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EFFICIENCY AND SAFETY OF LEFLUNOMIDE TREATMENT IN PATIENTS WITH PULMONARY SARCOIDOSIS

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Abstract

Patients who have contraindications to the prescription of GCs (glucocorticosteroids), or have developed serious side effects during treatment with GCs, as well as patients with resistance to GCs therapy, are prescribed immunosuppressants.

The aim of the research - to study the efficacy of leflunomide monotherapy in patients with pulmonary sarcoidosis with contraindications to prescription or serious side effects of glucocorticosteroids.

Fourteen patients with sarcoidosis of the respiratory system of stage II were examined – 12 women and 2 men aged 30 to 69 years. In 10 patients there were contraindications to the appointment of GCs (diabetes mellitus – 5, hypertension – 3, obesity – 1, exacerbation of gastric ulcer – 1), which caused the appointment of immunosuppressive therapy as a starting. In 4 cases, serious side effects of SCs were noted, requiring the drug to be abolished (osteoporosis – 3, steroid diabetes – 1). Leflunomide was administered at a dose of 20 mg per day, daily for 3 months. The evaluation of efficacy was carried out using computed tomography of the thoracic cavity organs, body plethysmography, spirometry and determination of the diffusivity of the lungs.

Monotherapy with leflunomide in patients with contraindications to prescription or serious side effects of GCs was successful in 7 out of 13 patients, in 2 patients there was a stabilization of the process, in 4 patients with leflunomide therapy progression of the disease was noted and in 1 case the treatment was discontinued due to serious side effects of preparation.

The results obtained make it possible to recommend the use of leflunomide as monotherapy in patients with pulmonary sarcoidosis with contraindications to the prescription and/or poor tolerability of GCs and methotrexate. It is necessary to continue studying the possibilities of combined use of leflunomide with other drugs of the first line.

Keywords: pulmonary sarcoidosis, treatment of sarcoidosis, leflunomide, side effects.

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1. Introduction

The main drugs for the treatment of sarcoidosis are glucocorticosteroids, their effectiveness has been proven in several randomized researches [1, 2]. Despite the fact that corticosteroids remain the first-line drugs for most patients, cytostatics have been recognized as alternative drugs for the treatment of sarcoidosis. Methotrexate is the most commonly used cytotoxic drug,

however, in a few studies it has been shown that azathioprine and leflunomide are also effective in treating sarcoidosis [3, 4]. In refractory sarcoidosis it is proposed to use infliximab, a drug that is a monoclonal antibody to the tumor necrosis factor (TNF-ά) [5, 6]. In connection with this, a strategy for the treatment of sarcoidosis has been developed. Patients who have contraindications to the appointment of the GCs, or have developed serious side effects during treatment with GCs, as well as patients with resistance to GCs therapy, are prescribed second-line drugs. The main place among which is occupied by immunosuppressants – methotrexate, azathioprine and leflunomide [7, 8].

The work on the study of immunosuppressants in the treatment of patients with respiratory sarcoidosis is few, only one randomized study of the effectiveness of methotrexate in a small group of patients (24 patients) was conducted [9, 10]. Experts of the World Association of Sarcoidosis and other Granulomatous Lesions (WASOG) analyzed literature data on the effectiveness of methotrexate in limited series of observations and developed general recommendations for its use [11, 12].

Leflunomide is an immunomodulating agent of the isoxazole series. It blocks the synthesis of pyrimidine by reversible inhibition of the enzyme dihydroorotate dehydrogenase, which has an antiproliferative effect on activated lymphocytes. The leflunomide efficacy was studied in small groups of patients, and the drug was administered to patients resistant to previous therapy or with poor methotrexate tolerance [13, 14]. Part of the patients received leflunomide in combination with GCs, which did not allow to establish its true efficacy [15, 16].

2. Aim of the research

To study the effectiveness of leflunomide monotherapy in patients with pulmonary sarcoidosis with contraindications to administration or serious side effects of glucocorticosteroids.

3. Materials and methods

The study was carried out on the basis of the clinico-functional department of the State Institution “National Institute of Phthisiology and Pulmonology named after. F. G. Yanovskogo NAMS Ukraine” during the 2017. Fourteen patients with sarcoidosis of the respiratory system of II stage were examined – 12 women and 2 men aged 30 to 69 years. In 10 patients there were contraindications to the appointment of GCs (diabetes mellitus – 5, hypertension – 3, obesity – 1, exacerbation of gastric ulcer – 1), which led to the appointment of immunosuppressive therapy as a starting. In 4 cases, serious side effects of GCs were noted, requiring the drug to be canceled (osteoporosis – 3, steroid diabetes – 1).

The diagnosis of sarcoidosis was verified by computed tomography (CT) scan of the thoracic cavity organs [17, 18]. The function of external respiration was also studied by spirometry body plethysmography, evaluation of lung diffusivity [19, 20]. Leflunomide was administered at a dose of 20 mg per day, daily for 3 months. Before the start of therapy and monthly during the therapy, a general blood test was carried out to determine the number of platelets, the concentration of AST, ALT, bilirubin and creatinine were determined. The results of treatment were evaluated after 3 months, taking into account clinical, functional data and CT results.

4. Results

In one patient during treatment with leflunomide serious side effects developed (pronounced pyrogenic reaction, increase in ALT, which is more than 3 times higher than normal), in connection with which the drug was canceled, the patient was prescribed methotrexate treatment.

In 7 patients out of 13 (53.8 %) after 3 months of treatment with leflunomide, regression of sarcoidosis was observed: a decrease in the density of nodular dissemination of the lung parenchyma, in 2 (15.4 %) – stabilization of the process (no changes in CT data), and 4 (30.8 %) of patients had progression.

Fig. 1, 2 show cases of regression and progression of sarcoidosis after a 3-month course of treatment with leflunomide.

a *b*

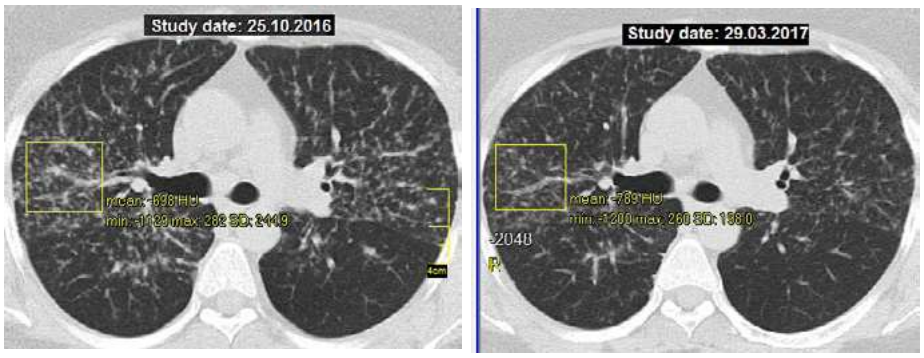

Fig. 1. CT of patient K., sarcoidosis of lungs, II stage: *a* – before leflunomide administration, parenchyma densitometry before treatment – (–698 HU); *b* – in 3 months of leflunomide treatment: a decrease in the density of nodular dissemination of the lungs (densitometry after 3 months of therapy – (–789 HU))

a *b*

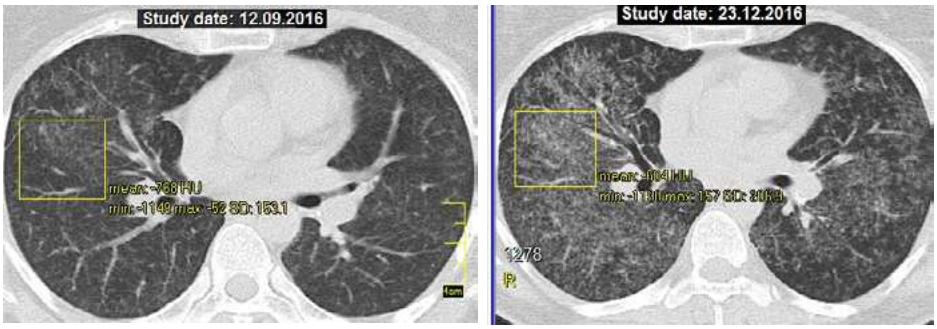

Fig. 2. CT of the patient G., sarcoidosis of the lung, stage II: *a* – before the appointment of leflunomide, (densitometry of the parenchyma before treatment – (–768 HU)); *b* – after 3 months of treatment with leflunomide: significant increase in the density of nodular dissemination of the lungs (parenchyma densitometry after 3 months of therapy – (-604 HU))

The parameters of the function of external respiration are presented in **Table 1, 2**.

Table 1

VC and DLCO indices in the course of treatment with leflunomide

No.	Patient	Result of the treatment	VC (% of normal)		DLCO (% of normal)	
			V1	V2	V1	V2
1	P. I. V.	Progression	110.8	113.2	80.6	85.9
2	K. S. V.	Regression	100.5	106.7	66.9	72.5
3	Ya. L. K.	Progression	92.0	88.9	75.1	64.5
4	Sh. E. A.	Regression	71.0	92.0	65.4	80.5
5	S. L. M.	Stabilization	91.0	92.4	85.0	86.2
6	P. V. M.	Progression	65.0	46.4	68.4	52.3
7	G. A. M.	Progression	101.9	87.1	60.6	60.3
8	Sh. L. F.	Regression	85.0	95.6	46.7	57.0
9	G. G. P.	Regression	125.0	120.7	65.9	65.1
10	S. A. O.	Cancel	101.8	–	52.5	–
11	S. O. M.	Stabilization	88.0	89.4	82.0	83.2
12	G. P. V.	Regression	86.4	90.4	73.4	63.7
13	K. A. V.	Regression	108.7	109.2	76.2	78.3
14	V. O. V.	Regression	93.8	–	82.8	–

Note: V1 – visit before treatment; V2 – visit after 3 months of therapy

In table 1 it is shown that the integral exponent of the external respiration function DLCO was reduced (≤70 %) in 7 of 13 patients. In patients with regression in 3 cases out of 7, the diffusive capacity of the lungs increased. Progression of the process in 2 out of 4 patients was accompanied by a further decrease in DLCO.

Table 2

Indicators of bronchial patency during leflunomide treatment

No.	Patient	Result of the treatment	FVC (% of normal)		FEV_1 (% of normal)		FEV_1/FVC (%)	
			V1	V2	V1	V2	V1	V2
1	P. I. V.	Progression	111.7	113.7	102.5	106.0	79.4	81.0
2	K. S. V.	Regression	97.8	101.6	88.4	96.2	77.4	81.1
3	Ya. L. K.	Progression	92.7	91.8	62.3	75.0	72.9	69.5
4	Sh. E. A.	Regression	65.6	84.8	58.0	75.7	76.8	77.4
5	S. L. M.	Stabilization	90.4	92.0	71.5	72.1	69.4	66.5
6	P. V. M.	Progression	66.0	46.2	58.0	36.3	87.0	67.3
7	G. A. M.	Progression	95.6	84.3	96.5	84.7	86.7	86.3
8	Sh. L. F.	Regression	78.4	84.6	80.5	86.8	84.2	84.1
9	G. G. P.	Regression	129.0	120.8	124.5	116.3	81.7	81.5
10	S. A. O.	Cancel	99.9	–	102.1	–	86.5	–
11	S. O. M.	Stabilization	90.1	91.7	71.2	71.8	69.1	66.2
12	G. P. V.	Regression	90.4	86.3	98.3	91.2	91.3	88.8
13	K. A. V.	Regression	105.6	106.5	98.7	99.7	78.2	79.6
14	V. O. V.	Regression	94.9	–	97.2	–	82.8	–

Note: V1 – visit before treatment; V2 – visit after 3 months of therapy

From table 2 that in 2 patients at the first visit a restrictive type of pulmonary ventilation disorder (FVC≤80 %) was observed, in 2 – obstructive disorders (FEV_1/FVC≤70 %), in other cases spirometry parameters were within the normal range.

Side effects of leflunomide in a dose of 20 mg per day were observed in 6 of 14 patients (42.9 %).

One patient had serious side effects: a pronounced pyrogenic reaction, an increase in ALT above the norm by more than 3 times, which led to the withdrawal of the drug.

In 2 patients (14.3 %) at the beginning of the treatment period, gastrointestinal disorders were observed: nausea, abdominal pain. Patients were recommended to distribute the dose of the drug for two doses – 10 mg twice a day, as a result of these gastrointestinal disorders were not repeated. Two patients (14.3 %) reported frequent respiratory viral infections during leflunomide treatment. One patient (7.1 %) had acute oral herpes. After reducing the dose of leflunomide to 10 mg per day and carrying out antiviral therapy, the patient noted a regression of herpetic infection and sarcoidosis of the lungs (according to CT data).

5. Discussion

Currently, the main drugs for the treatment of sarcoidosis are glucocorticoids [15, 17]. When appointing GCs, a large number of side effects of these drugs should be taken into account, the frequency of which increases with prolonged use [15]. With the development of serious side effects, such as osteoporosis, diabetes mellitus, and also in the presence of contraindications to GCs therapy, second-line drugs - cytostatics are used. The most studied of them is methotrexate [15]. In our clinic we also use it as the most preferable option of the second line. Other drugs of the second line include azathioprine, leflunomide, mycophenolate and antimalarial drugs. However, there are very few scientific data on their use in case of sarcoidosis [11].

Baughman and Lower [13] described the experience of using leflunomide in a small group of patients. According to their data, in 78 % there was a regression of the disease. It should be noted that patients who did not tolerate methotrexate were usually successfully treated with leflunomide. Similar data are presented in the work of D.H. Sahoo with co-authors [16]: of the 33 patients who

took leflunomide due to toxicity from other immunomodulating medications, 20 tolerated leflunomide well (67 %). In our work, we administered leflunomide to patients who had not previously taken cytotoxic drugs. In 10 patients out of 14 there were contraindications to the appointment of GCs, in 4 there were serious side effects of GCs, requiring withdrawal of the drug (osteoporosis – 3, steroid diabetes – 1). The effectiveness of leflunomide therapy in our group of patients was 53.8 %. Perhaps, the lower efficacy of therapy in our group of patients is due to the fact that all patients had stage 2 of pulmonary sarcoidosis. In previous studies, patients had 1 to 3 stages of pulmonary sarcoidosis. As is known, in the first stage of sarcoidosis, spontaneous regression is possible in 90 % of cases.

In our work, as well as in other studies on the efficacy of leflunomide, there was no statistical difference in the parameters of the function of external respiration before and after treatment.

According to a study by D. H. Sahoo with co-authors, side effects were observed in 34 % of cases, similar data were obtained from us – 42.9 %. According to a study by D.H. Sahoo with co-authors, the discontinuation of leflunomide intake due to its toxicity was observed in 18 % of cases. In our work – only 7.1 %. The dosage regimen was the same: 90 % of patients received 20 mg daily. Perhaps a higher level of side effects in the work of D. H. Sahoo and co-authors is associated with a longer period of follow-up.

The disadvantages of our study are a small group of patients and a short observation period. On the positive side of the work was the homogeneity of the group: all patients were with stage 2 of pulmonary sarcoidosis, did not take another therapy before the study.

6. Conclusion

1. Monotherapy with leflunomide in patients with contraindications to prescription or serious side effects of GCs was successful in 7 of 13 patients (53.8 %), in 2 patients there was a stabilization of the process (15.4 %), 4 patients with leflunomide therapy showed progression of the disease (30.8 %).

2. Leflunomide is characterized by satisfactory tolerability: the incidence of side effects from the use of the drug was 35.7 %. At the same time, the drug was withdrawn only in one case (7.1 %).

3. The results obtained make it possible to recommend the use of leflunomide as monotherapy in patients with pulmonary sarcoidosis with contraindications to the appointment and/or poor tolerability of GCs and methotrexate.

4. In the future, attention should be paid to the combined use of leflunomide with other drugs for the treatment of sarcoidosis.

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