливе значення відіграє активація та проліферація пулу Т-клітин із залученням синовіоцитів / хондроцитів, що, зі свого боку, призводить до руйнування суглобового хряща. Відомо, що механізм дії активного метаболіту лефлуноміду (А771726) блокує дигідрооротатдегідрогеназу, яка інгібує синтез піримідину в клітинах, що швидко діляться (в активованих

Т-лімфоцитах, макрофагах). Унаслідок цього лефлуномід блокує основну ланку патогенетичного механізму розвитку та прогресування ревматоїдного артриту.

У дослідженні взяли участь 52 пацієнти, що хворіли на ревматоїдний артрит. Ця група пацієнтів була представлена здебільшого жінками (46 пацієнтів); переважали серопозитивні за ревматоїдним фактором (РФ) – (42 пацієнти). Препарат призначали за стандартною схемою: 100 мг/добу перші 3 дні, потім 20 мг/добу. Дозу тимчасово знижували в деяких пацієнтів до 10 мг/добу в разі виникнення реакцій непереносимості.

Ефективність лефлуноміду оцінювали за впливом на показники активності та прогресування РА. У 30% пацієнтів тривалість ревматоїдного артриту на момент призначення лефлуноміду була менше ніж 3 роки, у 46% – 4–10 років, у 24% – понад десяти років. У 70% пацієнтів були зареєстровані рентгенологічні стадії III–IV. За винятком 2 пацієнтів, у яких активність ревматоїдного артриту була II–III ступеня, а за критеріями Європейської антиревматичної ліги з використанням індексу активності захворювання (Disease activity score – DAS) усі пацієнти мали помірну й високу активність ревматоїдного артриту. У 35 пацієнтів (70%) виявлені засуглобові прояви до початку терапії. Визначено швидкий ефект дії лефлуноміду за достовірного зниження показників синдрому артриту й лабораторних показників активності запалення через 1 місяць лікування.

Ключові слова: *ревматоїдний артрит, артритний синдром, Т-клітини, позасуглобові прояви, ранкова скутість.*

The urgency of the problem. Research into the pathogenesis of the inflammatory process in rheumatoid arthritis (RA) over the past 30 years suggests that T cells play a main role in the development and further progression of the disease [1]. This view of the pathogenesis of RA directed the efforts of scientists to create drugs capable of regulating the proliferation of activated T cells. Such a new means of basic therapy is leflunomide (Arava) (produced by the pharmaceutical company Aventis, Germany), created specifically for the treatment of RA. Leflunomide inhibits de novo pyrimidine synthesis by inhibiting the enzyme dehydroorotate dehydrogenase, which is necessary for the synthesis of uridine monophosphate. A decrease in the synthesis of pyrimidine nucleotides leads to inhibition of the proliferation of activated T-cells in the G1 phase of the cell cycle [3] and a change in the T-cell autoimmune response; the synthesis of anti-inflammatory cytokines (interferon and TNF-) is inhibited, the T-dependent synthesis of antibodies by B-cells decreases [4]. Under the influence of leflunomide, there is suppression of the transcription factor NF-k [5] (a factor necessary for the activation of genes that encode the synthesis of anti-inflammatory mediators), inhibition of COX-2 [6], synthesis of adhesion molecules [7], increased production of the cytokine TGF [8], which blocks the proliferation of T and B lymphocytes. Therefore, inhibiting the synthesis of T lymphocytes, leflunomide affects the production of antibodies and a number of cytokines, and the processes of cell adhesion.

The clinical effects of leflunomide in RA has been confirmed by many multicenter randomized controlled trials comparing leflunomide with placebo, methotrexate, and sulfasalazine [9].

According to the chemical structure, leflunomide is a low molecular weight derivative of isoxazole. In the gastrointestinal tract and plasma, leflunomide is rapidly transformed into the active metabolite malononitrilamide, which is 99.38% bound to plasma proteins.

The half-life of the drug is from 14 to 18 days. Leflunomide is excreted through the kidneys and the gastrointestinal tract in equal proportions [10]. Side effects during leflunomide treatment are observed in 5% of patients and are mostly mild or moderate in nature [10]. According to current data, the use of leflunomide is not consistent with an increased risk of malignant neoplasms [11]. In September 1998, leflunomide was approved by the US Food and Drug Administration for use in RA; since then, there are more than 200,000 patients in the world who take the drug for the treatment of RA [12].

The purpose: improvement of existing treatment regimens with the inclusion of modern drugs, namely leflunomide

Research materials and methods: 52 patients with rheumatoid arthritis participated in the study. This group of patients was represented mainly by women (46 patients); patients seropositive for rheumatoid factor (RF) prevailed – (42 patients); the average age was 54.5 ± 12.4 years; in 30% of patients, the duration of RA at the time of prescribing leflunomide was less than 3 years, in 46% – 4–10 years, and in 24% – more than ten years. In 70% of patients, radiological stages III–IV were registered. With the exception of 2 patients, the activity of RA was II–III degree, and according to the criteria of the European Antirheumatic League using the disease activity index (Disease activity score – DAS), all patients had moderate and high activity of RA. 35 patients (70%) had extra-articular manifestations before the start of therapy.

The drug was prescribed according to the standard scheme: 100 mg/day for the first 3 days, then 20 mg/day. The dose was temporarily reduced in some patients to 10 mg/day in case of intolerance reactions. The

effectiveness of leflunomide was evaluated in relation to the effect on indicators of RA activity and progression. The expressiveness of joint syndrome (number of painful and affected joints, intensity of pain and general state of health according to the visual analog scale, Ritchie index), duration of morning stiffness, functional state of patients (Lee test, health status questionnaire – HAQ), radiological progression were evaluated it was evaluated according to the modified method of Sharpe [20, p. 20] with the calculation of the number of erosions in the wrists and feet and the level of narrowing of the joint space; in order to assess the rate of progression of destruction and narrowing of joint spaces, the coefficient of progression (cpr.) was used. The presence and dynamics of extra-articular manifestations were assessed clinically using x-ray and ultrasound methods. ESR, CRP, and even biochemical, clinical blood parameters and urine tests were evaluated in the laboratory.

Research results and their discussion. The clinical and laboratory effect of leflunomide developed in 47 out of 50 patients (94%). All assessed parameters of the joint syndrome decreased with a high level of reliability after 6 and to an even greater extent after 12 months of treatment ($p < 0.001$). Evaluating the expressiveness of the reduction of the evaluated parameters, we have a very large percentage of improvement within 6 months – from 62% to 71%; after 12 months of treatment with leflunomide, the expressiveness of the positive effect on the parameters of the joint syndrome increased and is from 64% to 96% improvement against the initial level. According to modern criteria, 50% improvement corresponds to a good effect of therapy, and 70% improvement corresponds to a very good effect [13]. In most patients, the effect began to appear after 1 month of treatment. During the month of treatment, the expressiveness of joint syndrome decreases by 20–25%, and the concentration of CRP decreases by almost half – from 2.8 mg% to 1.5 mg% in total per group, reaching a normal level in 24 patients. It should be noted that CRP, according to many authors and according to our data [14], correlates much better with the activity of the inflammatory process in RA than erythrocyte sedimentation fluidity (ESF)

In this study, the reliability of the reduction of CRP in the first 6 months of treatment corresponded to the reliability and expressiveness of the reduction of the main manifestations of the joint syndrome, then the level of ESF changed little, being 35.26 ± 12.93 and 31.75 ± 14.61 mm/h before the beginning, respectively therapy, and after 6 months of treatment. A significant decrease in ESF to 27.5 ± 16.47 mm/h ($p < 0.01$) was revealed only after 12 months of treatment with leflunomide.

Evaluating the dynamics of the disease activity index (DAS) in its various modifications [15–17] – DAS 3, DAS 4, DAS 28, found that leflunomide and after 6, and after 12 months reliably reduced the activity of the disease, and the expressiveness of the reduction of DAS corresponded to a good effect of therapy (according to the EULAR criteria, a decrease in the activity index by 1.2 points or more corresponds to a good effect of therapy). So, after 6 months of treatment with leflunomide, clinical and laboratory remission occurred in 15% of patients, and after 12 months of treatment – in 1/4 of patients.

In addition to the anti-inflammatory effect, leflunomide has an effect on RF levels, reduces the severity of extra-articular manifestations of RA and slows down the rate of progression of destructive processes in small joints. Prior to the appointment of leflunomide, RF titers of 1 : 320 were noted in 21 patients, after a month of therapy – in 13 patients, after 4 months – in 6 patients, and with a duration of treatment of 6 or more months in our group of patients, only low RF titers were registered (8 patients). or its absence in the blood serum. The mean logarithm of serum RF titer decreased from 5.12 to 4.1–4.2 after 6 and 12 months of treatment ($p < 0.001$). It should be noted that such a rapid decrease in the concentration of RF in blood serum and treatment with other drugs was not noted by us. Extra-articular manifestations of RA decreased or disappeared in all patients. Rheumatoid nodules were present in 7 patients before the start of treatment with leflunamide, after 6 months they disappeared in 4 patients, and in 3 patients they decreased in size. The number of patients with anemia (Hb < 110 g/l) with chronic inflammation decreased from 20 to 4 during the year of therapy. There were clear positive dynamics in the manifestations of vasculitis: palmar erythema, skin vasculitis was minimized in half of the patients, and leg ulcers in all patients within 4 months of treatment. During the year of treatment with leflunomide, lymphadenopathy persisted in 2 out of 23 patients. The only extra-articular manifestation in which leflunomide did not have a positive effect in our study is secondary Sjogren's syndrome.

We evaluated the dynamics of erosive arthritis in the joints of the hands and feet using the modified Sharpe method. In each patient, the number of erosions was counted before the start of therapy, and every 6 months when using leflunomide. In patients with a good effect of therapy, a decrease in

the number of erosions was noted – during the first 6 months of treatment, 1.73 ± 1.79 and after the second 6 months – 0.6 ± 1.7.

After 6 months of treatment with leflunomide, 32% of patients did not notice an increase in the number of erosions in the joints of the hands and feet, after 12 months – in 41% of patients. After 18 months, the absence of an increase in erosions was noted in all patients with an excellent effect and in 1 patient with a good effect of therapy (in 62% of patients).

In the individual analysis of the effectiveness of leflunamide in patients with RA, we have a number of interesting data. The effect of leflunamide appeared most slowly in patients with RA more than ten years old: in the first 6 months, the degree of reduction in most activity parameters ranged from 20 to 30% in many patients, in contrast to patients with a disease duration of up to 3 years, who have the degree of improvement of the same parameters is 60–75%. According, leflunamide was somewhat less effective in patients with IIIb–IV stages of the disease (that is, in the presence of osteolysis and ankylosis in the small joints of the hands and feet). The most pronounced effect before the first half of the year in patients with moderate activity (more than 70% improvement), and with high activity, the expressiveness of the improvement was 53–64% of the initial level. Up to a year of leflunamide therapy, the maximum effect was noted with a high degree of RA activity. Leflunomide was approximately equally effective in patients with or without RF.

It should be noted that leflunomide is well tolerated. For the most part, intolerance reactions occurred in the first months of treatment, were severe and led to the final cancellation of the drug. The most frequent were reactions from the gastrointestinal tract (GIT), skin alopecia, 37 infectious diseases were noted in 1.5 years (all cases of SARS and other infections were recorded). Intolerance reactions from the gastrointestinal tract were noted in 24 patients. They were represented by diarrhea (in 6 patients) with cancellation for one time (recurrent diarrhea for 3 months, despite reducing the daily dose of leflunamide to 10 mg), nausea, flatulence, gastralgias. All these symptoms were severe, sometimes a short-term withdrawal of the drug or a reduction of the daily dose to 10 mg for 7–10 days was required, then returning to a dose of 20 mg/day allowed to continue the treatment. At the stages of treatment, an increase in the level of transaminases, alkaline phosphatase, glutamyltranspeptidase was noted in many patients (much higher than the norm), an increase in the concentration of these indicators more than 1.5 times higher than the norm was noted in 5 patients, which was the reason for stopping treatment with leflunamide. Skin reactions (26 patients) were mainly pruritus in 22 patients in combination with a weak erythematous-papular rash. In this case, we prescribed antihistamines, in case of its ineffectiveness we temporarily reduced the dose to 10 mg/day or made breaks in treatment. Unstable leukopenia (< 3.5 x 109) was noted in 5 patients, which did not become a reason for a long break in treatment (usually a break until a control analysis of peripheral blood in 1–2 weeks). Influenza-like syndrome (flu-syndrome), manifested by periods of malaise, tremors, low-grade fever, myalgias and increased pain in the joints associated with taking the drug, developed in 3 cases and passed after a temporary short-term break in treatment. During 18 months of treatment with leflunamide, 29 cases of SARS were registered, which had a short course, did not differ from respiratory diseases in the anamnesis. In all cases of the appearance of symptoms of infection, cytostatic treatment was interrupted, antibacterial therapy was carried out. After stopping the infectious disease, leflunamide was resumed.

Conclusions:

1. Leflunomide is effective in 94% of patients.
2. The rapid development of the effect of leflunomide with a significant decrease in indicators of joint syndrome and laboratory parameters of inflammatory activity is noted after 1 month of treatment, then the effect of treatment increases during 4–5 months.
3. The effect of leflunamide develops most quickly in patients with moderate activity, with a short duration of RA (up to 3 years), in the absence of osteolysis and ankylosis in the joints.
4. Leflunamide demonstrates not only basic activity, reliably reducing the RF titer, extra-articular manifestations of RA (in particular, vasculitis), reliably slowing down the rate of radiological progression, but also in the majority of patients with a good and excellent effect – stopping the destructive process.
5. Leflunamide is well tolerated by patients, withdrawal of the drug within 1.5 years was noted in 10% of patients.
6. At the stages of treatment, in the event of the development of undesirable reactions, it is possible to temporarily reduce the dose of the drug, to interrupt the treatment, which is not reflected in the overall effectiveness of the therapy.

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