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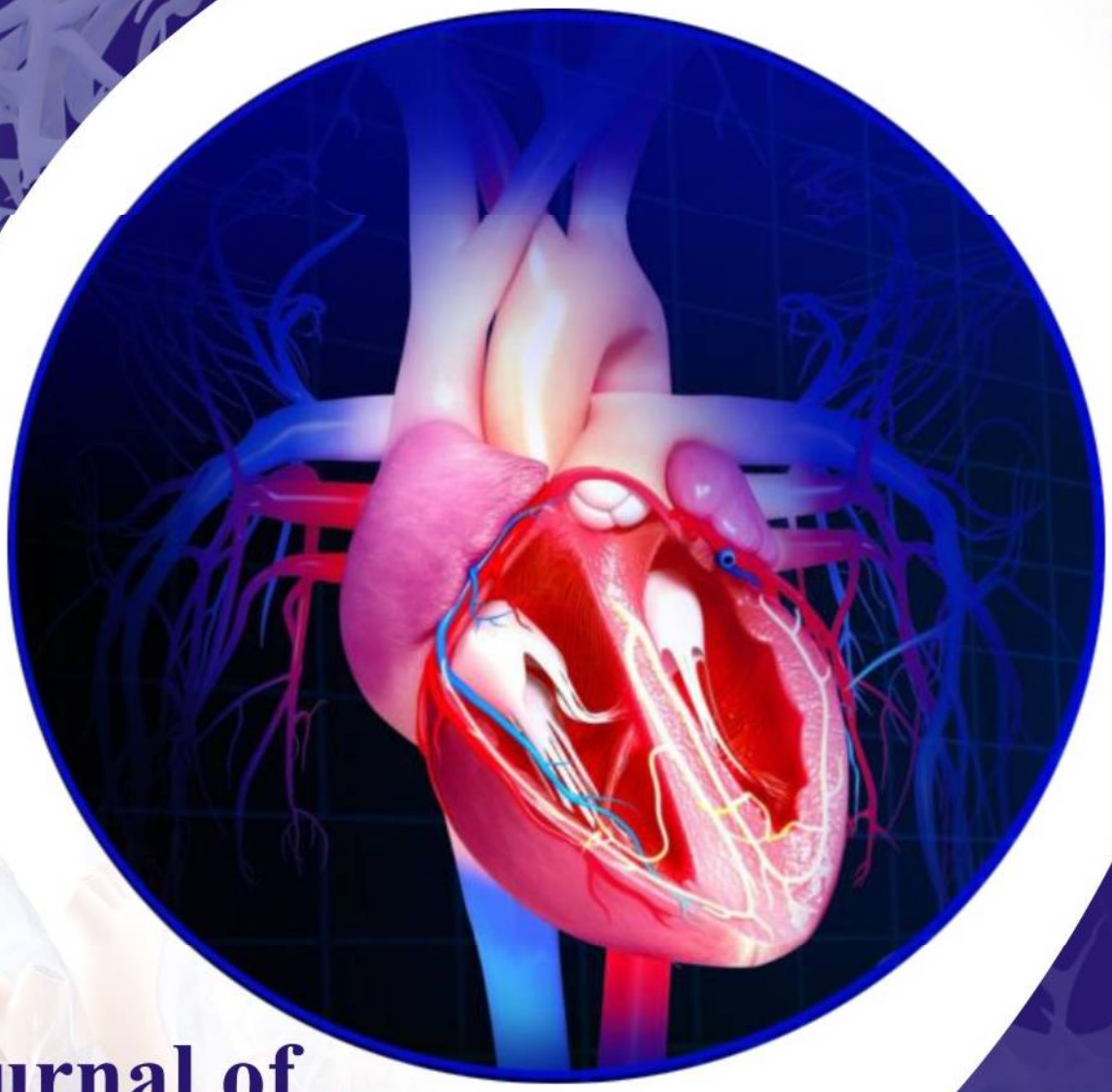

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АССОЦИАЦИЯ ТЕРАПЕВТОВ УЗБЕКИСТАНА

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ УЗБЕКИСТАН

САМАРКАНДСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ

# ИННОВАЦИОННЫЕ ТЕХНОЛОГИИ В ЗДРАВООХРАНЕНИИ:
## НОВЫЕ ВОЗМОЖНОСТИ ДЛЯ ВНУТРЕННЕЙ МЕДИЦИНЫ

**МАТЕРИАЛЫ**

международной научно-практической конференции
(Самарканд, 22 апреля 2022 г.)

Под редакцией
Ж.А. РИЗАЕВА

# ТОМ I

Самарканд-2022

## ОРГАНИЗАЦИОННЫЙ КОМИТЕТ КОНФЕРЕНЦИИ

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## РЕДАКЦИОННАЯ КОЛЛЕГИЯ:

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**Инновационные технологии в здравоохранении: новые возможности для внутренней медицины:** Материалы международной научно-практической конференции (г. Самарканд, 22 апрель 2022 г.) / отв. ред. РИЗАЕВ Ж.А. - Самарканд: СамГМУ, 2022. – 736 с.

В сборнике собраны материалы, которые содержат статьи и тезисы докладов, представленных на международной научно-практической конференции «Инновационные технологии в здравоохранении: новые возможности для внутренней медицины», проведенной в СамГМУ 22 апрель 2022 г. Значительная часть материалов отражает современные проблемы внутренней медицины, посвященные поиску эффективных методов диагностики, лечения и профилактики заболеваний внутренних органов.

Представленные материалы будут интересны специалистам всех направлений внутренней медицины и широкому кругу читателей, интересующихся вопросами возникновения и профилактики основных заболеваний терапевтического профиля.

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ
РЕСПУБЛИКИ УЗБЕКИСТАН

# ЖУРНАЛ КАРДИОРЕСПИРАТОРНЫХ ИССЛЕДОВАНИЙ

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# ОБНОВЛЕННЫЙ ПОДХОД К ЛЕЧЕНИЮ РЕВМАТОИДНОГО АРТРИТА НА РАННИХ СТАДИЯХ

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**АННОТАЦИЯ**

**Цель:** оптимизировать методы базисного лечения раннего ревматоидного артрита (РА).

**Материалы и методы**. В исследование включено 90 больных РА со значительным течением заболевания до 3 лет. Методом случайного распределения пациенты были рандомизированы на три группы: 1-я группа монотерапии метотрексатом (МТХ) 10-20 мг/нед (МТХ; n=40); 2-я группа — МТ в сочетании с малыми дозами глюкокортикостероидов (ГК) преднизолона в дозе 10 мг в сутки перорально (МТ + ГК; n = 30); 3-я группа - монотерапия лефлуномидом (ЛФ) 20 мг/сут (ЛФ; n=20). Больным разрешалось продолжать прием нестероидных противовоспалительных препаратов (НПВП) в прежних дозах, а также наружное применение противовоспалительных препаратов, лечебную физкультуру, физиотерапию и трудотерапию по требованию. При необходимости проводят внутрисуставные ГК, но не чаще 1 раза в 1 мес с использованием 1 мл дипроспана на одно введение. Всем больным до лечения и в последующем проведено стандартное клиническое, лабораторное и инструментальное обследование. Общую активность заболевания оценивают по индексу DAS28, рекомендованному EULAR с выделением 4 основных полномочий.

**Результаты.** Отмечена положительная динамика основных клинико-лабораторных проявлений раннего РА под влиянием всех анализируемых терапевтических возможностей. Таким образом, достоверное снижение активности заболевания по сравнению с исходным уровнем сохранялось через 3, 6 и 12 мес лечения. Это свидетельствует о значительном и длительном терапевтическом эффекте как при монотерапии ЛФ и метотрексатом, так и при сочетании метотрексата с ГК.

**Заключение.** Все изученные варианты терапии больных ранним РА продемонстрировали значительную эффективность и вполне приемлемую безопасность. Поэтому каждая из схем может быть использована для лечения этих больных с высокой вероятностью достижения значимого улучшения.

**Ключевые слова:** ранний ревматоидный артрит, комбинированная терапия, базисные противовоспалительные препараты.

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# RENEWED APPROACH TO MANAGMENT OF RHEUMATOID ARTHRITIS IN EARLY STAGES

**ANNOTATION**

**Objective:** To optimize the methods of the basic treatment of early rheumatoid arthritis (RA).

**Material and methods:** The study included 90 patients with significant RA disease with duration up to 3 years. By random assignment, patients were randomized into three groups: 1st group monotherapy with methotrexate (MTX) 10-20 mg / week (MTX; n = 40); 2nd group – MTX combined with small doses of glucocorticosteroids (GC) prednisolone in a dose of 10 mg per day orally (MTX + GC; n = 30); 3rd group - monotherapy with leflunomide (LF) 20 mg / day (LF; n = 20). Patients were allowed to continue taking nonsteroidal anti-inflammatory drugs (NSAIDs) in the previous doses, as well as external using of anti-inflammatory drugs, exercise therapy, physiotherapy and occupational therapy if demanded,. If necessary, conducted intra-articular GC, but no more than 1 per in 1 month using 1 ml diprospan per administration. All patients before treatment and during follow-held standart clinical, laboratory and instrumental examination. Total activity of disease assessed by DAS28 index which recommended by the EULAR with the release of the 4 major powers.

**Results:** The positive dynamics of the basic clinical and laboratory manifestations of early RA under the influence of all analyzed therapeutic options was evident. Thus a significant reduction of disease activity as compared to baseline was maintained at 3, 6 and 12 months of treatment. This represents a significant and long-term therapeutic effect as monotherapy LF and MTX as well as combination MTX with GC.

**Conclusion:** All the studied variants of therapy in patients with early RA have demonstrated a significant efficacy and a very reasonable safety. Therefore, each of the schemes can be used to treat these patients with a high probability of achieving a significant improvement.

**Keywords:** early rheumatoid arthritis, combination therapy, the basic anti-inflammatory drugs.

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## REVMATOID ARTRITNING ERTA BOSHQACHILARINI DAVOLASHGA YANGILANGAN YONDASHUVLAR

**ANNOTATSIYA**

**Maqsad:** erta revmatoid artritni (RA) asosiy davolash usullarini optimallashtirish.

**Materiallar va usullar.** Tadqiqotga kasallikning sezilarli kursi 3 yilgacha bo'lgan 90 nafar RA bemorlari kiritilgan. Bemorlar tasodifiy uchta guruhga ajratildi: 1-guruh metotreksat monoterapiyasi (MTX) 10-20 mg / hafta (MTX; n = 40); 2-guruh - og'iz orqali kuniga 10 mg dozada glyukokortikosteroidlar (GC) prednizolonning past dozalari bilan birgalikda MT (MT + GC; n = 30); 3-guruh - leflunomid (LF) 20 mg/kun (LF; n=20) bilan monoterapiya. Bemorlarga steroid bo'lmagan yallig'lanishga qarshi dori-darmonlarni (NSAID) bir xil dozalarda qabul qilishni davom ettirishga, shuningdek, yallig'lanishga qarshi dori-darmonlarni, jismoniy mashqlar bilan davolashni, jismoniy terapiya va kasbiy terapiyani talab bo'yicha tashqi foydalanishga ruxsat berildi. Agar kerak bo'lsa, intraartikulyar GKlar o'tkaziladi, lekin har bir in'ektsiya uchun 1 ml diprospan yordamida 1 oyda 1 martadan ko'p bo'lmagan. Barcha bemorlar davolanishdan oldin va undan keyin standart klinik, laboratoriya va instrumental tekshiruvdan o'tdilar. Kasallikning umumiy faolligi EULAR tomonidan tavsiya etilgan DAS28 indeksi bo'yicha 4 ta asosiy vakolatni taqsimlash bilan baholanadi.

**Natijalar.** Barcha tahlil qilingan terapevtik variantlar ta'siri ostida erta RA ning asosiy klinik va laboratoriya ko'rinishlarining ijobiy dinamikasi qayd etildi. Shunday qilib, 3, 6 va 12 oylik davolanishdan keyin boshlang'ich bilan solishtirganda kasallik faolligining sezilarli pasayishi davom etdi. Bu LF va metotreksatning monoterapiyasida ham, metotreksatning GC bilan kombinatsiyasida ham sezilarli va uzoq muddatli terapevtik ta'sirni ko'rsatadi.

**Xulosa.** Erta RA bo'lgan bemorlarni davolashning barcha o'rganilgan variantlari sezilarli samaradorlik va maqbul xavfsizlikni ko'rsatdi. Shuning uchun, rejimlarning har biri sezilarli yaxshilanishga erishish ehtimoli yuqori bo'lgan ushbu bemorlarni davolash uchun ishlatilishi mumkin.

**Kalit so'zlar:** erta revmatoid artrit, kombinatsiyalangan terapiya, asosiy yallig'lanishga qarshi dorilar.

**Introduction.** One of the most significant features of RA is a progressive course, which is accompanied by significant variability of the clinical picture. The progression of the disease leads to the generalization of the pathological process with the involvement of new joints and extra-articular structures, the formation of irreversible changes, as well as a violation of susceptibility to therapy. As the duration of the disease increases, persistent defects of the musculoskeletal system form, which cannot be eliminated with the help of drug therapy. These include destruction, subluxations and contractures of the joints, which in themselves can cause severe functional impairment and a decrease in the quality of life of patients [1].

It is known that the most aggressive course of RA is observed in the first few years after the onset of the disease. According to a biopsy of the synovial membrane of the joints, signs of chronic synovitis are detected at the very beginning of the disease, often even in clinically unaffected joints [2]. It is currently postulated that in the early period of RA, the reversibility of the disease is significantly higher due to the incompleteness of pathological autoimmune mechanisms and the absence of intra-articular pannus (the basis for the development of articular destruction) [3]. The period from the initiation of rheumatoid inflammation in the joints to the formation of pannus can be considered a morphological basis for the isolation of early RA, from a clinical point of view, this is the period from the moment the first signs of arthritis appear until the development of destructive changes in bone tissue [4]. The problem of early RA today is one of the most urgent for rheumatology. Early RA is a conditionally distinguishable clinical and pathogenetic stage of the disease without a clear time frame. Historically, early RA was considered a disease with a prescription of no more than 5 years, but since the 1990, this period has been reduced to 2 years or less and now tends to further decrease [5].

Judging by the data of clinical studies, the first 6 months of the disease is the time when the effect of basic drugs can be most pronounced and urgent measures are required to suppress RA activity. At this stage, the likelihood of spontaneous and drug-induced remissions, which are accompanied by a slowdown in the progression of pathological changes, is especially high. Therefore, the total duration of the early stage is largely determined by the characteristics of clinical symptoms and can significantly increase in the background of effective therapy.

At the same time, the variability of clinical symptoms at an early stage of RA can significantly complicate the diagnosis and delay the appointment of adequate therapy. The most typical, but far from universal, variant of the onset of the disease is symmetric arthritis with damage to the joints of the hands and feet. RA can also begin with pronounced general manifestations, such as fatigue, fever, weight loss, which in some cases are several weeks or months ahead of the appearance of the classic signs of joint inflammation [6]. Sometimes the disease begins as palindromic rheumatism with recurrent episodes of acute synovitis that occur suddenly, subside after 1-2 days and are usually limited to the involvement of one joint. Only 50% of these patients subsequently develop a typical picture of RA [7].

According to leading experts, there is an undoubted relationship between RA activity and the rate of its progression [8]. In this case, the correlation between the indicators of activity and the development of functional disorders is most pronounced in the first years of the course of the disease. It is during this period, while maintaining the activity of the disease, there is a risk of developing serious structural damage to the joints, which is irreversible and further leads to violations of biomechanics and a significant decrease in the quality of life even with a decrease in activity. Therefore, it is so important to suppress RA activity as fully and as soon as possible, ideally in the first months after the onset of the initial symptoms.

Currently, it is widely recognized that an improvement in the prognosis of RA is possible only under the condition of careful monitoring of the development of the disease [9]. This approach allows you to quickly respond to a possible lack of efficiency, the development of unfavorable reactions or complications of the disease [10]. The main goal of RA treatment is to achieve the lowest possible activity or remission of the disease [11]. Modern pharmacotherapy of RA is based on the targeted suppression of the immune-inflammatory process, which determines the rate of joint destruction, the development of life-threatening systemic complications and the formation of severe changes in the musculoskeletal system.

Adequate, individualized treatment of RA is impossible without a correct understanding of the relationship between the main clinical, functional and radiological parameters in this disease. However, such information can only be obtained as a result of long-term monitoring of the course of RA, which makes

it possible to one degree or another to predict the outcome and response to therapy and allows choosing the optimal tactics for managing patients [12].

Prescribing basic anti-inflammatory drugs (DMARDs) in the early period of the disease not only leads to a pronounced clinical effect and inhibition of joint destruction, but also prevents an increase in mortality inherent in patients with RA. The theoretical concept of the initial period of RA as a window of opportunity for the most successful treatment of the disease is confirmed by a significantly higher frequency of remissions with early prescription of basic therapy.

At the same time, among the classic DMARDs, MTX and LF come to the fore, the high efficiency of which has been confirmed in double-blind studies. At the same time, a number of issues of early RA therapy have not been finally resolved. First of all, the comparative efficiency of MTX and LF in these patients remains unclear. There is no final opinion on the advisability of combining GC with these drugs in the early stages of RA, although some authors point to a higher result of this combination. Therefore, despite the noticeable progress achieved in the treatment of RA in recent years, there are no detailed recommendations for the treatment of early RA in clinical practice. The recommendations of the European Antirheumatic League (EULAR) emphasize that there is no direct evidence of the advantage of MTX over other DMARDs in the treatment of early RA, but at the same time, Lf is considered its best alternative. Similarly, there have been no direct comparative studies of the systemic administration of GC to patients with early RA [13].

**The aim** of this work is to optimize the methods of basic therapy for early RA.

**The objectives** of the study were: 1) to assess the clinical efficacy and tolerability of three schemes of therapy: monotherapy with MTX, MTX and LF, and a combination of MT with low doses of GC 2) based on the results obtained, give a comparative assessment of the studied therapy regimens.

**Material and methods.** The study included 90 patients with reliable RA with a disease duration of up to 3 years. Among them were 82 women and 8 men aged 20 to 71 years (mean age 42.4 ± 9.8). The duration of the disease varied from 6 to 96 weeks. 70 patients were seropositive for rheumatoid factor (RF); the average DAS 28 was 5.8. Thus, among the patients, women (90%) of middle age predominated with a very high RA activity and the presence of RF. They were randomly assigned to three groups:

1st group - MTX monotherapy at 10–20 mg / week. (MTX; n = 40);

2nd group - MTX in combination with low doses of GC (prednisolone at a dose of 10 mg per day orally (MTX + GC; n = 30);

3nd group - Lf monotherapy in 20 mg / day. (LF; n = 20).

Patients were allowed to continue taking non-steroidal anti-inflammatory drugs (NSAIDs) in the same doses, as well as to use external anti-inflammatory drugs, exercise therapy according to indications, physical and occupational therapy. If necessary, intra-articular GC was administered, but no more than once every 1 month. using no more than 1 ml of diprospan per injection. All patients underwent standard clinical, laboratory and instrumental examination before treatment and during the observation process. Patient visits were carried out according to the schedule, with a tolerance of 2 weeks. The laboratory examination included a general clinical and biochemical blood test, an immunological blood test: determination of the concentration of C-reactive protein (CRP), RF, IgM, antibodies to cyclic citrullinated peptide (ACCP) and a general urinalysis. Clinical examination and all of the above analyzes were performed before the start of treatment and then after 3, 6 and 12 months. therapy.

To determine the activity of the disease and the effectiveness of RA therapy, the following indicators were used [14].

1) the severity of pain in the joints, assessed by the patient on a visual analogue scale (VAS), where 0 is taken to be the absence of pain, and 100 mm is the maximum intensity of pain;

2) the number of painful joints (PJ) - the number of joints painful on palpation (from 0 to 68);

3) the number of inflamed joints (IJ), determined by visual assessment and palpation (from 0 to 66);

4) the severity of the condition according to the separate assessment of the patient and the doctor according to the VAS (0 - well-being, 100 mm - the most bad state of health);

5) ESR (mm / h) according to Westergren.

The overall activity of the disease was assessed according to the recommended EULAR indexed by DAS28 with the allocation of 4 main degrees [15]. The functional status of the patient was determined according to the Stanford Health Assessment Questionnaire (1980), which consisted of 8 groups of

questions (dressing, body care, lifting and standing, flexibility, eating, walking, hygiene, gripping with a brush, general activity). The EULAR criteria were used to summarize the effectiveness of antirheumatic therapy.

A good effect of therapy corresponds to a decrease in DAS28 by more than 1.2 with its final value <3.2 points. The effect was assessed as satisfactory with a decrease in DAS28 by 0.6–1.2 and a final DAS28 from 3.2 to 5.1. With a decrease in DAS28 by 0.6–1.2 points and persisting high disease activity (DAS28> 5.1), the patient was considered not responding to treatment. To assess the tolerability of the drugs used, the hemoglobin level, the number of leukocytes and platelets in peripheral blood, the leukocyte formula, the serum bilirubin, creatinine, alanine amine transferase (ALT) and aspartate amino transferase (AST) levels were determined. All indicators were recorded at each control examination of patients in specially developed thematic charts.

**Results.** The studied groups were comparable in all indicators, there were no statistically significant differences between them. The majority of patients in each of the groups had a high degree of activity (DAS28> 5.1): MTX group –75.3%, MTX + GC - 80.4%, LF - 64.2%. Only two patients (in the MT group) had a low degree of activity. All 3 investigated schemes demonstrated a significant decrease in the main signs of the inflammatory process, which is most clearly illustrated by the dynamics of PJ and IJ. By the third month, there was a significant ($p < 0.01$) decrease in all groups. This result persisted throughout the entire subsequent observation period. ESR by the 3rd month of observation also significantly ($p < 0.01$) decreased in all groups with the most striking dynamics in the MTX + GC group. Analysis of the dynamics of the general activity of RA according to DAS28 showed that after 3 months. therapy, this indicator decreased in all three groups, and this decrease reached a statistically high level ($p < 0.001$). This marked decrease in disease activity remained unchanged up to 12 months. observations without significant differences between groups. The maximum number of patients who showed signs of remission and low disease activity after 3 months was in the MTX + GC group - 48.2% (remission in 19.7%, low activity in 28.5%). In the MTX and LF groups, the corresponding values were 27.8 and 23.4%. During the follow-up (by the $6^{th}$ month), the same dynamics was noted: the highest result (in terms of the sum of the number of remissions and the number of patients with low activity) was achieved in the groups with the inclusion of GC. After 12 months. therapy, the revealed early pattern becomes even more pronounced. In the MTX + GC group, there was the maximum number of patients who achieved low activity. As in the previous stages of follow-up, the Lf group had the largest number of patients with high activity. By the end of the follow-up, in the MTX + GC group, 16 (53%) patients managed to completely cancel GC. 14 patients continued to take them GC: 8 - at a dose of 10 mg / day, in the remaining 6 people the average dose of GC was reduced to 5 mg / day. The results obtained indicate a significant and stable therapeutic effect of both MTX and LF monotherapy and the combination of MTX with GC. At the same time, during the entire observation period in the groups with the inclusion of GC into therapy, the most pronounced decrease in the disease activity was revealed in comparison with the other groups. After 6 months. in the MT + GC group, remission was in 12 (39.7%) patients, LF - in 5 (24.6%), MTX - in 8 (20.2%). The number of patients in remission was significantly higher in the MTX + GC group compared with MTX monotherapy. After 12 months. this tendency persisted: most often remissions were recorded in the MTX + GC groups (42.3%); significantly less frequently - among those who received monotherapy with Lf (27.3%) and MTX (22.4%) Compared with monotherapy with MTX, remissions of RA were significantly more often registered in the groups of patients receiving GC.

Thus, the obtained data demonstrate a significantly more frequent development of remissions when GC is included in the therapy of early RA.

When assessing the individual effectiveness of treatment according to the EULAR criteria after 12 months. Observations revealed that the largest percentage of patients with a good treatment effect was observed in the MTX + GC group. A good effect was more often achieved with the combination of GC with MTX compared with MTX monotherapy ($p < 0.05$). With an individual assessment of efficacy according to the criteria of the American College of Rheumatology (ACR) after 12 months. the number of patients who achieved 70% improvement was significantly higher in the MTX + GC group (46%).

**Discussion.** The positive dynamics of the main clinical and laboratory manifestations of early RA under the influence of all variants of the analyzed therapy was obvious. At the same time, a significant

decrease in the activity of the disease compared with the initial level persisted after 3, 6 and 12 months. from the start of treatment. This indicates a significant and long-term therapeutic effect of both MTX and LF monotherapy and the combination of MTX with GC. All the studied treatment options for patients with early RA demonstrated in our study both significant efficacy and quite acceptable safety. Therefore, each of the regimens used can be used to treat these patients with a significant probability of achieving significant improvement. A comparative assessment of the treatment regimens used reveals certain advantages of the regimens with the inclusion of GC. Thus, in the groups that included GC, a pronounced clinical improvement was observed already in the first days of GC intake.

After 12 months observation the incidence of remission was significantly higher in patients who received MTX in combination with GC. The therapeutic effect of MTX and LF monotherapy did not reveal significant differences. This seems to be quite natural, since both drugs are antimetabolites: MTX disturbs the metabolism of mainly purines, and LF - pyrimidines, which ultimately leads to a violation of the incorporation of these bases into the DNA molecule. As a result, actively proliferating immunocompetent cells die in the S-phase, i.e., in the synthesis phase. At the same time, MTX tolerance turned out to be somewhat better, which once again confirms the advisability of its appointment as the first basic drug in early RA. The data of our work definitely indicate the advisability of combining MTX with low doses of GC if the MTX effect turns out to be insufficient.

**Conclusion.** Summarizing the above materials, it should be concluded that all used scheme of early therapy of disease can be recommended for use in rheumatological practice. The individual characteristics of the patient and, above all, concomitant pathology should determine the choice of a specific scheme. The lack of a therapeutic effect of the considered treatment regimens can serve as one of the indications for the appointment of genetically engineered biological therapy.

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