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CLINICAL FEATURES OF JUVENILE IDIOPATHIC ARTHRITIS ONSET AND COURSE IN THE CONDITIONS OF ENVIRONMENTALLY UNFAVORABLE DONETSK REGION

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Juvenile idiopathic arthritis develops before the age of 16 years. It has chronic severe progressive course and, as a rule, unfavorable prognosis. The article presents clinical features of the disease onset and course, adverse prognostic factors of juvenile idiopathic arthritis. Under the conditions of the ecologically unfavorable Donetsk region, juvenile idiopathic arthritis had a severe course. Thus, two-thirds of patients had stages 2-3 of the process activity, one-fourth of patients had radiographic stages 2-3, two-thirds of patients had functional disorders class 2. Almost half of the patients had a polyarticular variant of juvenile idiopathic arthritis. More than half of children with juvenile idiopathic arthritis needed biological therapy because they had unfavorable prognostic factors for the disease course.

Key words: children, juvenile idiopathic arthritis, clinical features.

The present study is initiative, due to the extreme severity and unfavourable prognosis of the disease/

Juvenile idiopathic arthritis (JIA) is a severe, making children invalid disease that develops before the age of 16, with no established etiology, with complex immunoaggressive pathogenesis, has a chronic, progressive course and, as a rule, a poor prognosis [3,5,6,12].

JIA is one of the most common rheumatic diseases in childhood, the incidence of which in different regions of the globe ranges from 0.05% to 0.8% [1,5,7], the morbidity is from 2 to 16-20 cases a year per 100 000 child population [1,2,3,4,7,11], mortality - 0.5-1% [1,7]. In 30-50% of patients develop a disability after 3-5 years of being diseased [1,2,6].

According to the classification suggested by the International League of Rheumatological Associations, the following subtypes of JIA (ILAR 2007) are distinguished: oligoarticular (persistent or common), polyarticular seronegative (RF-) and seropositive (RF +), systemic (sJIA), psoriatic, enthesitis-associated, undifferentiated arthritis [4,8,9,12,13]. In terms of prevalence, polyarticular JIA (20-30%) occupies the second place (after oligoarticular, 50%) among all the JIA variants [1,4,7,12,13]. The polyarticular variant has an unfavorable prognosis, a high risk of developing severe destructive arthritis and disability of the child [1,7,9,12,13].

The most severe variant of JIA is sJIA (10-20%), in which not only joints are affected, but also many organs and systems [1,2,3,7,9]. In sJIA there is the highest among all the JIA variants risk of developing macrophage activation syndrome, in which the mortality makes 8-22% [2,7,9,10,12].

Eyes are often involved in the pathological process of JIA. Late diagnosis of uveitis, as well as its uncontrolled course, lead to the development of complications (cataract, glaucoma), and reduce visual acuity up to blindness [1,3,9,12]. The most difficult to diagnose should be considered cases of rheumatoid uveitis, preceding the appearance of articular syndrome [3].

The variety of clinical symptoms often causes difficulties in the diagnosis of JIA and the choice of the correct treatment strategy. In a quarter of patients, the diagnosis is established at the first visit to a doctor, after a year of observation possible diagnostic errors also constitute a quarter of the cases, which is determined by the complexity of the clinical diagnosis in children with this pathology [5]. Therefore, knowledge on the issues of clinical polymorphism of the disease onset and course will permit faster and more accurate identification of this disease, to timely assign adequate therapy, which will lead to earlier stabilization and remission of the disease.

The purpose of the work was to study the clinical features of the JIA onset and course in the environmentally unfavorable Donetsk region.

Materials and methods. There were 61 children with JIA under supervision living in ecologically unfavorable industrial Donetsk region, treated in the Mariupol Territorial Medical Association "Child and Woman Health".

The diagnosis of JIA was verified according to the criteria of the International League of Rheumatological Association ILAR, 1997. Definition of JIA clinical variants was carried out according to the JIA diagnostic criteria of (Edmonton, 2001). JIA activity was determined on by the JADAS (Juvenile Arthritis Disease Activity Score) scale. All children underwent standard clinical and laboratory

examination (complete blood count, blood chemistry values, urinalysis. The acute phase of inflammation (C-reactive protein, ESR- erythrocyte sedimentation rate) was analyzed.

The immunological study included the RF test, antibodies to cyclic citruline peptide - A-CCP, antinuclear antibodies - ANA, interleukins - IL-1 and IL-6, tumor necrosis factor- α (TNF- α). The presence of HLA B27 was determined. All the children were examined by an ophthalmologist. Among the instrumental methods x-ray, ultrasound, ECG were used. To assess the functional status of the child the CHAQ questionnaire was used. The therapy efficacy was assessed in compliance with the pediatric criteria of the American College of Rheumatology - ACR pedi.

Statistical analysis of the results included standard descriptive and analytical statistics methods: calculation of the mean values, relative values, standard deviations, standard errors, Student's criterion.

Results of the study and their discussion. Demographic and clinical characteristics of the JIA patients are presented in table 1.

Table 1

Demographic and clinical characteristics of the JIA patients

Parameter	Number of patients, n=61
Girls/Boys	44 (72%)/17(28%)
Urban dwellers/ Rural dwellers	49(80%)/12 (20%)
Disease was preceded by: ARVI	22 (36%)
factor is unascertained	22 (36%)
preventive vaccinations	7 (12%)
traumas	10 (16%)
JIA subtype: polyarticular	29 (48%)
oligoarticular	16 (26%)
enthesitis-associated	7 (12%)
systemic variant	7 (12%)
psoriatic arthritis	1
undifferentiated	1
Mean age of the JIA onset, months	67.62 \pm 12.32
Observation time	63.97 \pm 11.92

The clinical manifestations of JIA are diverse. The earliest, main clinical manifestation of the disease is the articular syndrome. In the studied group of children with JIA, articular syndrome was characterized by a variety of manifestations: from transient arthralgia to severe joint deformities (Fig.1). Most often the knee joints were involved in the inflammatory process (55 patients out of 61; 90%), ankle (40 patients out of 61; 66%), wrist (24 patients out of 61; 39%). More than half of the patients have paired involvement of these joints into the inflammatory process. Restriction of mouth opening, pain during chewing, which indicates the involvement of the temporomandibular joints, was found in 6 out of 61 patients with a polyarticular variant of the JIA course. Pain in the cervical spine was observed in 20 patients out of 61 (33%), including 7 patients with sJIA and 13 patients with polyarticular variants. Pain in the lumbar spine was observed in all children with enthesitis-associated variant of the disease.



Fig. 1. Photo 1, 2 - Joint damage in a 9-year-old child with JIA (knee, ankle, hip, wrist, hand joints), onset at 3 years of age, progression of the disease due to the therapy cancellation by the parents.

Pain in the hip joints was found in 18 patients out of 61 (30%): in 5 patients with sJIA, in 8 patients with polyarticular and in 5 patients with enthesitis-associated variants. However, pain in the hip joints in

the disease onset was only in 2 patients out of 61, but with the disease relapses they were much more common, in 16 patients. The hip joints or cervical spine damage in JIA indicates a severe course of JIA, the occurrence and subsequent development of generalized arthritis or systemic form of the disease.

Much less frequently, the elbows (12 patients out of 61) and shoulder joints (6 patients out of 61) were involved in the inflammatory process, and a unilateral, non-symmetrical damage was observed. The small joints of hands in the disease onset were affected (pain, swelling, impaired function) in 13 patients out of 61, however, destructive changes were later found only in 4 patients out of 61.

The mean number of active joints in the disease onset was 6.7 ± 1.1 . Pain, swelling, impaired mobility of the joint were detected in 58 patients out of 61 (95%), gait was disturbed in 50 patients out of 61 (82%). Morning stiffness was noted in all the patients, but more than 30 minutes-long was determined in 40 children out of 61 (66%) and severe, persisting stiffness throughout the day - in 8 patients.

In the onset of the disease, 17 out of 61 children (28%) had the 3rd degree of activity, 24 patients (39%) had the 2nd degree of activity, and 20 (33%) children had the 1st degree of activity. 40 patients out of 61 (66%) had x-ray stage 1, x-ray stage 2 was found in 12 patients out of 61, and 3 patients had severe destructive changes in the joints, which corresponded to x-ray stage 3. X-ray changes in the joints were characterized by periarticular osteoporosis of bone epiphyses, effusion into the joint cavity in 40 patients out of 61 (66%), osteoporosis in combination with cystiform radiolucency in 12 patients out of 61, narrowing of the joint space in 12 patients out of 61, common osteoporosis, osseocartilaginous destruction in 3 patients.

In all patients, the inflammatory process in the joints was confirmed by ultrasonography of the joints. Symptoms of synovitis with prevalence of the exudative component were detected in the majority of patients (41 children from 61; 67%), exudative-proliferative process was observed in 20 of 61 patients (33%), degenerative and destructive manifestations were determined in 3 patients.

Disease relapses were detected in 38 patients out of 61 (62%), including half of the patients having repeated relapses. The disease relapses were most frequently developed against the background of acute respiratory viral infections (20 patients out of 61; 33%), while reducing the dose of glucocorticosteroids (GC) (8 patients out of 61), in case of the therapy self-cancellation by parents (20 patients out of 61; 33%). It should be noted that if a child has a source of infection in the form of multiple carious teeth, it is impossible to achieve clinical improvement of the patient's condition, even against the background of the gene engineering biologic drugs (GEBD) used (16 children out of 61).

In 12 patients out of 61, JIA course included eye lesions. Rheumatoid uveitis was detected after 38.7 ± 30.95 months from the articular syndrome onset. Among patients with rheumatoid uveitis, preschool-age children prevailed (9 patients out of 12) predominantly with the articular form of the disease (polyarticular - 5, oligoarticular - 5, enthesitis-associated variant - 1) and 1 patient with sJIA.

In 2 children with polyarticular and oligoarticular variants of the disease, rheumatoid uveitis preceded the articular syndrome for 2 years and in 1 child with JIA it developed 14 years after the onset of the disease. 8 out of 12 patients had a single-eye uveitis, 4 patients had bilateral uveitis. Almost all the children with rheumatoid uveitis (11 patients out of 12) had high titer ANA (1: 320 - 1: 3200). However, ANA were detected not only in patients with rheumatoid uveitis, they were detected in half of the patients with JIA (36 patients out of 61; 59%).

The RF was determined in 6 patients out of 61, a high level of A-CCP was observed in 7 patients out of 61. The presence of HLA B27 was detected in 7 patients with enthesitis-associated disease. High levels of TNF- α were detected in 11 patients out of 61, with a joint variant of the disease. The level of IL-6 was increased in 14 patients out of 61, including 7 children with sJIA, 5 children with a polyarticular variant, 2 patients with an enthesitis-associated variant. In the disease onset, the ESR was increased in 46 patients out of 61 (75%), more than 25 mm / h in 28 (46%). C-reactive protein was increased in 38 patients out of 61 (62%).

In the study group, a seropositive variant of the disease (RF +) was detected in 6 patients out of 61. These were 5 adolescent girls with a polyarticular JIA variant and 1 girl with psoriatic arthritis. All the children in this group had a high degree of the disease activity (2-3 degrees of activity), the number of active joints in the disease onset ranged from 9 to 13, the hands joints being involved, 4 patients had destructive changes in the joints, corresponding to x-ray stages 2-3.

An important indicator for JIA is a disorder of the joints functional ability. In most patients, dysfunction of the joints was most pronounced in the disease onset, associated with severe pain and inflammatory swelling of the soft tissues. Thus, 40 patients out of 61 (66%) had class 2 of functional disorders.

All organs and systems can be involved in the pathological process of JIA. This is most pronounced in sJIA, which has a severe course of this variant of the disease. All patients with sJIA (7 patients - 100%) had fever, generalized lymphadenopathy, hepatomegaly and splenomegaly, serositis in varying degrees of severity; 4 patients had pericarditis, 1 had myocarditis, 1 had hepatitis, 1 had infarction of the spleen, 1 had alveolitis. Volatile erythematous rash was in 2 patients. Children with sJIA have a high degree of the disease activity - 3, class 2 of the joints functional disorders in the onset of the disease. In addition to marked arthralgia, these children had arthritis with radiographic stages 1-2, all of them being seronegative.

The diagnosis of JIA was set at an average of 11.52 ± 4.02 months. Immediately after the diagnosis verification, basic therapy was administered to all patients. The treatment strategy of JIA is reflected in the unified clinical protocol of medical care for children suffering from juvenile arthritis (Order of the Ministry of Health of Ukraine dated October 22, 2012 No. 832) [6].

Currently, methotrexate is the main basic drug for treatment of various JIA variants. All the children (100%) received methotrexate at a dose of 15 mg / m² / week, in the case of refractoriness to the methotrexate therapy, the route of administration was changed, combined therapy with sulfasalazine and cyclosporin A was carried out. The mean duration of methotrexate therapy was 50.49 ± 10.48 months. In connection with the refractory effect to methotrexate, 2 children received imuran (azathioprine 1.5–3.0 mg / kg / day). Combined therapy of methotrexate with sulfasalazine (at a dose of 30–50 mg / kg / day orally in 2–3 doses, no more than 6 months) was received by 9 patients, methotrexate with cyclosporin A (2.5–5 mg / kg / day orally in 2 admission) was received by 3 children with uveitis.

Glucocorticoids (GC) were prescribed to 43 children out of 61 (71%): at a dose of 0.5 mg / kg / day in patients with severe polyarthritis refractory to another therapy, and with sJIA - 1 mg / kg / day with a duration of no more than 1 month. Maintenance dose of GC was 0.1-0.15 mg / kg / day. The mean duration of GC therapy, taking into account maintenance therapy, lasted 36.1 ± 11.73 months, since in three-fourths of patients hormone dependence was noted, and with the cancellation of the GC maintenance dose, the disease recurred. All the children with sJIA (7 patients, 100%) underwent pulse therapy with GC — solu-medrol (methylprednisolone) 10 mg / kg i.v./day for 3-5 days. Intra-articular injection of GC was performed to 25 children out of 61 (41%), mainly to the large joints – those of the knee.

The presence of adverse prognostic factors of the disease course in JIA children, such as high activity of the process and insufficient therapy efficacy for 6 months, significant active systemic manifestations for more than 6 months, progressive course of uveitis, damaged hip joints or cervical spine, presence of erosions and joint space narrowing while X-ray examination, served as an indication for prescribing genetically engineered biological drugs (GEBD).

Methotrexate and GEBD were received by 36 children out of 61 (59%). Duration of the prestudy therapy with methotrexate prior to GEBD administration was at least 2 years, averaging to 29.25 ± 8.86 months. Tocilizumab - Actemra® - was used to treat sJIA, manufactured in Switzerland - recombinant humanized monoclonal antibodies to the IL-6 receptor, registered in Ukraine for the JIA treatment since 2 years of the child's life. Actemra was received by 6 patients with sJIA. Actemra is administered intravenously / by drop infusion 1 time in 2 weeks, in a dose of 8 mg / kg (with a child's weight more than 30 kg) or 12 mg / kg (with a child's weight less than 30 kg).

Adalimumab was used to treat articular variants of JIA. Humira® (Adalimumab), manufactured in the UK and Germany is human recombinant monoclonal antibodies to TNF- α . This is the only TNF- α inhibitor registered in Ukraine for the JIA treatment in children since 4 years of age. It is administered subcutaneously 1 time per 2 weeks at a dose of 24 mg / m² (no more than 40 mg). 30 patients with JIA out of 36 patients who received GEBD (83%) with polyarticular, oligoarticular, enthesitis-associated JIA, and psoriatic arthritis received Humira. The mean duration of the GEBD therapy was 26.89 ± 7.48 months.

On the background of the therapy, a significant positive clinical and laboratory dynamics is observed. 15 patients out of 61 achieved remission, including 5 patients out of 61 in whom the therapy was canceled. The 1 st degree of disease activity against the background of therapy was detected in the majority of patients (33 patients out of 61; 54%), the disease activity degree 2 - in 8 out of 61 patients, the disease activity degree 3 remained in 5 out of 61 children. The number of active joints in 30 patients of 61 (49%) was -1-2, in 8 patients out of 61 there were 3-6 active joints, no active joints were detected in 20 patients out of 61 (33%). Only in 3 patients the number of active joints was 10 or more. The mean number of active joints was 1.8 ± 0.6 . ESR remained elevated in 10 patients out of 61. C-reactive protein was elevated in 5 patients out of 61.

When studying clinical manifestations of the debut and course of JIA, we obtained data that correspond to the results of other researchers [1, 3, 4, 7, 9, 12, 13]. According to the literature, children with JIA are dominated by children with oligoarticular disease (50%), which is characterized by moderate

disease activity, low indices of laboratory activity, moderate functional disorders. The polyarticular variant makes 20–30% among children with JIA, has high activity, aggressive, recurrent and progressive course of the disease, is characterized by the rapid onset of structural changes in the joints and early development of disability in children.

Under the conditions of environmentally unfriendly Donetsk region, as well as a result of the war stress factors influence, JIA proceeded more severely. Almost a half of patients with JIA revealed a polyarticular variant of the disease. In $\frac{2}{3}$ of patients, there was the 2nd-3rd degree of the process activity, in $\frac{1}{4}$ patients, 2-3 x-ray stages were detected, in $\frac{2}{3}$ patients - functional disorders of class 2. More than half of the children with JIA had unfavorable prognostic factors in the course of the disease and needed prescription of GEBD. Therefore, the study of JIA debut and course clinical features in environmentally unfriendly Donetsk region is important for early diagnosis and timely appointment of adequate therapy even before the development of structural changes in the joints, which can change the prognosis of the disease.

Conclusions

1. In the environmentally unfavorable Donetsk region, JIA proceeded in the severe form. Thus, two thirds of the patients had activity degrees 2-3 of the process, in one fourth of the patients radiographic stages 2-3 were revealed, in two thirds of the patients - class 2 of functional disorders.

2. A quarter of the patients had an oligoarticular variant of the disease. Almost half of the patients had a polyarticular JIA variant, which is severe and prognostically unfavorable.

3. More than half of the children with JIA need GEBD prescription because they have unfavorable prognostic factors of the disease, such as high activity of the process and lack of the therapy efficacy for 6 months, significant active systemic manifestations for more than 6 months, progressive course of uveitis, damaged hip joints or cervical spine, the presence of erosions and the joint space narrowing, the presence of progressive changes during X-ray examination.

4. Knowledge of the clinical polymorphism issues of the disease onset and course will permit timely verification of the diagnosis and timely assigning adequate modern therapy.

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Рефераты

**КЛІНІЧНІ ОСОБЛИВОСТІ ДЕБЮТУ
ТА ПЕРЕБІГУ ЮВЕНІЛЬНОГО
ІДІОПАТИЧНОГО АРТРИТУ В ЕКОЛОГІЧНО
НЕСПРИЯТЛИВИХ УМОВАХ ДОНЕЦЬКОГО
РЕГІОНУ**

**Конюшевська А.А., Вайзер Н.В., Пастернак Д.В.,
Сидоренко Н.В., Таран І.Д.**

Ювенільний ідіопатичний артрит розвивається
у віці до 16 років, має хронічне, важке прогресуюче

**КЛИНИЧЕСКИЕ ОСОБЕННОСТИ ДЕБЮТА И
ТЕЧЕНИЯ ЮВЕНИЛЬНОГО ИДИОПАТИЧЕСКОГО
АРТРИТА В УСЛОВИЯХ ЭКОЛОГИЧЕСКИ
НЕБЛАГОПОЛУЧНОГО
ДОНЕЦКОГО РЕГИОНА**

**Конюшевская А.А., Вайзер Н.В., Пастернак Д.В.,
Сидоренко Н.В., Таран И.Д.**

Ювенільний ідіопатичний артрит розвивається в
возрасте до 16 лет, имеет хроническое, тяжелое

перебіг і, як правило, несприятливий прогноз. У статті представлені клінічні особливості дебюту і перебігу захворювання, несприятливі прогностичні фактори ювенільного ідіопатичного артриту. В умовах екологічно неблагополучного Донецького регіону ювенільний ідіопатичний артрит протікав важко. Так, $\frac{2}{3}$ хворих мали 2-3 ступінь активності процесу, у $\frac{1}{4}$ хворих виявлено 2-3 рентгенологічна стадія, $\frac{2}{3}$ хворих мали 2 клас функціональних порушень. Майже у половини хворих виявлено поліартикулярний варіант ювенільного ідіопатичного артриту, більше половини дітей потребували призначення біологічної терапії в зв'язку з наявністю у них несприятливих прогностичних факторів перебігу хвороби.

Ключові слова: діти, ювенільний ідіопатичний артрит, клінічна характеристика.

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прогрессирующее течение и, как правило, неблагоприятный прогноз. В статье представлены клинические особенности дебюта и течения заболевания, неблагоприятные прогностические факторы ювенильного идиопатического артрита. В условиях экологически неблагополучного Донецкого региона ювенильный идиопатический артрит протекал тяжело. Так, $\frac{2}{3}$ больных имели 2-3 степень активности процесса, у $\frac{1}{4}$ больных выявлена 2-3 рентгенологическая стадия, $\frac{2}{3}$ больных имели 2 класс функциональных нарушений. Почти у половины больных выявлен полиартикулярный вариант ювенильного идиопатического артрита, более половины детей нуждались в назначении биологической терапии в виду наличия у них неблагоприятных прогностических факторов течения болезни.

Ключевые слова: дети, ювенильный идиопатический артрит, клиническая характеристика.

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КОНЦЕПТУАЛЬНІ ПІДХОДИ ОБГРУНТУВАННЯ МОДЕЛІ ОПТИМІЗАЦІЇ МЕДИЧНОЇ ДОПОМОГИ НА ЕТАПІ РОЗВИТКУ СІМЕЙНОЇ МЕДИЦИНИ

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У статті представлено нові концептуальні підходи обґрунтування моделі оптимізації медичної допомоги в умовах стресу. Базуючись на матеріалах роботи нами доведено існування комплексного взаємозв'язку між психічними та фізичними порушеннями, встановлено чинники, що визначають їх формування, зокрема стресу. Держава дбаючи про здоров'я нації впроваджує систему «сімейний лікар – пацієнт», основою якої є вчасне виявлення усіх чинників, що впливають на здоров'я людини. Таким чином, впровадження оптимізованої моделі первинної медичної допомоги із врахуванням ранньої діагностики, лікування, реабілітації та індивідуальної профілактики порушень психічного здоров'я у хворих із соматичними захворюваннями – є актуальним і обґрунтованим. Дані результатів дослідження цілком можуть бути базисом для створення нових програм, комплексних заходів стосовно виявлення, лікування, профілактики порушень психіки та поведінки на первинному рівні надання медичної допомоги в умовах сьогодення.

Ключові слова: первинна медична допомога, психічне здоров'я, психосоматика, модель оптимізації ПМД, стрес.

Робота є фрагментом НДР «Медико-соціальне обґрунтування моделі оптимізації первинної медичної допомоги в умовах стресу» (номер державної реєстрації 0118U100198).

В умовах реформи системи охорони здоров'я України, запровадження нових принципів надання первинної медичної допомоги населенню та страхової медицини [8], погіршення загального здоров'я нації, негативна динаміка захворюваності та поширеності хвороб в Україні, скорочення середньої тривалості життя, зниження та втрата працездатності населення, підкреслює проблему, та доводить невідворотній вплив стресу [6]. Трансформаційні процеси на первинній ланці направлені на побудову в Україні пацієнто-орієнтованого та профілактичного напрямку в системі охорони здоров'я, створення відповідного нормативно-правового поля щодо популяризації здорового способу життя та зменшення впливу факторів ризику на здоров'я нації в цілому [8].

Метою роботи було обґрунтувати концептуальні підходи моделі оптимізації медичної допомоги на етапі розвитку сімейної медицини.

Матеріал та методи дослідження. Проведений аналіз літературних джерел, отримані результати дослідження, вимагають наукового обґрунтування моделі оптимізації медичної допомоги на первинному рівні в умовах стресу з урахуванням саме тих чинників ризику, які мають вплив на розвиток та перебіг захворюваності. Актуальність цієї проблеми потребує розробки оптимізованої моделі для виокремлення окремих елементів системи надання медичної допомоги на первинній ланці, та методології її впровадження.

Пацієнто-орієнтована та профілактично-трансформаційна модель відтворює стратегічне бачення та цілі: збереження здоров'я населення, через ключову фігуру на первинній ланці - лікаря загальної практики-сімейної медицини. Тактичним кроком моделі стало проведення комплексної