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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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REFRACTORY PULMONARY SARCOIDOSIS: INCIDENCE AFTER TREATMENT WITH METHYLPREDNISOLONE AND/OR METHOTREXATE IN PATIENTS WITH NEWLY DIAGNOSED DISEASE

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Abstract.

Introduction: Pulmonary sarcoidosis is considered refractory if glucocorticoids (GCs) at a maintenance dose of at least 10 mg/day (prednisolone equivalent) and methotrexate (MTX), including their combined use, are not effective enough to achieve clinical remission.

Aim: To study the rate of refractory pulmonary sarcoidosis after conventional treatment with methylprednisolone (MP) and/or MTX in patients with newly diagnosed disease.

Materials and Methods: 250 patients with newly diagnosed pulmonary sarcoidosis (106 men and 144 women; mean age 44 years) were examined. Radiological stage II was established in 237 (94.8%) patients, stage III – in 13 (5.2%). GCs therapy was carried out using MP in 190 patients at an initial dose of 0.4 mg/kg/day for 4 weeks with a gradual decrease to a maintenance dose (0.1 mg/kg/day) by the end of the 6th month. In the presence of contraindications or serious adverse effects of MP (60 patients), MTX was used at a dose of 15 mg/week. Patients without contraindications and serious adverse effects of MP treated with MTX, in case of initial therapy failure, were prescribed combined therapy with MP (12 mg/day) and MTX (10 mg/week).

Results: Based on combination therapy outcomes, as well as taking into account the cases of MTX therapy failure in patients with contraindications or serious adverse effects of GCs therapy, refractory pulmonary sarcoidosis was diagnosed in 27 (10.8%) patients. Patients with refractory pulmonary sarcoidosis were more likely to have stage III disease (Pearson's $\chi 2$ test = 5.766, p = 0.018), as well as extrapulmonary lesions ($\chi 2$ test = 4.672, p = 0.031).

Conclusion: The high rate of conventional therapy failure using first- and second-line medications in patients with newly diagnosed sarcoidosis determines the relevance of further study of the causes, development of risk criteria and new approaches to the treatment of refractory pulmonary sarcoidosis.

Key words. Refractory pulmonary sarcoidosis, incidence, methylprednisolone, methotrexate.

Introduction.

Sarcoidosis is a multisystem disorder of unknown cause(s). It commonly affects young and middle-aged adults and frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions. The liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones, and other organs may also be involved. The diagnosis is established when clinical and radiological findings are supported by histological evidence of noncaseating epithelioid cell granulomas [1,2]. In 2021, the ERS Task force report "ERS clinic practice guidelines on treatment of sarcoidosis" was published, which identified completely new approaches to the treatment of patients with sarcoidosis [3]. The main principle of treatment of patients with pulmonary sarcoidosis is to achieve a balance between: a) minimizing the risk of disability, death due to lung damage or reduced quality of life; and b) the risk of comorbidity and a decrease in the quality of life as a result of the effects of GCs and other types of therapy [3].

According to the European Respiratory Society (ERS) 2021 guidelines, GCs remain the first-line therapy for patients with pulmonary sarcoidosis. In the treatment of pulmonary sarcoidosis without an involvement of heart, central nervous system (CNS), and eyes, GCs are used in medium doses (the initial dose is usually 0.5 mg/kg of body weight per day, prednisolone equivalent, for at least 4 weeks). The dose is then tapered within 8 weeks so that by the end of the third month it is 0.25 mg/kg. After 3 months from the start of treatment, its efficacy is assessed. If clinical and radiological condition improved, the dose should gradually be tapered to 0.125 mg/kg by the end of the 6th month. During the subsequent period of treatment, the dose remains unchanged [4].

However, some patients may have contraindications to GCs. In addition, GCs therapy may be not effective or lead to the development of serious adverse effects. In such cases, treatment with a second-line drug MTX is recommended. If GCs and MTX failed, treatment with the third-line drug infliximab should be suggested [3].

About 5% of patients with sarcoidosis die of this disease [3,5,6]. Pulmonary and cardiac complications are the most common causes of death from sarcoidosis in its chronic course, which in turn is due to refractoriness.

There is no generally accepted definition of refractory sarcoidosis, and there are no recommendations for its treatment.

In 2016, Korsten et al. proposed the following definition for refractory pulmonary sarcoidosis:

1. Progressive pulmonary disease despite GCs therapy at adequate dosage defined as at least 10 mg of prednisone once a day and duration of therapy of at least 3 months after initial dosages of 20–40 mg per day for 1–3 months and need for additional therapy due to lack of efficacy, GCs toxicity or severe side effects

2. Treatment started for impaired quality of life due to progressive pulmonary symptoms with or without additional disease manifestations (e.g., disfiguring disease, neurosarcoidosis, etc.) [7].

Thus, this definition of refractory sarcoidosis is limited only to refractoriness to GCs therapy without considering the potential effect of alternative (MTX) treatment. Goldman and Judson proposed to use the term "Corticosteroid refractory sarcoidosis" to characterize this disease state [8].

In the STAT cohort (sarcoidosis treated with tumour necrosis factor antagonists), refractory sarcoidosis was defined as a

condition in which second-line immunosuppressants were not sufficient to achieve satisfactory control of the disease [9].

In a prospective trial, Sweiss et al. defined refractory pulmonary sarcoidosis as the disease in patients with symptomatic sarcoidosis taking GCs over 10 mg/day or symptomatic sarcoidosis with a GCs sparing agent [10].

El Jammal et al suggested to define refractory sarcoidosis as a situation in which GCs and second-line treatment(s) (MTX, azathioprine, leflunomide, antimalarials, or mycophenolate mofetil) are not sufficient to achieve clinical remission with a GCs dosage under 10 mg/day [11].

Considering the 2021 ERS recommendations providing for MTX only as a second-line drug, and considering the need for a combination treatment in cases of monotherapy failure, the definition by El Jammal et al. can be formulated as follows:

Pulmonary sarcoidosis should be considered refractory if GCs at a maintenance dose of at least 10 mg/day (prednisolone equivalent) and MTX, including their combined use, are not effective enough to achieve clinical remission.

Below are the main options of therapy failure, to be considered refractory pulmonary sarcoidosis.

1. Insufficient efficacy of MTX monotherapy prescribed as a starting agent due to contraindications to GCs, or due to serious adverse effects of GCs.

2. Insufficient effectiveness of combination therapy using GC and MTX, prescribed due to resistance to GCs.

Data on the incidence of refractory sarcoidosis are highly variable, ranging from 10% to 20–40% of patients after GCs treatment, including GCs sparing agents [7,12].

Aim.

The aim was to study the rate of refractory pulmonary sarcoidosis after treatment with MP and/or MTX in patients with newly diagnosed disease.

Materials and Methods.

250 patients with pulmonary sarcoidosis (general group) were examined, including 106 men (42.4 %) and 144 women (57.6 %), mean age 44 years (22–74). Radiological stage II was established in 237 (94.8 %) patients, stage III – in 13 (5.2 %).

In accordance with an official document of American Thoracic Society (ATS) “Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline” [13], the diagnosis of sarcoidosis was based on three main criteria: compatible clinical manifestations, the presence of non-necrotizing granulomatous inflammation in one or more tissue samples (if a lung biopsy was necessary), and the exclusion of alternative causes of granulomatous process.

All patients were examined by high-resolution computed tomography (CT) using an Aquilion TSX-101A multislice CT scanner (Toshiba). CT results were evaluated using the criteria described by Veltkamp and Grutters [14].

The main criterion for inclusion of patients in the study was the diagnosis of newly diagnosed pulmonary sarcoidosis without any prior specific therapy. The second important inclusion criterion was the absence of CT signs of interstitial lung fibrosis, which allows to exclude patients with a long-term disease with the maximum probability.

Table 1. *Extrapulmonary manifestations of sarcoidosis.*

Extrapulmonary lesions	n	%
Skin	17	6.8
Liver	5	2.0
Peripheral lymph nodes	4	1.6
Joints	3	1.2
Heart	3	1.2
Bones	3	1.2
CNS	1	0.4
Eyes	1	0.4
In total	37	14.8

Extrapulmonary manifestations of sarcoidosis were observed in 14.8 % of patients (Table 1). At the same time, skin lesions were more often observed (6.8 %).

Treatment of patients with pulmonary sarcoidosis was prescribed according to the recommendations of the Regulations of the ATS, ERS and the World Association of Sarcoidosis and Other Granulomatous Diseases (WASOG) "Statement on Sarcoidosis", 1999 [2] and the national clinical protocol "Sarcoidosis" (2014). Patients with newly diagnosed pulmonary sarcoidosis are prescribed first-line medications (GCs) in the following cases:

- At all stages of sarcoidosis with extrapulmonary manifestations – sarcoidosis of heart, CNS, eyes.
- At stage II sarcoidosis with clinical manifestations (cough, shortness of breath, chest pain, decreased physical activity) and/or with moderate lung function impairment.
- Progression of the disease according to CT data (enlargement of lymph nodes, increase in areas of parenchymal lesions) after a 3-month follow-up period after spontaneous remission.
- At stage III of the disease, spontaneous remissions are relatively rare in this category of patients. In addition, most patients with stage III sarcoidosis have pronounced clinical manifestations (shortness of breath, cough), impaired ventilation and diffusing capacity of the lungs.

It should be noted that the above indications for GC therapy are in compliance with ERS 2021 recommendations [3].

GCs therapy using MP was initiated in 190 patients (Group 1 - MP). The initial MP dose was 0.4 mg/kg daily for 4 weeks, and then the dose was gradually reduced to 0.2 mg/kg by the end of the 3rd month and to 0.1 mg/kg (maintenance dose) by the end of the 6th month. After the achievement of clinical cure phase, MP therapy at a dose of 0.1 mg/kg/day continued for at least 6 months. Since in the majority of patients the normalization of the clinical condition and CT data usually occurs at the 3rd visit (after 6 months of treatment), the total duration of GCs therapy was at least one year on average.

Based on the data of numerous studies on the efficacy and safety of MTX in patients with pulmonary sarcoidosis, including large retrospective studies, MTX was prescribed in the presence of contraindications to GCs therapy [3,15-18]. The following contraindications for GCs use were established: diabetes mellitus, osteoporosis, severe arterial hypertension, peptic ulcer of the stomach and duodenum, thrombophlebitis, mental diseases. MTX as monotherapy was also prescribed in cases of serious adverse effects of GCs (uncontrolled hyperglycemia,

mental disorders, osteoporosis). Eighteen patients with newly diagnosed pulmonary sarcoidosis had a negative attitude towards long-term systemic hormonal therapy, and therefore preferred the alternative treatment with MTX. In total, MTX monotherapy was used in 60 patients (Group 2 - MTX).

MTX was prescribed at a dose of 15 mg once a week. Before starting therapy and monthly during treatment, a complete blood count and blood chemistry were performed to determine the concentration of ALT, creatinine, leukocytes, and platelets.

Treatment outcomes were assessed on the basis of clinical examination and CT scans at 3, 6, and 12 months of therapy and until clinical cure was achieved. With the disease progression or the absence of a positive effect of GCs (improvement) after 6 months of treatment, patients were prescribed combination therapy: MP at a dose of 12 mg/day daily and MTX at a dose of 10 mg weekly. A group of patients without contraindications and serious adverse effects of MP who received MTX, with initial therapy failure, was also prescribed combination therapy.

In patients with progression or stabilization of the disease, despite the combined therapy for 6 months, the course of pulmonary sarcoidosis was assessed as refractory. In addition, a few cases of MTX monotherapy failure in patients with contraindications or serious adverse effects of GCs were considered refractory sarcoidosis.

Statistical methods.

Pearson's $\chi 2$ test was used to compare data on categorical variables presented as numbers and percentages. All measurements were two-sided with a significance level of $p < 0.05$.

Results.

Analysis of treatment outcomes in patients with newly diagnosed pulmonary sarcoidosis showed that the therapy was effective in 188 (75.2 %) patients. At the same time, treatment with MTX did not significantly differ from GCs therapy with MP in terms of the success rate (Table 2).

Resistance to GCs therapy (progression or stabilization during treatment) was observed in 55 (28.9%) patients. MTX therapy failure was observed significantly less frequently (7 patients - 11.7%; $\chi 2$ test = 7.300; $p = 0.007$), predominantly in patients with macronodular lesions of the parenchyma.

Combination therapy with MP and MTX was prescribed due to the insufficient efficacy of GCs therapy, and in patients from the MTX group who had no contraindications or serious adverse effects of GCs requiring the MP discontinuation.

Based on the outcomes of combination therapy, as well as considering cases of MTX failure in patients with contraindications or serious adverse effects of GCs therapy, refractory pulmonary sarcoidosis was diagnosed in 27 (10.8%) patients.

Table 3 shows the characteristics of patients with refractory pulmonary sarcoidosis.

As it can be seen from the table, women prevailed (66.7 %) among patients with refractory pulmonary sarcoidosis, the average age was 46 years (25–74), same as in general group. Patients with refractory pulmonary sarcoidosis were significantly more likely to have stage III disease, as well as extrapulmonary lesions.

Table 2. *Treatment outcomes.*

Outcomes	**General Group (n = 250)**	**Group 1 – MP (n = 190)**	**Group 2 – MTX (n = 60)**
Clinical remission with CT data normalization	188 (75.2 %)	135 (71.1 %)	53 (88.3 %)
Progression or stabilization of the disease	62 (24.8 %)	55 (28.9 %)	7 (11.7 %)

Table 3. *Characteristics of patients with refractory pulmonary sarcoidosis.*

Characteristics of patients	**Successful therapy n = 223**	**Refractory sarcoidosis n = 27**	**χ^2 test**
Median age (range)	44 (22–74)	46 (25–74)	n/a
Males	97 (43.5 %)	9 (33.3 %)	1.019 p=0.313
Females	126 (56.5 %)	18 (66.7 %)	1.019 p=0.313
Radiological stage II	214 (96 %)	23 (85.2 %)	5.766 p=0.018*
Radiological stage III	9 (4 %)	4 (14.8 %)	5.766 p=0.018*
Extrapulmonary lesions	25 (11.2 %)	7 (25.9 %)	4.672 p=0.031*
Including: skin	15 (6.7 %)	2 (7.4 %)	0.018 p=0.895
liver	4 (1.8 %)	1 (3.7 %)	0.448 p=0.504
joints	2 (0.9 %)	1 (3.7 %)	1.600 p=0.206
heart	2 (0.9 %)	1 (3.7 %)	1.600 p=0.206
bones	2 (0.9 %)	1 (3.7 %)	1.600 p=0.206
CNS	0	1 (3.7 %)	8.292 p=0.004*

Discussion.

Most investigators consider pulmonary sarcoidosis to be refractory when first-line medicinal products (GCs) at a maintenance dose of at least 10 mg/day (prednisolone equivalent) and second-line medicinal products (MTX), including their combined use, are not effective enough to achieve clinical remission [9,10,11].

Goldman and Judson proposed considering all cases of disease progression at the stage of tapering the dose of GCs from initial to the maintenance one (at least 10 mg/day prednisolone equivalent) “corticosteroid refractory sarcoidosis” [8].

Significant variability in the incidence of refractory sarcoidosis seems to be due to the lack of generally accepted criteria for the diagnosis, as well as the inclusion of patients with a different course of sarcoidosis, from newly diagnosed to chronic with a long history of the disease, in the study.

The main inclusion criterion in our study was the diagnosis of newly diagnosed sarcoidosis without previous specific therapy, as well as the absence of CT signs of interstitial pulmonary

fibrosis in order to exclude patients with a long history of the disease.

Even though the criteria for the diagnosis of sarcoidosis and the methods of treatment corresponded to international standards, refractory sarcoidosis after treatment with MP and/or MTX was observed in a significant proportion of cases - in 10.8 % of patients [2,3,13].

Conclusion.

The high rate of conventional therapy failure in patients with newly diagnosed pulmonary sarcoidosis using first- and second-line medications determines the relevance of further study of the causes, development of risk criteria and new approaches to the treatment of refractory pulmonary sarcoidosis.

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Conflict of interest.

The authors declare that they have no conflict of interest.

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Цель: изучить частоту рефрактерного саркоидоза легких после стандартного лечения метилпреднизолоном (МП) и/или МТХ у пациентов с впервые диагностированным заболеванием. **Материалы и Методы:** Обследовано 250 больных впервые диагностированным саркоидозом легких (106 мужчин и 144 женщины; средний возраст – 44 года. II рентгенологическая стадия была установлена у 237 (94,8 %) больных, III – у 13 (5,2 %). GC-терапия проводилась с использованием МП у 190 больных в начальной дозе 0,4 мг/кг/день в течение 4-х недель с постепенным ее снижением до поддерживающей (0,1 мг/кг/день) к концу 6-го месяца. При наличии противопоказаний или серьезных побочных эффектов МП (60 пациентов), применяли МТХ в дозе 15 мг/нед. Пациентам без противопоказаний и серьезных побочных эффектов МП, получавших МТХ, при неэффективности инициальной терапии назначали комбинированную терапию МП (12 мг/день) и МТХ (10 мг/нед). **Результаты:** По результатам комбинированной терапии, а также с учетом случаев неуспешной МТХ терапии у пациентов с противопоказаниями или серьезными побочными эффектами GC терапии, рефрактерный саркоидоз легких был констатирован у 27 (10,8 %) пациентов. У больных с рефрактерным саркоидозом легких чаще отмечалась III стадия заболевания (критерий χ^2 Пирсона = 5,766, p =

0,018), а также экстрапульмональные поражения (критерий $\chi^2 = 4,672$, $p = 0,031$).

Заключение: Высокая частота случаев неуспешной стандартной терапии препаратами первой и второй линии у пациентов с впервые диагностированным саркоидозом обусловливает актуальность дальнейшего изучения причин, разработки критериев риска и новых подходов к лечению рефрактерного саркоидоза легких.

Ключевые слова: Refractory pulmonary sarcoidosis, incidence, methylprednisolone, methotrexate.