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ORIGINAL PAPER

THE CLINICAL AND PARACLINICAL EFFICACY OF TOCILIZUMAB IN JUVENILE IDIOPATHIC ARTHRITIS

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Abstract

Introduction. Juvenile idiopathic arthritis (JIA) is a persistent type of arthritis with no defined cause that starts before the age of 16 years and lasts for at least 6 weeks.
The objective of the study was to determine the clinical and laboratory efficacy of tocilizumab treatment in patients with systemic and polyarticular seropositive forms of JIA.
Material and methods. The study took place in the Division of Rheumatology, Public Healthcare Institution – Mother and Child Institute, Chisinau, Republic of Moldova. The parents of the patients signed the written consent to participate in the study. The study was approved by the Ethics Committee of the institute. The inclusion criteria for enrolling the patients who underwent the biological treatment were both the systemic and polyarticular JIA forms (seronegative or positive) and active sacroiliitis. The exclusion criteria were the patients with active infections, tuberculosis, sepsis, malignancies, and immunodeficiency disorders. This study included 20 children with JIA, in whom tocilizumab was administered every two weeks. The number of painful joints, the number of swollen joints, and the global evaluation of the disease by the

Résumé

L'efficacité clinique et paraclinique du tocilizumab dans l'arthrite juvénile idiopathique

Introduction. L'arthrite juvénile idiopathique (AJI) se réfère à un type persistant d'arthrite sans cause définie, qui débute avant l'âge de 16 ans et dure 6 semaines au minimum.
L'objectif de l'étude a été de déterminer l'efficacité clinique et paraclinique de l'utilisation du tocilizumab dans le traitement de l'AJI systémiques et polyarticulaires formes séropositives.
Matériel et méthodes. L'étude a eu lieu dans la Division de Rhumatologie, Etablissement Public de Santé – Institut de la Mère et de l'Enfant, Chisinau, République de Moldova. Les parents des patients ont signé le consentement écrit pour participer à l'étude. L'étude a été approuvée par le Comité d'éthique. Les critères d'inclusion pour le recrutement des patients ayant subi le traitement biologique : les formes systémique et polyarticulaire (séronégative ou positive) et la sacro-iliite active de l'AJI. Les critères d'exclusion: les patients atteints d'infections actives, de tuberculose, de septicémie, de tumeurs malignes et de troubles d'immunodéficience. L'étude a été faite sur 20 enfants

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doctor (GEDD) and by the patient (GEDP), as well as via the Childhood Health Assessment Questionnaire (CHAQ), were determined. Furthermore, paraclinical tests, that included complete blood count and C-reactive protein (CRP), were determined.

Results. Children treated with tocilizumab exhibited a decreased number of painful and swollen joints, as well as the GEDD, GEDP, and CHAQ scores. Moreover, a decrease of the erythrocyte sedimentation rate (ESR) and CRP was observed.

Conclusions. Children with JIA treated with tocilizumab showed a considerable clinical improvement and the paraclinical indices revealed a lower active inflammatory response.

Keywords: juvenile idiopathic arthritis, tocilizumab, inflammatory markers.

List of abbreviations:
JIA – juvenile idiopathic arthritis
NPJ – number of painful joints
NSJ – number of swollen joints
GEDD – global evaluation of disease by the doctor
GEDP – global evaluation of disease by the patient
CHAQ – Childhood Health Assessment Questionnaire
ESR – erythrocyte sedimentation rate
CRP – C-reactive protein
DAS – Disease Activity Score
ACR Pedi 30 – American College of Rheumatology Pediatric 30 criteria
JADAS-10 – Juvenile Arthritis Disease Activity Score-10

souffrant d'AJI, qui ont reçu du tocilizumab toutes les deux semaines. Le nombre des articulations douloureuses, d'articulations tuméfiées et l'évaluation générale de la maladie ont été déterminés par le médecin et le patient ainsi que le questionnaire d'évaluation fonctionnelle de l'enfant (CHAQ). Les indicateurs paracliniques ont été identifiés, y compris l'analyse générale du sang et de la protéine C-réactive.

Résultats. Les enfants souffrant de l'AJI traités avec du tocilizumab, ont présenté la diminution du nombre d'articulations douloureuses et tuméfiées, ainsi que la baisse de l'évaluation globale de la maladie par le médecin et les patients et des valeurs du questionnaire d'évaluation fonctionnelle de l'enfant (CHAQ). L'étude a montré aussi une baisse des indicateurs en phase aigue, de la vitesse de sédimentation des érythrocytes et de la protéine C-réactive chez les patients traités par le tocilizumab.

Conclusions. Les enfants atteints d'AJI et traités par tocilizumab ont montré une amélioration clinique considérable et les indices paracliniques ont présenté une réponse inflammatoire active plus faible.

Mots-clés: arthrite juvénile idiopathique, tocilizumab, marqueurs de l'inflammation.

Introduction

Juvenile idiopathic arthritis (JIA), as defined by ILAR (International League of Associations for Rheumatology)[1], refers to a persistent type of arthritis with no defined cause, which starts before the age of 16 years and lasts for at least 6 weeks[1]. JIA is the most common rheumatic disease in children that can significantly impair joint function, resulting in joint deformities, growth failure and persistent active disease in the adulthood. The disease is characterized by chronic synovial inflammation, cartilage damage and bone erosion. It is an autoinflammatory disease related to a possible abnormality in the innate immune system. Interactions between macrophages, T cells, B cells and fibroblasts are an important feature in JIA pathogenesis. These interactions are facilitated by the effects of cytokines, which induce the production of other proinflammatory cytokines[2].

JIA is an autoinflammatory condition, which involves the pivotal inflammatory cytokine IL-1 and histiocytes. High levels of TNF-α, IL-1β and IL-6 have been reported in JIA-diseased joints[3]. Due to some factors, not yet determined, there is an aberrant activation of phagocytes, monocytes, macrophages and neutrophils, with the release of proinflammatory cytokines IL-1, IL-6, IL-18 and proinflammatory proteins S100, which results in systemic inflammatory response[4,5].

Interleukin-6 (IL-6) is one of the key cytokines that plays an important role in the systemic JIA pathogenesis. IL-6 overproduction contributes to fever and thrombocytosis. IL-6 stimulates the production of acute-phase proteins (C-reactive protein, fibrinogen and haptoglobin), as well as inhibits the albumin and transferrin synthesis. IL-6 also stimulates hepcidin production. Hepcidin decreases the intestinal iron absorption and inhibits iron release from macrophages, which might induce iron deficiency, followed by anemia[6]. Normal concentrations of IL-6 stimulates the adrenocorticotropic hormone (ACTH) and cortisol synthesis, as well as procalcitonin and the growth hormone[7]. High concentrations of IL-6 inhibit the synthesis of these hormones, contributing

to the development of fatigue, depression, asthenia and physical disabilities in children with JIA[7,8]. The development of amyloidosis is also associated with IL-6 activity.

Given the aforementioned, inhibition of IL-6 activity should be considered as a current issue in the treatment of systemic JIA.

Tocilizumab is approved for the treatment of the hormone-dependent systemic and polyarticular JIA[9]. This drug is the antagonist receptor of IL-6. Tocilizumab is administered in a 60-minute intravenous infusion every 2 weeks. The tocilizumab dose is adjusted depending on the patient's weight. In children weighting >30 kg the dose is 8 mg/kg, and in those weighing <30 kg the dose is 12 mg/kg[9]. During treatment the blood count, aminotransferases and serum lipid levels should be monitored. Tocilizumab can be administered either as monotherapy or in combination with methotrexate or other drugs[10,11]; however, it should not be given in combination with biological agents[9].

Multiple studies have reported the efficacy and safety of biological tocilizumab treatment in children with systemic JIA[12-16].

The objective of study was to determine the clinical and laboratory efficacy of tocilizumab treatment in patients with systemic and polyarticular seropositive forms of JIA.

Material and methods

The study took place in Division of Rheumatology, Public Healthcare Institution – Mother and Child Institute, Chisinau, Republic of Moldova, between 2011-2020. The parents of the patients signed the written consent to participate in the study. The study was approved by the Ethics Committee of the institute.

The inclusion criteria were: patients with systemic and polyarticular JIA forms (seronegative or positive) and active sacroiliitis, who underwent biological treatment.

The exclusion criteria were: patients with active infections, tuberculosis, sepsis, malignancies, and immunodeficiency disorders.

The prospective study included 20 children with JIA (11 girls and 9 boys). 19 children were diagnosed with systemic JIA and one child with seropositive polyarticular JIA, with rheumatoid factor 24 IU/mL. The average age of patients included in the study was 12 years (ranging from 2 to 17 years old). The disease duration at the time of inclusion in the study was on average 6 years (lasting from 4 months to 14 years). The clinical data and paraclinical tests were determined throughout and at the end of the study. The clinical indices included the number of painful joints (NPJ) and the number of swollen joints (NSJ), the global evaluation of the disease by the doctor (GEDD) and the patient (GEDP)[17]. The Childhood Health Assessment Questionnaire (CHAQ) was used to assess physical function in children, proposed by the American College of Rheumatology[18]. The CHAQ score included 13 questions. Special scores are added to the scoring obtained in questions 1-10 and the gained score from questions 11-13 is added to the index obtained. The paraclinical tests included complete blood count (leukocytes, neutrophils, and erythrocyte sedimentation rate (ESR)), acute-phase markers of inflammation (C-reactive protein (CRP)), aminotransferases and cholesterol levels. The median biological treatment with tocilizumab involved 14 therapy courses (from 6 to 24 courses).

Results

The research protocol included the following data: the patient's first and last name, date of birth, age, duration of disease at inclusion in the study, weight (kg) and height (cm), diagnosis and inclusion criteria, disease activity patterns and prognostic factors, and tocilizumab dosage.

The following data were determined at inclusion in the study: NPJ between 3 and 52 (average value 14.5), NSJ between 2 and 46 (average value 9.7), GEDD and GEDP[18] revealed similar values, averaging 80 mm (ranging from 50 mm to 100 mm). The CHAQ scores showed values between 10 and 20 (average value 14).

The paraclinical data available at inclusion in the study revealed an active inflammatory process: ESR up to 65 mm/h (average value 33 mm/h) and CRP between 12-384 IU/mL (average value 54.5 IU/mL). The Disease Activity Score (DAS28)[19] at inclusion showed a high level of activity, the average value being 6 (ranging from 4.3 to 10).

The first treatment did not show any clinical or paraclinical improvement in children with JIA, being unchanged until the end of the study. Thus, NPJ showed an average value of 7.7, whereas NSJ had an average value of 5 after a 3-month period biological treatment. GEDD and GEDP exhibited lower values, being on average 45 mm. The CHAQ score decreased to an average value of 8.5.

After a 3-month period biological treatment, the inflammatory tests significantly improved. Thus, the ESR average value was 10 mm/h and the C-reactive protein average value was 3 IU/mL. DAS28 revealed a moderate disease activity, the average value being 3.5.

After 6 months of treatment with tocilizumab, the average NPJ and NSJ values were 3.5 and 1.5, respectively. The GEDD and GEDP showed a decrease, averaging 30 mm. The CHAQ score decreased to an average of 7.

The paraclinical assessment after six months treatment with tocilizumab exhibited an ongoing improvement of the inflammatory process. Thus, the average ESR and CRP values were 6.5 mm/h and 5 IU/mL, respectively. DAS28 showed a milder disease activity, with an average value of 2.7.

After one year of treatment with the IL-6 inhibitor, an obvious clinical and paraclinical improvement was obtained. Thus, the mean NPJ and NSJ values were 1 and 0.5, respectively. The GEDD and GEDP decreased to an average of 16 mm. The CHAQ score decreased to an average value of 5. The inflammatory markers were normal after one year of treatment with the IL-6 inhibitor. Thus, the average ESR value was 4 mm/h, whereas the CRP was negative. DAS28 showed a drug-induced recurrence, the average value being 1.6.

Figure 1 shows that the average NPJ value was 14.5 at inclusion in the study, whereas after one year treatment with tocilizumab it decreased to an average value of 1. NSJ had an average value of 9.7 at inclusion in the study, decreasing to 0.5 after one year of treatment.

Figure 2 shows that the average value of the global evaluation of the disease on inclusion within the study was 80 mm, which decreased to an average value of 16 mm after one year of biological treatment.

Figure 3 shows that the average CHAQ score was 14 at inclusion in the study and decreased to an average value of 5 after one year of biological treatment.

The ESR had high values (average value 33 mm/h) at inclusion in the study, and decreased to normal values (4 mm/h), after one year of biological treatment (Figure 4a). CRP had also high values (average value 54.5 g/L) at inclusion in the study, and decreased to zero after one year of biological treatment (Figure 4b).

DAS28 at inclusion in the study showed high activity (average value 6), and decreased after one year of biological treatment, proving a drug-induced relapse (average value 1.6) (Figure 5).

The children included in the study experienced some side effects of tocilizumab treatment. Elevated cholesterol was found in 10 children (50%), which lowered to normal ranges after diet. Elevated aminotransferases were reported in 2 children (10%), which returned to normal levels after diet and treatment with hepatoprotective drugs. Headaches were recorded in 6 children (30%), vertigo in one child (5%), respiratory infections in 4 children (20%) – acute bronchitis was found in 3 children and bronchopneumonia in one child. We had one case of abscess in the upper third of the left arm. One patient had an allergic sensitization, which led to cessation of tocilizumab treatment.

The main limitation of the study is related to the small number of patients.

Discussion

JIA is a severe disease, which leads to a considerable functional impairment or even physical disability due to osteoarticular injuries, as well as premature death related to systemic disease, having a major medical, social and economic impact. To date, there are no sufficient data to highlight the JIA pathogenic patterns.

In a study of 112 children and adolescents with systemic JIA, who did not properly respond to the treatment with NSAIDs and systemic corticosteroids, intravenous tocilizumab was compared with placebo. This study reported that 85% of patients treated with tocilizumab responded to treatment and did not develop fever within three months, compared to 24% of placebo-treated patients[20]. Another clinical study was carried out in 11 Japanese children with severe and active systemic JIA, refractory to long-term treatment with high-dose corticosteroids, who underwent treatment with tocilizumab. Tocilizumab was found to abruptly reduce the disease activity in 10 out of 11 children, and was considered safe and well-tolerated by patients. American College of Rheumatology Pediatric 30 criteria (ACR Pedi 30) response was achieved in 91% of patients, ACR Pedi 50 in 91% of patients and ACR Pedi 70 in 64% of patients[21].

In the United Kingdom and in France, 15 Caucasian patients with systemic JIA were enrolled in an open-label trial of tocilizumab. ACR Pedi 30 responses were reported in 73% of patients and ACR Pedi 50 in 53% of patients[22].

A study on the efficacy and safety of tocilizumab was performed in 56 patients with systemic JIA who were refractory to conventional treatment. ACR Pedi 30, 50 and 70 responses were obtained in 91%, 86% and 68% of studied patients, respectively. The tocilizumab efficacy has been steadily increasing over time[23].

A randomized, double-blind, placebo-controlled, multinational study, which lasted for over 5 years, studied the safety and efficacy of intravenous tocilizumab administered within 12 weeks in 112 children with active systemic JIA. The patients' average age was 9.5 years and the average disease duration was 5 years. About half of the children presented fever and had an average of 19 affected joints. 85% of children who underwent tocilizumab treatment achieved a ACR Pedi 50 response and 71% of children achieved a ACR Pedi 70 response over a 12-week period[24].

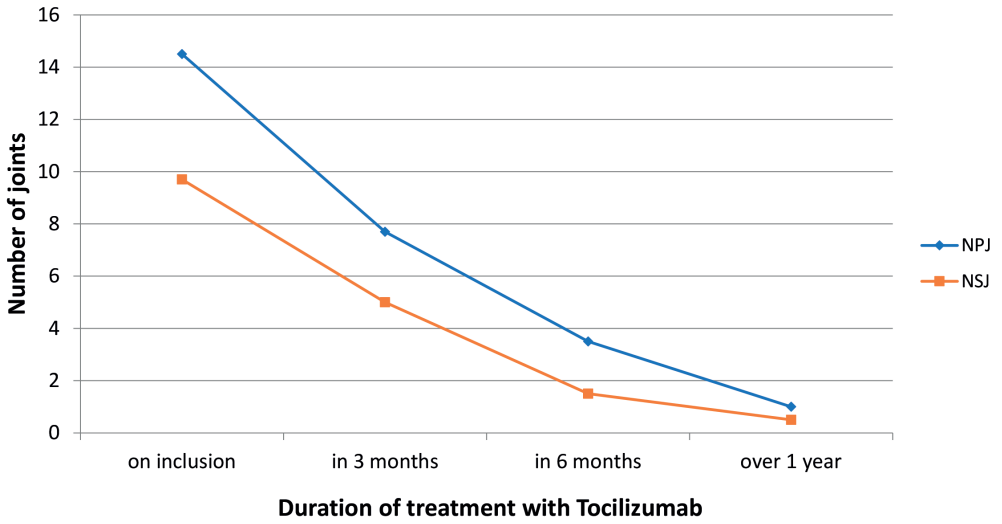

Figure 1. The dynamics in the number of painful joints (NPJ) and number of swollen joints (NSJ) in patients with JIA treated with tocilizumab.

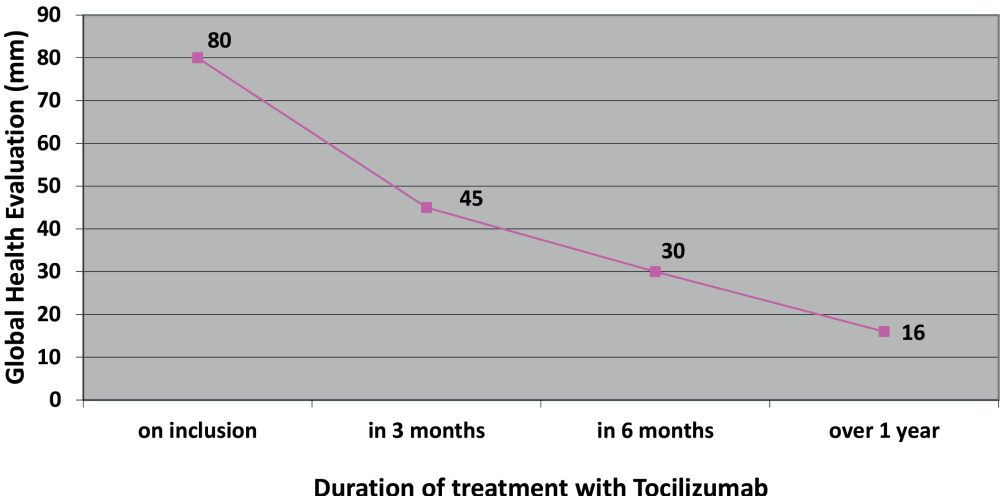

Figure 2. Dynamics of the global evaluation of the disease in patients with JIA treated with tocilizumab.

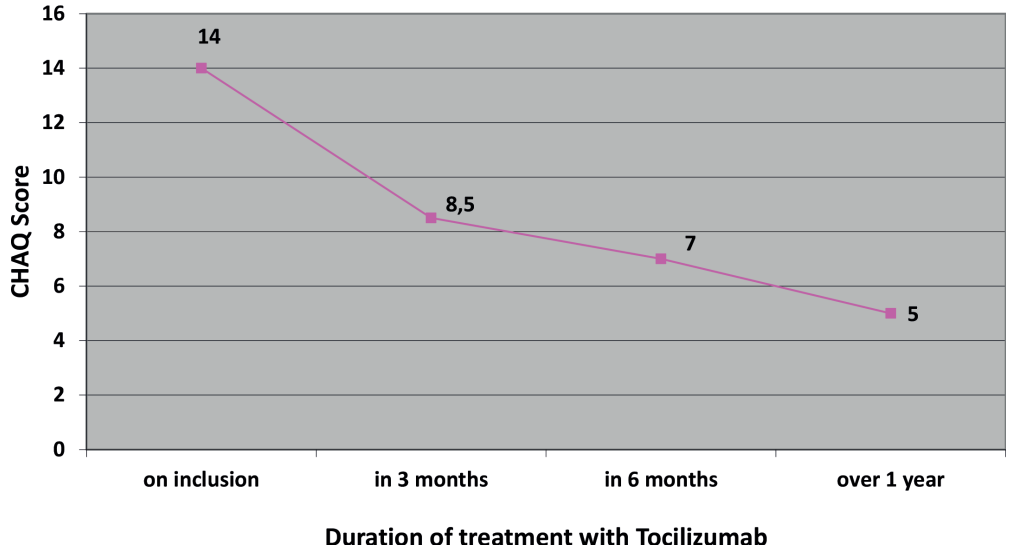

Figure 3. Dynamics of the Child Health Assessment Questionnaire (CHAQ) in patients with JIA treated with tocilizumab.

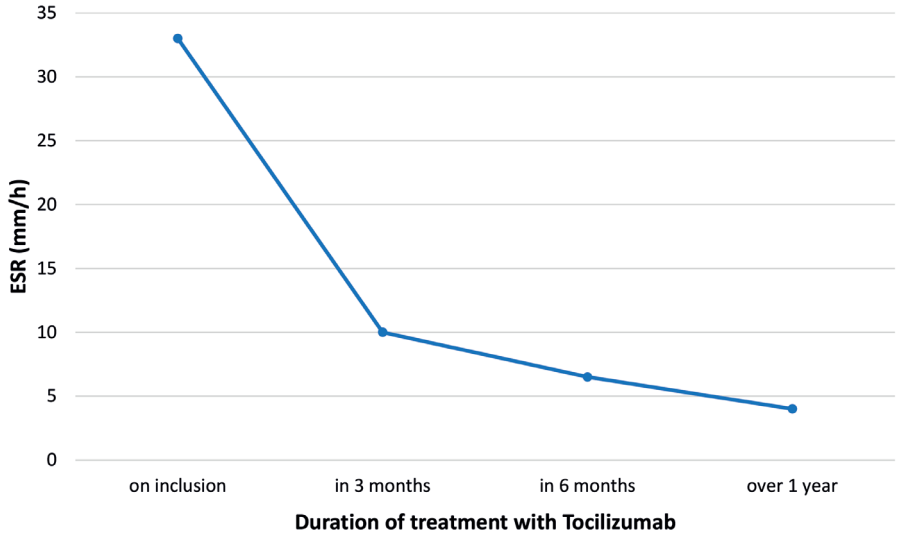

Figure 4a. Dynamics of erythrocyte sedimentation rate (ESR) in patients with JIA treated with tocilizumab.

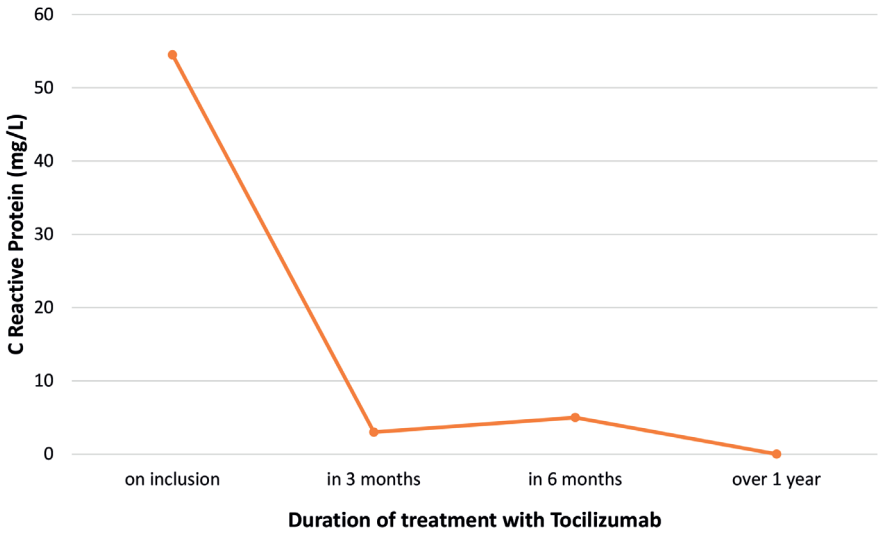

Figure 4b. Dynamics of C-reactive protein (CRP) in patients with JIA treated with tocilizumab.

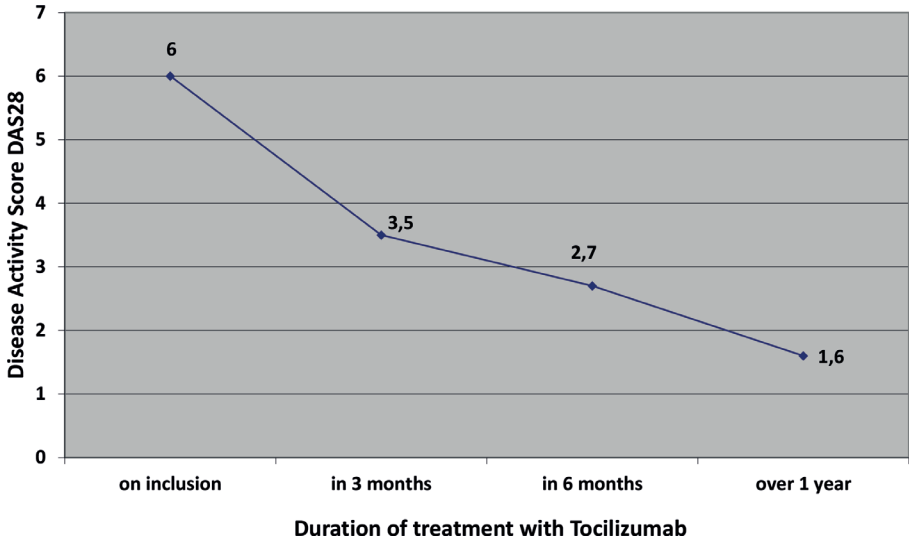

Figure 5. Dynamics of Disease Activity Score (DAS28) in patients with JIA treated with tocilizumab.

An observational study was performed in 56 patients with polyarticular JIA who were given tocilizumab during 24 months. The average disease duration was 5.2 years. Juvenile Arthritis Disease Activity Score-10 (JADAS-10) of 3.9 was reported in 58% of cases at 12 months and in 84% of cases at 24 months; inactive disease (JADAS-10 of 0.7) was found in 19% of cases at 12 months and 44% at 24 months; the clinically inactive disease was registered in 28% of cases at 12 months and in 46% at 24 months[25].

All the studies show that tocilizumab was safe and well-tolerated by patients, it reduced the disease activity and presented high efficacy in JIA.

Conclusions

Children with JIA treated with tocilizumab showed a considerable clinical improvement in terms of a low number of painful and swollen joints, as well as of the overall assessment of the disease activity by the patient and the doctor and the CHAQ score.

The paraclinical tests revealed a lower active inflammatory response following the tocilizumab treatment.

Author Contributions:

N.R., A.C., L.M.-N., S.F., R.E., O.G., V.I., L.B. were responsible for clinical diagnosis, paraclinical investigations, treatment decisions and follow up of the patients. N.R., A.C. wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patients included in the study"

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