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EFFECTIVENESS OF IMMUNOSUPPRESSANTS IN THE TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS IN CHILDREN

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Abstract
The article presents the results of a comparative study of the effectiveness of leflunomide and methotrexate in children with juvenile idiopathic arthritis. The study included 96 children aged 2 to 16 years: the main group included 56 children treated with leflunomide, the comparison group included 40 patients treated with methotrexate in an average dose. Therapy with leflunomide was significantly more effective than methotrexate in standard doses. A clear improvement in children treated with leflunomide was observed after 12 weeks. 15% of patients had inactive disease. In children from the comparison group, systemic manifestations continued to recur, active arthritis persisted, laboratory values were high, and disability progressed.

Keywords: juvenile idiopathic arthritis, leflunomide, methotrexate, children.

Introduction

Juvenile idiopathic arthritis (JIA) remains important as one of the most important problems in scientific and practical rheumatology. The disease is characterized by widespread prevalence (about 1% of the population), persistent progressive course, complex pathogenesis, and heterogeneity of clinical and immunological forms. In the absence of adequate treatment, disability may occur in the first years of the disease. The “gold standard” for the treatment of JIA is, of course, methotrexate. GEBD have radically improved treatment outcomes for previously incurable patients. It is well known that only 50-60% of patients respond satisfactorily to standard therapy with basic anti-inflammatory drugs (DMARDs), such as methotrexate (MTX), leflunomide, sulfasalazine, in combination with glucocorticosteroids (GCS) (in early RA, when the duration of the disease is not exceeds 1 year, the results may be better) [5]. Thus, about 50% of patients are resistant to DMARDs. For the treatment of JIA over the past 20 years, about 10 innovative biological medications have been specially developed - monoclonal antibodies and recombinant proteins that inhibit the activity of the most important pro-inflammatory cytokines and pathological activation of T- and B-lymphocytes involved in the immunopathogenesis of RA [1–3].

In pediatric rheumatology, despite a number of specific problems, including the “off label” status of a number of biologically active drugs for children, the importance of these new medications is constantly increasing. First of all, we received drugs that can effectively treat the systemic variant of juvenile idiopathic arthritis (JIA) – Still’s disease and severe polyarticular JIA. This article provides a short overview of the biological medications currently used to treat JIA. BIBPs –

cytokine inhibitors The important role of cytokines in the pathogenesis of JIA [5] has led to the idea of using cytokine blockers in the treatment of this disease. It seems that anti-cytokine therapy provides quite satisfactory results and can significantly improve the prognosis even in those severe forms of JIA in which conventional therapeutic treatment strategies have often failed to produce a positive result. Elevated concentrations of TNFα were detected in the joints of patients with rheumatoid arthritis and correlated with disease activity. In patients with rheumatoid arthritis, treatment with leflunomide resulted in decreased infiltration of inflammatory cells into inflamed joints, as well as decreased expression of molecules mediating cell adhesion, chemoattraction, and tissue destruction. After treatment with leflunomide, there was a decrease in serum concentrations of interleukin-6 (IL-6) and C-reactive protein (CRP), as well as an increase in hemoglobin concentration in patients with rheumatoid arthritis with a decreased hemoglobin concentration compared to the baseline level. TNFα inhibitors The role of TNFα in the development of inflammation TNFα is a cytokine involved in the formation of a systemic inflammatory process [6, 7]. It primarily has a regulatory effect on the growth, survival and function of cells of the immune system [8–10]. The biological functions of TNF α include the induction of proinflammatory cytokines such as IL 1 and 6, as well as TNF α itself, increasing the mobility of leukocytes and their migration from the bloodstream into tissues by increasing the permeability of the endothelial layer of microvasculature blood vessels and increasing the expression of cell adhesion molecules. TNFα is capable of inducing cell death through apoptosis, triggering inflammation, and inhibiting carcinogenesis and viral replication. It plays a very important role in the pathogenesis of rheumatic inflammation, triggering a cascade of inflammatory and destructive processes that involve osteoclasts, synovial fibroblasts and chondrocytes, which leads to the development of pain, swelling, the formation of bone erosions and narrowing of the joint space. By blocking the action of TNF α, we can count on the inactivation of the above processes.

Purpose of the study

Exploreeffectiveness of immunosuppressants in the treatment of juvenile idiopathic arthritis in children.

Materials and methods

The study included 96 children (34 boys and 62 girls) aged 2 to 16 years with systemic juvenile idiopathic arthritis. The diagnosis was made based on ILAR (International League of Associations for Rheumatology) diagnostic criteria. All patients were divided into two groups depending on the nature of immunosuppressive therapy. The first (main) group included 56 children treated with leflunomide, the second group (comparison) included 40 patients who received methotrexate at a dose of 15 to 25 mg/m2 of standard body surface area per week.

The majority of patients in both groups fell ill in preschool age; the average age of onset was 5.3 and 5.6 years, the minimum age of onset was 9 and 7 months, the maximum was 18 and 16 years, in the first and second groups, respectively (Table 1).

At the time of initiation of therapy, the majority of patients in both groups had a polyarticular articular syndrome (Table 2). Active joint syndrome was accompanied by functional impairment in the majority of children included in the study. 30 (40%) and 26 (65%) patients in the main group and the comparison group, respectively, had significant limitations in the ability to self-care, which corresponded to functional class III (see Table 2). 7 (10%) and 6 (15%) patients were completely

unable to care for themselves due to severe damage to the musculoskeletal system (FC IV), a slight limitation of daily activity (FC II) was observed in 26 (35%) and 8 (20%) children from the first and second groups,respectively.

Table 1. Demographic characteristics of patients included in the study.

Index	Main group (n = 56)	Comparison group (n = 40)
Girls (abs.) Boys (abs.)	29 26	22 18
Age, years Me (25; 75%)	10.7 (3.0; 12.0)	9.1 (2.4; 10.5)
Duration of disease, years Me (25; 75%)	4.32 (0.7; 8.0)	3.5 (0.7; 3.8)

Table 2. Baseline clinical characteristics of patients included in the study.

Index	Main group (n = 56)	Comparison group (n = 40)
Clinical variant of JIA, abs.	56	40
Number of joints with active arthritis Me (25; 75%)	10.5 (3.0; 28.0)	14.0 (11; 19)
Number of joints with dysfunction Me (25; 75%)	12.0 (2.0; 25.0)	12.0 (7; 16)
Functional class (%) I II III IV	 15 35 40 10	 20 65 15
Duration of antirheumatic therapy (years)	3.2 (0.6; 3.8)	2.9 (0.8; 3.4)
Number of systemic manifestations per patient	4.5 (2.0; 6.0)	4.8 (2.5; 6.0)
Hemoglobin, g/l	91 (84; 112)	101 (88; 105)
ESR, mm/h	38 (40; 66)	46 (42; 56)
CRP, mg/dl	86 (45; 160)	81 (50; 100)
Platelets×109/l	620 (490; 810)	670 (450; 860)

In 11 (15%) patients of the main group (see Table 2) there were no impairments in functional ability (FC I). Extra-articular manifestations of the disease included febrile fever - in 55 (75%) and 34 (85%), carditis - in 15 (20%) and 12 (40%), lymphadenopathy - in 68 (92%) and 36 (90%), maculopapular rash on the skin - in 40 (55%) and 26 (65%), hepatomegaly - in 29 (40%) and 16 (40%), splenomegaly - in 15 (20%) and 6 (15%) patients from the main group and comparison group, respectively. The number of systemic manifestations per patient was 4.5 and 4.8 in both groups.

High clinical activity of the disease was accompanied by a general inflammatory reaction. The median values of ESR exceeded the normal value by 4.2 and 3.3 times, and the serum concentration of CRP by 18 and 16 times in both groups, respectively.

Thus, at the start of the study, all patients with systemic juvenile idiopathic arthritis included in the study had active joint syndrome, severe extra-articular manifestations, high laboratory indicators of disease activity and an increasing degree of disability. According to demographic, clinical and laboratory parameters, patients in the main group and the comparison group did not differ statistically.

Study design

. The criteria for inclusion in the main group were: juvenile idiopathic arthritis, active joint syndrome, continuous recurrence of systemic manifestations, ineffectiveness of therapy with glucocorticoids, NSAIDs, and at least two immunosuppressants with the mandatory use of methotrexate in standard doses, ineffectiveness of therapy with TNF α inhibitors, side effects and development of secondary failure of anti-TNF α therapy. Exclusion criteria were: increased serum concentrations of urea, creatinine, bilirubin, ALT, AST; the presence of significant foci of acute and chronic infection.

Methotrexate was prescribed at a dose of 15 to 25 mg/m2 of standard body surface area per week. The average dose was 18.7 ± 4.3 mg/m2/week. The drug was administered intramuscularly.

All patients underwent a standard clinical and laboratory examination before prescribing drugs and during treatment. The level of hemoglobin, number of red blood cells, platelets, leukocytes, leukocyte formula, ESR, concentration of urea, creatinine, uric acid, bilirubin, transaminases in the blood serum and clinical urine analysis were monitored once every 2 weeks. Blood pressure was measured daily.

The number of joints with active arthritis (swelling, pain, dysfunction), the number of systemic manifestations of the disease, and the serum concentration of CRP were determined once every 3 months. The functional activity of patients was assessed in accordance with the Steinbrocker criteria: functional class (FC) I - complete safety of performing daily activities without limitation, FC II - adequate safety of performing normal daily activities, despite certain difficulties, FC III - limited ability to perform normal daily activities, FC IV - complete loss of the ability to perform normal daily activities.

Table 3. Background antirheumatic therapy

A drug	Dose (M ± m)Number of patients (n)	
	Main group (n = 56)	Comparison group (n = 40)
Methotrexate mg/m2/week	22.5 ± 2.5 (n = 14)	
Prednisolone mg/kg/day	—	0.7 ± 0.3 (n = 32)
Methotrexate mg/m2/week + Cyclosporine mg/kg/day	21.3 ± 3.7/4.0 ± 0.7 (n = 30)	—
Prednisolone mg/kg/day + Methotrexate mg/m2/week + Cyclosporine, mg/kg/day	0.56 ± 0.2/19.3 ± 5.7/4.1 ± 0.56 (n = 31)	—
NSAIDs	56	40

Note. NSAIDs are non-steroidal anti-inflammatory drugs.

The target indicators of the effectiveness of the therapy were the frequency of reaching the stage of inactive disease. The inactive phase of the disease was established in the absence of active synovitis, systemic manifestations of the disease, the presence of normal ESR and serum CRP concentrations, as well as in the absence of disease activity according to the physician's general assessment (VAS). The effectiveness of therapy was assessed after 12 and 24 weeks.

Statistical data processing was carried out using the STATISTICA 6.0 program (StatSoft Inc., USA). Quantitative characteristics are presented as median (25th, 75th percentiles). Differences were considered statistically significant at $p < 0.05$.

Resultand Discussion

Dynamics of extra-articular manifestations. By 12 weeks of observation, in the group of children treated with leflunomide, the number of systemic manifestations significantly decreased. Such life-threatening manifestations as carditis and pneumonitis stopped in 90% of patients, skin rashes in 20%, the size of the liver and spleen returned to normal in 80%, and fever stopped in 60% of patients. In the comparison group, the dynamics of systemic manifestations was insignificant. Fever persisted in 70% of patients, carditis - in 24%, pneumonitis - in 10%, maculopapular skin rash - in 60% of children. In 30% of patients the severity of lymphadenopathy decreased, in 15% the size of the liver decreased, in 10% the size of the spleen decreased.

After 24 weeks, the number of systemic manifestations per patient in children of the main group decreased significantly and amounted to 2.8; in the comparison group there was no change in this indicator (4.3). Fever persisted in 10 and 80% of children, rash in 20 and 60%. Pneumonitis continued to recur in 10% of patients treated with methotrexate (Figs. 2 and 3). Dynamics of articular syndrome. By 12 weeks, children treated with leflunomide had a statistically significant ($p < 0.01$) decrease in the number of joints with active arthritis (pain, stiffness and exudation). In patients receiving methotrexate, there was only a tendency towards a decrease in this indicator (Fig. 4).

After 24 weeks, in children of the main group, the median number of joints with active arthritis decreased by 3.5 times; in the comparison group, no statistically significant dynamics were observed: the number of joints with active arthritis was 3 times higher than in patients receiving leflunomide.

Analysis of the effect of the studied drugs on the functional ability of the joints showed that after 12 weeks in patients of both groups there was a tendency to reduce the number of joints with impaired function.

CONCLUSION

Methotrexate at a standard dose of 15–25 mg/m2/week in combination with glucocorticoids was not effective in children with long-term systemic JIA with active joint syndrome. Over the course of 24 weeks of treatment, 90% of patients continued to experience recurrence of systemic manifestations, including life-threatening ones, as well as articular syndrome; High laboratory indicators of process activity remained and disability increased, as evidenced by an increase in the proportion of children unable to care for themselves. The opposite pattern was observed in patients treated with leflunomide. A clear improvement in the patients' condition was observed already by 12 weeks. During this period, life-threatening systemic manifestations stopped in 90% of children, the activity of the articular syndrome decreased, and laboratory parameters improved.

The preliminary data obtained allow us to conclude that if methotrexate in standard doses in combination with glucocorticoids is ineffective for 12 weeks in children with systemic JIA and active joint syndrome, it is advisable to either adjust the methotrexate dose upward or switch patients to leflunomide.

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