

THE EFFECTIVENESS OF THE TREATMENT OF PSORIATIC ARTHRITIS

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ABSTRACT

Goal. To evaluate the efficacy and tolerability of leflunomide, administered at a dose of 100 mg/ day for 3 days and 20 mg / day for 6 months, in patients with an active form of psoriatic arthritis (PA).

Materials and methods. An open, uncontrolled study was conducted. 15 patients aged 37 to 60 years were examined, the duration of arthritis averaged 7.4 years. Leflunomide was prescribed at 100 mg / day for the first 3 days, and then 20 mg / day for 6 months. The dynamics of the number of painful and swollen joints, the severity of pain and the activity of the disease were evaluated on a visual analog scale, The Likert scale is both in the opinion of the doctor and the patient himself.

Results. Against the background of leflunomide treatment, there was a significant decrease in the number of painful and swollen joints by 54.3 and 65.7%, respectively. The high efficacy of leflunomide according to the PsARC (Psoriatic Arthritis Response Criteria) and ACR 50 (American College of Rheumatology) criteria was noted in 86.7% of cases, which makes it possible to recommend it to patients with a polyarticular form of the disease. The tolerability of leflunomide was assessed as satisfactory. In 3 patients, therapy was canceled due to the development of leukopenia and urticaria.

Conclusion. High efficacy of leflunomide has been demonstrated in patients with polyarticular PA.

Keywords: psoriatic arthritis, leflunomide, psoriasis

INTRODUCTION

Psoriatic arthritis (PA) is a chronic systemic progressive disease, usually associated with psoriasis, leading to the development of erosive arthritis, bone resorption, multiple enteritis and spondyloarthritis. The main immunological disorders in PA are: hyperproduction of circulating immune complexes containing immunoglobulin A (IgA), polyclonal hypergammaglobulinemia, predominance of CD4+ T lymphocytes in synovial cell infiltrates, depression of lymphocyte response to specific and non-specific antigens, increased expression of platelet-dependent growth factor. The infiltrate of the skin includes activated T cells localized in the papillary the dermis layer, which are also found in the subsynovial tissue and ligament attachment

sites, is predominantly perivascular. At the same time, CD4⁺ T lymphocytes predominate in tissues (ratio CD4⁺/CD8⁺ is 2:1), whereas the inverse relationship is determined in the synovial fluid (CD8⁺/CD4⁺ — 2:1).

Dendritic cells and macrophages are also key cells. Fibroblasts in the skin and synovial membrane have increased proliferative activity. All these cells produce a large number of pro-inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1) and interleukin-6 (IL-6). Proinflammatory cytokines, in turn, activate endothelial cells, which leads to the expression of adhesion molecules such as intracellular adhesion molecules-1 (ICAM-1), vascular adhesion molecules-1 (VCAM-1), E-selectin, which promote the migration of lymphocytes to the inflammatory region. Keratinocyte proliferation and prolongation of their cellular life are noted in the skin indirectly through TNF- α , which leads to thickening of the skin and plaque formation. The role of B lymphocytes has not been sufficiently studied, although their activation and significant release from primary generation centers (spleen, lymph nodes). One of the earliest and most distinctive links of PA pathogenesis is angiogenesis in both the skin and synovia. Neovascularization is considered as an important component not only of the inflammatory nature of this disease, but also of erosive bone destruction. Pathological bone remodeling is a key feature of PA and is regulated by the dynamic balance between osteoclasts and osteoblasts. Osteoblasts of mesenchymal origin are involved in the production of bone matrix. Periarticular osteoporosis and erosive joint damage leads to digital osteolysis. The researchers note a significant increase in the transition of both differentiated and undifferentiated monocytes into osteoclast progenitor cells, and subsequently into mature osteoclasts under the influence of activated TNF- α , NF- κ B ligand receptors (RANKL) and IL-1. RANKL is expressed on the surface of osteoblasts and stromal cells in the bone in the brain, T-lymphocytes and synoviocytes — in the affected joints, interacts with RANK, which in the presence of macrophage colony stimulating factor (M-CSF) determines the process of bone resorption. PA should be considered as one of the socially significant diseases of the musculoskeletal system due to a significant decrease in the quality of life and early disability of patients. Thus, the purpose of therapeutic measures is not only a decrease in the activity of the disease at any given moment, but also the prevention of its further progression, the increase in functional insufficiency of the joints and spine. The drug therapy of PA includes 2 directions: the use of symptommodifying (SMP) and disease-modifying (BMP) drugs. For the treatment of PA, a relatively new drug is used as a BMP — leflunomide (Arava, "Sanofi Aventis") — an inhibitor of pyrimidine synthesis, the effectiveness of which is shown in relation to both skin lesions and joint syndrome in PA. The aim of the study was to evaluate the efficacy and tolerability of leflunomide administered at a dose of 100 mg/ day for 3 days and 20 mg /day for

6 months, in patients with an active form of PA.

MATERIALS AND METHODS OF RESEARCH

The diagnosis of PA was established in the presence of the main and any 3 additional criteria.

1. The main criterion is a history of clinically obvious psoriasis of the skin or nails, confirmed by a doctor, in combination with pain and swelling and / or restriction of movement in at least one joint, lasting at least 6 weeks.

2. Additional criteria:

— arthritis of the distal interphalangeal joints (a specific exception is the nodules of Geberden or Bouchard);

— sausage-shaped deformity of the fingers of the hands or feet;

— asymmetric involvement of the joints of the arms and legs;

— absence of subcutaneous nodules;

— negative rheumatoid factor in blood serum;

— X-ray of peripheral joints showing erosive arthritis of small joints and relatively mild osteoporosis (a specific exception is erosive osteoarthritis of the joints of the hands);

— radiograph of the axial skeleton, reflecting one (or more) of the following signs:

sacroiliitis, syndesmophytes, sometimes atypical, paravertebral ossifications.

15 patients with PA aged 37 to 60 years (average age — 50.5 ± 6.4 years) were examined, including 9 women and 6 men. The duration of the disease ranged from 3 to 10 years, an average of 7.4 years. All patients included in the study had grade II disease activity. The vast majority of patients (87%) corresponded to class II functional insufficiency according to ACR. Most of the patients ($n = 14$, or 93%)

received 1 or more BMP — methotrexate, sulfasalazine before inclusion in the study, 8 patients were treated with GCS (mainly in the form of intra-articular injections). All patients were prescribed various medications before participating in the study NSAIDs in standard anti-inflammatory dosages. All patients after entering the phase (visit 0) of treatment visited a doctor to assess the effectiveness and safety of therapy every 30 days (visits 1-6), as well as 30 days (visit 7) after the end A 6-month course of treatment to assess the persistence of the therapeutic effect. The main performance criteria in this study were the PsARC response, as well as the improvement parameters ACR (American College of Rheumatology) 20, 50, 70 (modified for PA), ESR, C-reactive protein. The assessment of the articular syndrome included a joint score used to determine the activity of the peripheral arthritis in PA, proposed by ACR, modified for PA. 76 joints were examined to identify painful ones among them (temporomandibular, sternoclavicular, clavicular-acromial, shoulder,

elbow, wrist, metacarpophalangeal, proximal and distal interphalangeal arms and legs, hip, knee, ankle, tarsal, tarsal-calcaneal, metatarsophalangeal) and 74 - in order to detect swollen joints (hip joints were not included). Also, the effectiveness of treatment was determined based on the overall assessment of the activity of the disease according to both the doctor and the patient on a 5-point Likert scale: 0 is very good, 1 is good, 2 is satisfactory, 3 is bad, 4 is very bad. The general assessment of the state of health by the doctor and the patient himself was carried out on a 100-millimeter visual analog scale (VAS).

The PsARC response included the following indicators:

- the number of painful joints (CHBS) — out of 78;
- the number of swollen joints (NPV) — out of 76;
- the patient's overall assessment of the disease activity according to Likert;
- the general assessment of the disease activity by the doctor according to

Likert.

In order for the patient to meet the concept of "responding to treatment" according to PsARC, improvement must be achieved in at least 2 of the 4 indicators, and one of them of these, BBS or BPS, the number of which should be reduced by at least 30%, and the assessment of the activity of the disease by the doctor and the patient should decrease by at least 1 unit according to 5-point Likert scale; there should be no deterioration in any of the 4 indicators. The efficiency criterion according to ACR 20, 50, 70, modified for PA, is a complex indicator reflecting a 20, 50, 70% improvement in both CHBS (out of 78) and CHPS (out of 76), as well as 3 of the 5 following parameters: assessment of disease activity by YOUR doctor and by the patient, the patient's assessment of pain syndrome (according to YOUR), the indicator of functional ability according to the HAQ questionnaire and acute phase indicators (ESR according to Westergren or C-reactive protein), which was evaluated in this study on the 3rd and 6th visits. The assessment of the safety of treatment was established with the help of physical examination, vital signs, clinical and biochemical blood tests, general urine analysis and monitoring of adverse events determined at each visit.

THE RESULTS AND THEIR DISCUSSION

All 15 patients included in the analysis took leflunomide for at least 1 month, 12 (80%) patients completed a 6-month course of treatment in accordance with the study protocol. 3 (20%) patients prematurely stopped participating in the study due to the development of adverse events. The indicator of morning stiffness in patients with PA before treatment averaged 100 minutes, and after therapy with leflunomide — 37.5 minutes, $p < 0.001$. When assessing the CHBS during treatment, the pronounced effectiveness of therapy was revealed from the first month of therapy: so, on average, the BBS when turned on. The number of patients in the study was 21.4 ± 7.9 , and at the end of treatment — 9.8 ± 3.0 ($p = 0.0013$), i.e. an improvement of 54.2 can be noted%.

Similarly, a significant decrease in heart rate was observed when comparing the indicator before the appointment of basic therapy with leflunomide (15.2 ± 5.9) and after the end of treatment (5.2 ± 2.7), which demonstrates a decrease in this indicator by 65.7%. The severity of pain syndrome in the affected joints in patients with PA decreased statistically significantly: from 65.0 at visit 0 to 32.6 at visit 6; $p < 0.001$. When evaluating the main indicators reflecting the activity of PA, the rapidity of the onset of the effect of leflunomide therapy was noted, with a statistically significant decrease in the levels of all parameters after the first month of treatment ($p < 0.001$). By the end of the follow-up, a decrease in the activity of the disease was revealed to an equal extent, both according to the patient's assessment — by 43.1%, and according to the doctor's assessment — by 42.1%, compared with the initial values. The main parameter of treatment effectiveness in the present study was PsARC. By the end of therapy, 13 out of 15 patients (87%) were "responding to treatment" in accordance with PsARC and ACR 50. A decrease in ESR from 40.4 to 20.9 mm/h was recorded during 6 months of treatment with leflunomide ($p < 0.001$). The tolerability of leflunomide treatment in general can be regarded as satisfactory. The frequency and spectrum of adverse events reported during treatment did not differ significantly from the side effects of leflunomide described earlier. Adverse events during treatment with leflunomide were observed in 8 (53%) patients, and in 5 patients they had a mild degree of severity and did not require discontinuation of the studied drug. Clinically significant leukopenia was detected in 1 patient by the 1st and in another by the 5th month of treatment, which led to the cancellation of the studied drug. In one case, during the 2nd week of taking leflunomide, intolerance to the drug in the form of medicinal urticaria developed, which also caused the interruption of treatment. The obtained results on the effectiveness of leflunomide in PA patients are comparable with the data of the TOPAS study, and in our study even the largest proportion of patients who achieved improvement in PsARC by the end of treatment (87 and 59%, respectively) was demonstrated, which can be explained by a small sample. Patients meeting the ACR 20 improvement criteria are also more among our patients (87 and 36%). As a result of the study, it was shown that leflunomide has a distinct symptom-modifying effect in relation to joint syndrome in patients with polyarticular PA.

CONCLUSIONS

1. The use of leflunomide in patients with PA for 6 months significantly reduces BBS and NPV (by 54.2 and 65.7%, respectively).
2. The high efficacy of leflunomide according to the PsARC and ACR50 criteria was noted (in 87% of cases), which makes it possible to recommend it to patients with a polyarticular form of the disease.

3. The tolerability of leflunomide was assessed as satisfactory. In 3 cases, therapy was discontinued due to the development of leukopenia (2) and urticarial (1). In the remaining 7 reported cases, adverse events were mild and did not require the patient to be excluded from the study.

PA treatment is a complex therapeutic task, as it must combine high efficacy and safety. The use of leflunomide at a daily dose of 100 mg in the first 3 days, followed by a transition to 20 mg once a day, is characterized by significantly high efficacy and satisfactory tolerability in patients with polyarticular PA.

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