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EFFICACY AND TOLERABILITY OF METHOTREXATE AT A DOSE OF 15 mg/week AND 10 mg/week IN PATIENTS WITH PULMONARY SARCOIDOSIS

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Цитування: Медичні перспективи. 2021. Т. 26, № 4. С. 56-61

Cited: Medicni perspektivi. 2021;26(4):56-61

Key words: pulmonary sarcoidosis, methotrexate, efficacy, tolerability

Ключові слова: саркоїдоз легень, метотрексат, ефективність, переносимість

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Abstract. Efficacy and tolerability of methotrexate at a dose of 15 mg/week and 10 mg/week in patients with pulmonary sarcoidosis. Gavrysyuk V.K., Merenkova I.O., Gumeniuk G.L., Pentalchuk N.V., Morska N.D., Vlasova N.A. The objective of this study is to conduct a comparative study of the efficacy and safety of methotrexate (MT) at a dose of 10 mg/week and 15 mg/week in patients with pulmonary sarcoidosis having contraindications to GCS therapy. Material and Methods. The study involved 44 patients with stage II pulmonary sarcoidosis (26 females and 18 males aged 24 to 70) with contraindications to the appointment of therapy glucocorticosteroid (GCS). In group 1 (28 patients), methotrexate was prescribed at a dose of 10 mg/week, in group 2 (16 patients), methotrexate was prescribed at a dose of 15 mg/week. The diagnosis and assessment of the dynamics of sarcoidosis were carried out taking into account clinical symptoms based on the results of high-resolution computed tomography and body plethysmography. The significance of differences in indicators was determined using the Student's t-test and Fisher's exact test. The number of cases of clinical treatment without residual changes of a fibrous nature in the lung parenchyma in patients after treatment with methotrexate at a dose of 15 mg/week significantly increased compared to the same indicator in the group of patients after treatment at a dose of 10 mg/week (81.3% and 42.4% respectively, $p=0.025$). An increase in the therapeutic dose of methotrexate from 10 mg/week to 15 mg/week leads to a decrease in the time to achieve a clinical cure (10.1 ± 0.5 months and 12.8 ± 0.8 months respectively, $p<0.02$), indicating an accelerating rate of regression of sarcoidosis. Immunosuppressive therapy of patients with pulmonary sarcoidosis using the drug at doses of 10 and 15 mg/week is characterized by satisfactory tolerability.

Реферат. Ефективність і переносимість метотрексату в дозах 15 мг/тиждень та 10 мг/тиждень у хворих на саркоїдоз легень. Гаврисюк В.К., Меренкова Є.О., Гуменюк Г.Л., Пендальчук Н.В., Морська Н.Д., Власова Н.А. Мета роботи – провести порівняльне вивчення ефективності та безпеки метотрексату (МТ) в дозах 10 мг/тиждень і 15 мг/тиждень у хворих на саркоїдоз легень II стадії (26 жінок і 18 чоловіків, вік – від 24 до 70 років), що мають протипоказання до призначення ГКС-терапії. У 1 групі (28 пацієнтів) метотрексат призначали в дозі 10 мг 1 раз на тиждень, у 2 групі (16 пацієнтів) – у дозі 15 мг/тиждень. Діагностику й оцінку динаміки саркоїдозу проводили з урахуванням клінічних симптомів на основі результатів комп'ютерної томографії високої роздільної здатності і бодіплетизмографії. Достовірність відмінностей показників визначали за допомогою t-критерію Стьюдента та точного критерію Фішера. У пацієнтів після лікування метотрексатом у дозі 15 мг/тиждень достовірно збільшується кількість випадків клінічного лікування без залишкових змін фіброзного характеру в паренхімі легень порівняно з аналогічним показником у групі хворих після лікування препаратом у дозі 10 мг/тиждень (81,3% і 42,4% відповідно, $p=0,025$). Підвищення лікувальної дози метотрексату з 10 мг/тиждень до 15 мг/тиждень зумовлює зменшення термінів досягнення стану клінічного вилікування ($10,1\pm 0,5$ міс. і $12,8\pm 0,8$ міс. відповідно, $p<0,02$), що вказує на прискорення темпів регресії саркоїдозу. Імуносупресивна терапія хворих на саркоїдоз легень з використанням препарату в дозах 10 і 15 мг/тиждень характеризується задовільною переносимістю.

Sarcoidosis is a polysystemic disease of unknown aetiology characterized by the formation of epithelial cell granulomas in various organs without caseous necrosis. Intrathoracic lymph nodes and lung parenchyma are affected the most frequently [11].

The main drugs in the treatment of sarcoidosis are systemic glucocorticosteroids (GCS) [11, 6]. Their effectiveness has been proven in randomized studies [10, 12], the results of which testified to the positive dynamics of the clinical and radiological symptoms of sarcoidosis, the improvement of pulmonary ventilation and diffusion parameters under the influence of GCS.

GCS therapy is impossible in patients of three categories. The first category includes patients with contraindications to GCS treatment, the second one includes patients with severe side effects of GCS treatment, requiring drug withdrawal, and the third one includes patients with resistance to GCS therapy [7].

In cases of contraindications, severe side effects and resistance to GCS therapy, methotrexate (MT), the second-line drug is used [1, 5, 8].

According to the recommendations of experts from the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) for the use of MT in the treatment of patients with sarcoidosis, the drug is prescribed at a dose of 5 to 15 mg/week, depending on the extent of the process and the tolerability of the drug [9]. The experience was accumulated in observing a significant number of cases of insufficient effectiveness of the drug at a dose of 10 mg/week (slow rates of regression, stabilization of the process) in the course of our earlier studies [3]. At the same time, increasing the MT dose to 15 mg/week increased the effectiveness of immunosuppressive therapy.

The objective of this study is to conduct a comparative study of the efficacy and safety of MT at a dose of 10 mg/week and 15 mg/week in patients with pulmonary sarcoidosis having contraindications to GCS therapy.

MATERIALS AND METHODS OF RESEARCH

The study was carried out in the clinic of the State Organization "National Institute of Phthisiology and Pulmonology named after F.G. Yanovsky of NAMS of Ukraine" (accreditation certificate dated October 7, 2020, valid until September 4, 2023 at No. 014999, highest category, series M3 of the Ministry of Health of Ukraine) after agreement with the Ethics Commission of the NIPhP of NAMS. All patients were familiarized with the list of procedures and signed the informed consent to participation in the study.

The main inclusion criterion: patients with newly diagnosed pulmonary sarcoidosis, confirmed by the

results of computed tomography (CT) of the thoracic organs (TO) from the number of patients with contraindications to GCS therapy. The main exclusion criteria are 1) concomitant chronic lung diseases; 2) the presence of CT signs of interstitial pulmonary fibrosis in the period before treatment.

A comparative analysis of the efficacy and tolerability of MT in two doses was carried out in 44 patients with stage II pulmonary sarcoidosis (26 females and 18 males at the ages from 24 to 70), who were divided into two groups. In group 1 (28 patients), MT was prescribed at a dose of 10 mg/week, and in group 2 (16 patients), MT was prescribed at a dose of 15 mg/week. Before the start of immunosuppressive therapy and monthly in the course of treatment, a complete blood count was performed to determine the number of platelets, the concentration of ALT, bilirubin, and creatinine.

All patients were examined by high-resolution CT using Aquilion TSX-101A multislice CT scanner (Toshiba). Evaluation of the results of computed tomography was carried out using the criteria described by M. Veltkamp, J.C. Grutters [13].

Evaluation of the dynamics of the process during the treatment during CT was carried out using the K-Pacs software by simultaneous analysis of two series of images obtained in the initial state and after the therapy. In order to objectify the assessment of the data, the method of computed lung densitometry was used.

The state of the respiratory function was assessed based on the analysis of the forced expiratory flow-volume curve, body plethysmography, and the study of the diffusion capacity of the lungs on the MasterScreen spirometric system (Viasys Healthcare GmbH) with the corresponding modules [4].

The reliability of differences in quantitative indicators expressed as the arithmetic mean and the error of the mean ($M \pm m$) was determined using the Student's t-test. The analysis of differences in frequency indicators expressed in absolute values in the study groups was carried out using the Fisher exact test since the frequency of some indicators was represented by small values [2].

Mathematical processing was performed using licensed software products contained in Microsoft Office Professional 2003, Russian Academic Open No Level license No. 17016297).

RESULTS AND DISCUSSION

Evaluation of the results of MT efficacy showed that successful completion of treatment with the confirmation by CT results was achieved in 18 patients (64.3%) of group 1 and in 14 patients (87.5%) of group 2, but Fisher's exact test (0.160) exceeds the critical level of significance (0.05)

and does not allow us to assert that increasing a dose of MT to 15 mg/week increases the effectiveness of immunosuppressive therapy in patients with pulmonary sarcoidosis.

At the same time, the analysis of the quality of the outcomes (Table 1) showed that after treatment with MT at a dose of 15 mg/week, the number of cases of clinical cure without residual changes in the parenchyma in the form of limited interstitial or focal fibrosis according to CT data significantly increased in patients of group 2.

After treatment with MT at a dose of 10 mg/week, residual changes in the lung parenchyma in the form of fibrosis were observed in 6 patients, which in relation to the total number of patients in the group was 21.4%. In group 2 (15 mg/week) only one patient (6.3%) had residual changes in the lungs according to CT data. However, in statistical analysis, Fisher's exact test (0.39) exceeded the critical level of significance. In this regard, we can only talk about a tendency towards a decrease in the frequency of fibrosis with an increase in the therapeutic dose of MT.

Table 1

Outcomes in patients with pulmonary sarcoidosis depending on the dose of methotrexate (MT)

Outcomes	Group 1 (MT – 10 mg/week), n = 28		Group 2 (MT – 15 mg/week), n = 16		Fisher's exact test (p)
	abs.	%	abs.	%	
Outcomes with CT data normalization	12	42.9	13	81.3	0.025*
Outcomes with limited interstitial or focal pulmonary fibrosis on CT data	6	21.4	1	6.3	0.39
Regression followed by stabilization of the process	10	35.7	2	12.4	0.16

Note: * – the difference in the value of the indicator in the groups is statistically significant with a critical level of significance =0.05.

If we consider the frequency of residual fibrotic changes in the lungs in relation to the total number of cases of successful therapy more correct, then this tendency increases, namely 33.3% in group 1 and 7.1% in group 2; Fisher's exact test is 0.10, which, nevertheless, does not allow us to speak about the statistical significance of the differences.

Along with the study of the frequency of cases of successful therapy depending on the dose of MT, we analyzed the timing of achieving clinical remission in both groups of patients from the moment of initiation of therapy to the moment of successful completion of treatment. In group 1, this indicator was (12.8±0.8) months, in group 2 – (10.1±0.5) months; t=2.84; p<0.02. Thus, in patients treated with MT at a dose of 15 mg/week, the average time spent to achieve the clinical remission was significantly shorter than in patients of group 1 (10 mg/week). This suggests that increasing the dose of MT to 15 mg/week accelerates the rate of regression of pulmonary sarcoidosis.

Regression of sarcoidosis was observed in more than one-third of cases (35.7%) (see table) in patients of group 1 during the treatment period, which gradually passed into the stabilization phase, i.e. a period lasting at least 3 months from the moment of

the last visit during which there was no any CT dynamics of the process. Depending on the nature and severity of pathological changes in the lungs, in the phase of stabilization of sarcoidosis, the observation was carried out with subsequent CT control, the dose of MT was increased to 15 mg/week, or the combined therapy with a first-line drug (pentoxifylline, hydroxychloroquine) was prescribed.

In group 2 patients, there was a tendency towards a decrease in the incidence of stabilization of sarcoidosis against the background of immunosuppressive therapy (2 patients – 12.4%).

It should be noted that the only case of residual fibrotic changes in the lungs after MT therapy at a dose of 15 mg/week was observed in patient S., 27 years old, with an atypical form of pulmonary sarcoidosis – massive consolidations in both lungs, respiratory failure (MRC 3), moderate-severe disorders of pulmonary ventilation and diffusion capacity of the lungs. At the same time, the patient had subcompensated diabetes mellitus, which excluded the possibility of GCS therapy. In this regard, the patient was prescribed a monotherapy with methotrexate at a dose of 15 mg/week resulting in a pronounced positive dynamics of subjective symptoms as soon as at the 2nd visit (after 3 months of

treatment) involving the occurrence of shortness of breath only when performing the usual load (MRC 1), the disappearance of cough, and body temperature normalization. Figure 1 shows a CT

scan of TO (axial slice at the level of tracheal bifurcation): almost complete resorption of consolidations in S_{3,6} of both lungs is clearly visible.

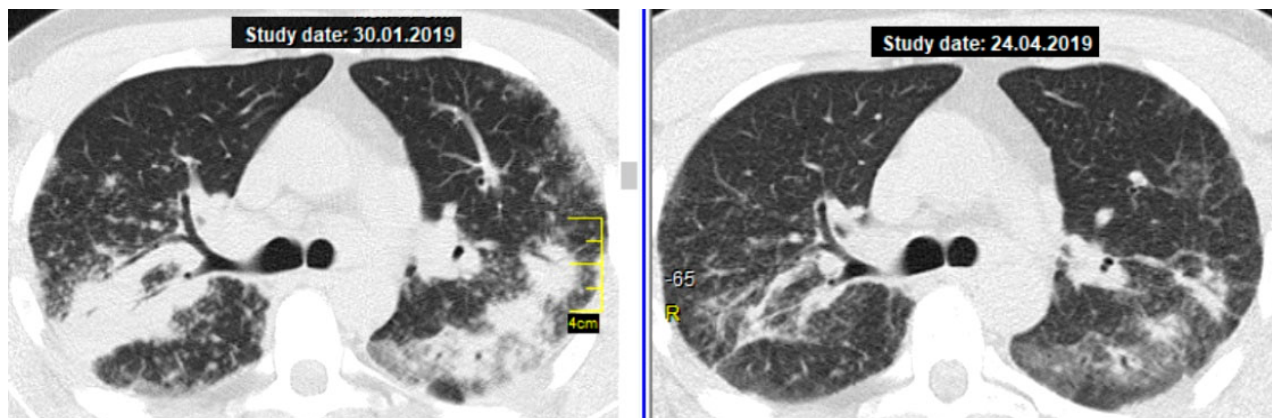


Fig. 1. Patient S., age 27, pulmonary sarcoidosis, stage II, atypical form - multiple massive consolidations in both lungs, respiratory failure (MRC 3); CT of TO (axial slice at the level of tracheal bifurcation): on the left - before treatment, on the right - regression after 3 months of treatment with MT (15 mg/week)

The tolerability of MT was satisfactory: there were no dyspeptic symptoms, at 7 months of the treatment period; moderate leukopenia and slight thrombocytopenia were found during the clinical blood test, while the value of these parameters did

not require the correction of dose and administration schedule of MT.

Figure 2 shows axial CT scans: on the left - on the day of diagnosis, on the right - after the end of MT therapy.

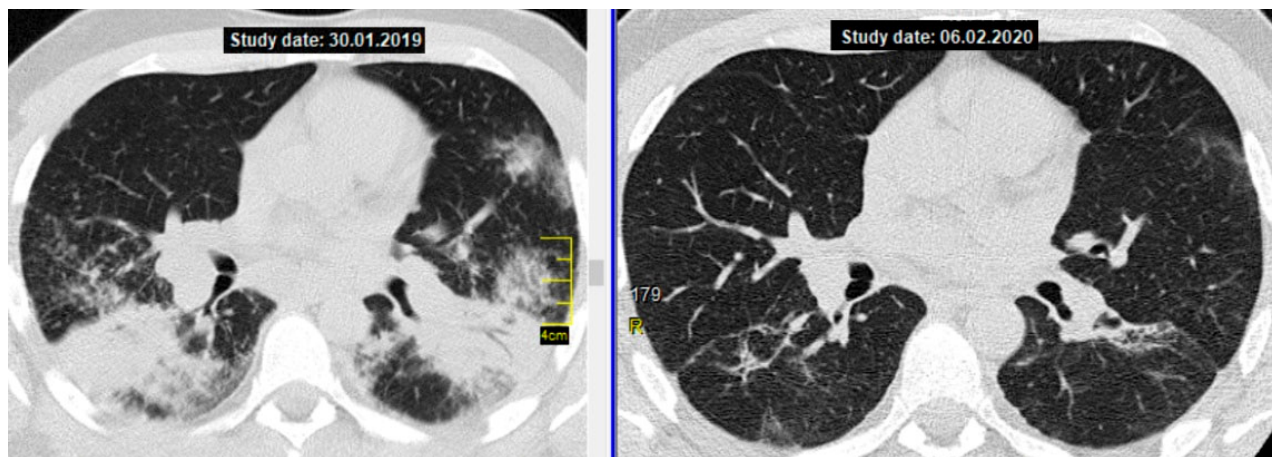


Fig. 2. Patient S., 27 years old, pulmonary sarcoidosis, stage II; CT of TO (axial section at the level of division of the main bronchi). On the left - before treatment, on the right - at the end of treatment with MT (15 mg/week): complete regression with residual changes in the form of limited interstitial pulmonary fibrosis

Side effects of MT at a dose of 10 mg/week were observed in 10 of 28 patients (35.7%).

Severe side effects of MT requiring discontinuation of the drug (drug-induced pneumonitis) or temporary discontinuation followed by the continuation of treatment with this drug at a half dose (more than threefold increase in ALT levels in the blood) were observed in 2 patients (7.1%). Gastrointestinal disorders at the beginning of the treatment

period were observed in 2 cases (7.1%) and were stopped by dividing the dose into two intakes of 5 mg with an interval of 12 hours. In 6 patients, a slight increase in ALT levels (4 cases – 14.1%) and slight thrombocytopenia (2 cases – 7.1%) did not require changes in the therapy regimen.

In group 2, three patients (18.8%) experienced an increase in ALT levels by more than 3 times during treatment. After 5 months of treatment with MT

tablets with regular monitoring of ALT, leukocytes and platelets in the blood, the ALT level of one patient suddenly increased to 386 u/l, in connection with which treatment with MT was stopped, hepatoprotectors and additional examination were prescribed, a positive test for antibodies to the hepatitis B virus was received. Obviously, in the past, the patient suffered this form of hepatitis in a latent form, which could enhance the hepatotoxic effect of MT. After 3 weeks, the blood ALT level returned to normal, the treatment with parenteral MT was continued and successfully completed without any deviations in liver function parameters. In two other patients, an injectable drug was also prescribed after a two-week break, and therefore the ALT level remained within acceptable limits for the entire period of treatment.

In 3 patients (18.8%), a decrease in the number of leukocytes and platelets to a level not requiring an adjustment of the drug dose or the therapy regimen was observed.

Thus, it can be concluded that immunosuppressive therapy of patients with pulmonary sarcoidosis using MT at doses of 10 and 15 mg/week is characterized by satisfactory tolerability.

The limitation for a wider MT prescription in pulmonary sarcoidosis patients is due to a common perception among practicing pulmonologists that MT as opposed to CS results in less pronounced clinical effect and is associated with serious hepatotoxicity and haematotoxicity. In recent years, rebuttal clinical studies were conducted [1, 5, 8].

A retrospective methotrexate efficacy and tolerability study in pulmonary sarcoidosis patients conducted by Fang C. et al. [5] has shown a good clinical response to MT in 80% of patients. Well drug tolerability and low drug withdrawal rate were observed in these patients even without folic acid supplements in clinical practice.

A large retrospective study by Baughman R.P. et al. [8] assessed haematotoxicity and hepatotoxicity of MT at the dose of 10 mg weekly in 607

sarcoidosis patients over a 6-year period. Leukopenia and elevated hepatic transaminases were reported in about 10% of cases. Only one patient had severe leukopenia. Only nine patients were presented with transaminases elevated $>3 \times \text{ULN}$. MT was effective in the majority of these patients. The authors did not reveal other adverse effects resulted in MT withdrawal at that time.

The results of retrospective observational study conducted by Vizel' A.A. et al. [1] allowed to conclude that 15 mg MT weekly per os in patients with advanced sarcoidosis who were previously on systemic GCS is an effective 2nd line drug. The sufficient safety level of MT allows its long-term prescription from 3 months to ≥ 1 year.

Our findings are in line with the above data on methotrexate efficacy and tolerability in the management of patients with pulmonary sarcoidosis. At the same time, we have shown that increasing the MT dose from 10 to 15 mg/week increases the rate of regression of sarcoidosis, improves the effectiveness of treatment and does not affect the rate of serious side effects.

CONCLUSIONS

1. In patients with pulmonary sarcoidosis, the number of cases of clinical cure without residual changes of fibrous nature significantly increases after treatment with methotrexate at a dose of 15 mg/week compared to the same indicator in the group of patients after treatment at a dose of 10 mg/week.

2. An increase in the therapeutic dose of methotrexate from 10 mg/week to 15 mg/week leads to a reduction in time to achieve a state of clinical cure, which indicates acceleration in the rate of regression of sarcoidosis.

3. Immunosuppressive therapy of patients with pulmonary sarcoidosis using methotrexate at doses of 10 and 15 mg/week is characterized by satisfactory tolerance.

Conflict of interests. The authors declare no conflict of interest.

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Стаття надійшла до редакції
10.02.2021