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ORIGINAL PAPER

TREATMENT WITH GOLIMUMAB 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 golimumab treatment in patients with 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 and exclusion criteria for patients to undergo the biological treatment were according to ACR (American College of Rheumatology) recommendations. This study included 17 children with JIA, in whom golimumab was administered every month. The number of painful and swollen joints, the global evaluation of the disease by the 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.

Résumé

Le traitement au golimumab 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 golimumab dans le traitement de l'AJI.
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 et d'exclusion des patients dans le traitement biologique ont été selon les recommandations de l'ACR (Collège Américain de Rhumatologie). L'étude a été faite sur 17 enfants souffrant d'AJI, qui ont reçu du golimumab toutes les quatre semaines. Le nombre d'articulations douloureuses, d'articulations tuméfiées et l'évaluation générale de la maladie ont été déterminés par le médecin et le patient ainsi que

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Results. Children treated with golimumab exhibited fewer 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 golimumab showed a considerable clinical improvement and the paraclinical indices revealed a lower active inflammatory response.

Keywords: juvenile idiopathic arthritis, golimumab, 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

Résultats. Les enfants souffrant de l'AJI traités avec du golimumab, 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 aiguë, de la vitesse de sédimentation des érythrocytes et de la protéine C-réactive chez les patients traités par le golimumab.
Conclusions. Les enfants atteints d'AJI et traités par golimumab ont montré une amélioration clinique considérable et les indices paracliniques ont présenté une réponse inflammatoire active plus faible.

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

Introduction

Juvenile idiopathic arthritis (JIA), as defined by International League of Associations for Rheumatology (ILAR)[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.

JIA is an autoinflammatory disease that is likely to be related to innate abnormality of the immune system. Interactions between macrophages, T cells, B cells, and fibroblasts play an important role in the pathogenesis of JIA. These interactions are stimulated by cytokines, which might induce the production of other pro-inflammatory cytokines[2]. JIA is an autoinflammatory condition in which IL-1 (interleukin-1) is involved as a pivotal cytokine, whereas lympho-histiocytes play a key role. High levels of TNF-α (tumour necrosis factor alpha), IL-1β and IL-6 have been reported in joints affected by JIA[3]. Under the action of several unknown factors, the abnormal activation of phagocytes, monocytes, macrophages, and neutrophils occurs by releasing pro-inflammatory cytokines IL-1, IL-6, IL-18, and pro-inflammatory proteins S100, resulting in a systemic inflammation[4,5].

TNF-α is a pro-inflammatory cytokine. It is a 26 kDa membrane-bound molecule from which a 17 kDa soluble active TNF-α molecule is released by the TNF-α converting enzyme. The circulating TNF-α levels are highly variable[6].

The cytokine TNF-α is involved in several biological processes such as tissue remodelling, epithelial cell barrier permeability, macrophage activation, inflammatory cell recruitment, local and systemic inflammation efficiency, and activation of other cytokine pro-inflammatory actions. The biological functions of TNF-α are related to the concentration and length of exposure to the TNF-α molecule[6].

Under acute conditions, local TNF-α production might positively result in increased expression of adhesion molecules on the vascular endothelium, which allows macrophages and neutrophils to reach the impaired tissue sites. TNF-α activates phagocytes to remove infectious agents and cellular debris. A systemic or long-term exposure to TNF-α may be harmful. The regulation of TNF-α gene expression is involved in the pathogenesis of several autoimmune

inflammatory diseases such as systemic lupus erythematosus, juvenile idiopathic arthritis, and inflammatory bowel disease[6].

TNF-α acts by binding to the cellular TNF receptor (TNFR) present in all the body cells. The TNFR family members include the first two discovered viz. TNFR1 and TNFR2. TNFR2 has a higher affinity for TNF-α, especially at lower molecular concentrations, and induces T-lymphocyte proliferation. TNFR1 requires high concentrations of TNF-α and induces cell death due to cytotoxicity and apoptosis. Both TNFRs are produced in soluble forms, neutralizing the TNF-α activation by competing with cell-bound receptors. Soluble TNF receptors stabilize TNF-α molecules and prevent their degradation. Mutations in TNFR are likely associated with autoinflammatory syndromes[6].

Elevated levels of TNF-α are associated with acute inflammatory response. In some patients, high levels of circulating TNF-α are much higher than in others[6].

TNF-α plays a key role in initial and long-term inflammatory process and joint destruction by controlling the production of interleukin-1 (IL-1) and other pro-inflammatory cytokines, including interleukin-6 (IL-6) and interleukin-8 (IL-8). TNF-α mediates inflammation and joint destruction by inducing cells to synthesize and release inflammatory metalloproteinases, prostaglandins, and nitric oxide in numerous cell types, as well as by inhibiting the production of matrix components. High levels of TNF-α are found in the synovial fluid of the JIA patients, thus confirming the key role of TNF-α[6].

In the light of the foregoing, the inhibition of TNF-α activity is a current issue in JIA therapy.

Golimumab is a human IgG1 monoclonal antibody specific for human tumour necrosis factor alpha (TNF-α) that exhibits multiple glycoforms with a molecular mass of approximately 150-151 kilodaltons. Golimumab is a sterile antibody solution supplied either as a single-dose prefilled syringe (with a passive safety needle guard) or as a single-dose prefilled autoinjector. Golimumab is administered in two dosages, viz. 50 mg golimumab antibody in 0.5 ml solution and 100 mg golimumab antibody in 1 ml solution. At a dose of 50 mg, each 0.5 ml of Golimumab contains 50 mg of the Golimumab antibodies. At a dose of 100 mg, each 1 ml of Golimumab contains 100 mg of Golimumab antibodies[7].

Golimumab is a human monoclonal antibody that binds to both soluble and transmembrane bioactive forms of human TNF-α. This interaction prevents TNF-α from binding to its receptors, thus inhibiting the biological activity of TNF-α. There was no evidence of the golimumab antibody binding to other TNF superfamily ligands; in particular, the golimumab antibody did not bind or neutralize human lymphotoxin. Golimumab does not lyse human monocytes expressing transmembrane TNF in the presence of complement or effector cells. Elevated levels of TNF-α in the blood, synovium, and joints have been involved in the pathophysiology of several chronic inflammatory diseases, such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. TNF-α is an important mediator of joint inflammation that is characteristic of these diseases. Golimumab modulates the in vitro TNF-mediated biological effects within several biological assays, including the adhesion protein expression involved in leukocyte infiltration (E-selectin, ICAM-1 and VCAM-1) and the secretion of proinflammatory cytokines (IL-6, IL- 8, G-CSF and GM-CSF)[8].

The clinical studies showed a decrease in the level of C-reactive protein, interleukin-6 (IL-6), matrix metalloproteinase-3 (MMP-3), intercellular adhesion molecule (ICAM-1) and vascular endothelial growth factor (VEGF) following golimumab intake[8].

Golimumab is administered at a dose of 30 mg/m^2 body surface area, up to a maximum of 50 mg/dose every 4 weeks. Following subcutaneous administration of golimumab, the median time to reach time to peak concentration (Tmax) ranged from 2 to 6 days. The absolute bioavailability of subcutaneously administered golimumab accounted for approximately 53%. Administration of non-steroidal anti-inflammatory drugs, oral corticosteroids, or sulfasalazine combined with golimumab does not affect its clearance[8].

Numerous studies have shown the efficacy and safety of golimumab biological therapy in children with JIA[13,14,15].

The objective of study was to determine the clinical and laboratory efficacy of golimumab treatment in patients with JIA.

Material and methods

The prospective study took place in Division of Rheumatology, Public Healthcare Institution – Mother and Child Institute, Chisinau, Republic of Moldova, between 2018-2021 (11th of October 2018 – 29th of November 2021). 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 (approval number 3, from 10.09.2018).

The inclusion criteria for patients to undergo the biological treatment according to ACR (American College of Rheumatology) recommendations[9]:

- Golimumab can be given to patients aged 2 years and older.
- Active RF (rheumatoid factor)-positive/RF-negative polyarticular JIA with onset ≥6 months.
- Systemic JIA with no systemic manifestations and polyarthritis lasting ≥ 6 months.
- Oligoarticular JIA (extended).
- Active psoriatic arthritis with polyarticular involvement.
- Active JIA, despite the use of oral/subcutaneous/intramuscular methotrexate therapy for at least 3 months at a weekly dose of ≥10 mg/m^2;
- If glucocorticosteroids are administered, a constant dose of prednisolone ≤10 mg or 20 mg/kg/day for ≥4 weeks should be given prior to golimumab intake;
- The patients do not have a history of latent or active TB; there are no signs and symptoms suggestive of active TB on clinical examination.

Criteria for exclusion of patients from the biological therapy group according to ACR recommendations[9]:

✓ Allergies, hypersensitivity or intolerance to golimumab or other immunoglobulins or their excipients;
✓ Prior macrophage activation syndrome;
✓ Initiation of DMARDs (Disease-modifying antirheumatic drugs) and/or immunosuppressive therapy 4 weeks prior to starting the research;
✓ Presence of another inflammatory disease that may interfere with the assessment of golimumab therapy, including, but not limited to, systemic lupus erythematosus and Lyme disease;
✓ Treatment with intra-articular, intramuscular or intravenous glucocorticosteroids, 4 weeks prior to the first administration of the drug under study;
✓ Severe infections, tuberculosis;
✓ Malignancy;
✓ Immunodeficiency;
✓ Organ failure.

The prospective study included 17 children with JIA (10 girls and 7 boys). Polyarticular JIA was found in 8 children, extended oligoarticular JIA – in 6 children, arthritis with enthesitis – in 3 children. The average age of patients included in the study was 12 years (ranging from 5 to 17 years old). The disease duration at the time of inclusion in the study was on average 46 months (lasting from 4 months to 120 months). 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)[10]. The Childhood Health Assessment Questionnaire (CHAQ) was used to assess physical function in children, proposed by the American College of Rheumatology[11]. 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 biological treatment with golimumab involved 6 therapy 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 golimumab dosage.

The following data were determined at inclusion in the study: NPJ between 1 and 28 (average value 10.7), NSJ between 0 and 22 (average value 5.2), GEDD and GEDP[10] revealed similar values, averaging 64.7 mm (ranging from 50 mm to 90 mm). The CHAQ scores showed values between 4 and 16 (average value 9.8).

The paraclinical data available at inclusion in the study revealed an active inflammatory process: ESR up to 50 mm/h (average value 18 mm/h) and CRP up to 48 IU/mL (average value 10.9 IU/mL). The Disease Activity Score (DAS28)[12] at inclusion showed a moderate level of activity, the average value being 4.3 (ranging from 3 to 7.82).

The first treatment showed some clinical or paraclinical improvement in children with JIA. Thus, NPJ showed an average value of 5.8, whereas NSJ had an average value of 2.4 after a 3-month period biological treatment. GEDD and GEDP exhibited lower values, being on average 37.8 mm. The CHAQ score decreased to an average value of 6.1.

After a 3-month period biological treatment, the inflammatory tests significantly improved. Thus, the ESR average value was 10.1 mm/h and the C-reactive protein average value was 6.8 IU/mL. DAS28 confirmed drug-induced remission, with a mean of 2.4.

After 6 months of treatment with golimumab, the average NPJ and NSJ values were 5.6 and 1.2, respectively. The GEDD and GEDP showed a decrease, averaging 30 mm. The CHAQ score decreased to an average of 5.

The paraclinical assessment after six months treatment with golimumab exhibited an ongoing improvement of the inflammatory process. Thus, the

average ESR and CRP values were 11.3 mm/h and 1.3 IU/mL, respectively. DAS28 revealed a drug-induced remission, with a mean value of 2.4.

Figure 1 shows that the average NPJ value was 10.7 at inclusion in the study, whereas after six months treatment with golimumab it decreased to an average value of 5.6. NSJ had an average value of 5.2 at inclusion in the study, decreasing to 1.2 after six months of treatment.

Figure 2 shows that the average value of the global evaluation of the disease on inclusion within the study was 64.7 mm, which decreased to an average value of 30 mm after six months of biological treatment.

Figure 3 shows that the average CHAQ score was 9.8 at inclusion in the study and decreased to an average value of 5 after six months of biological treatment.

The ESR had high values (average value 18 mm/h) at inclusion in the study, and decreased to 11.3 mm/h, after six months of biological treatment (Figure 4). CRP had also high values (average value 10.9 g/L) at inclusion in the study and decreased to 1.3 g/L after six months of biological treatment (Figure 5).

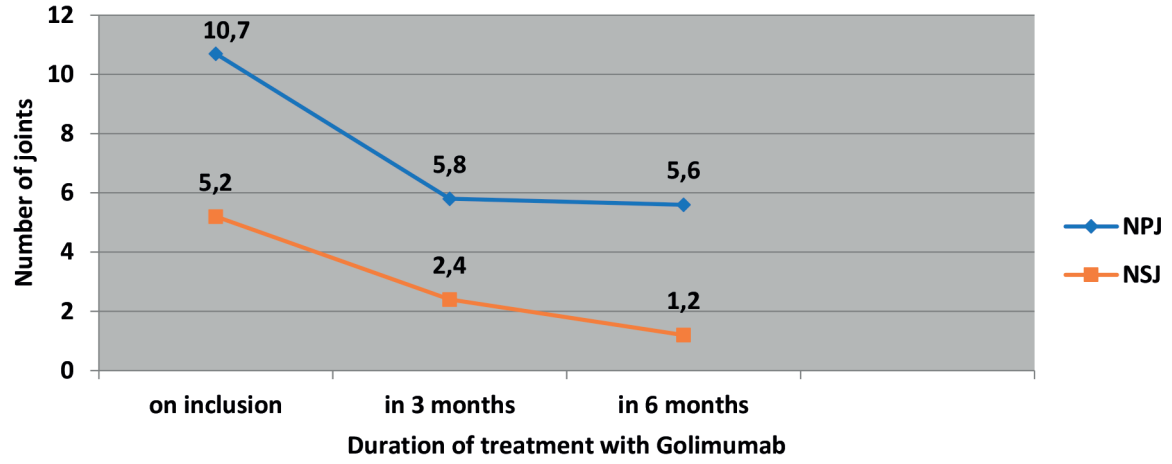

Figure 1. The dynamics in the number of painful joints (NPJ) and number of swollen joints (NSJ) in patients with JIA treated with golimumab.

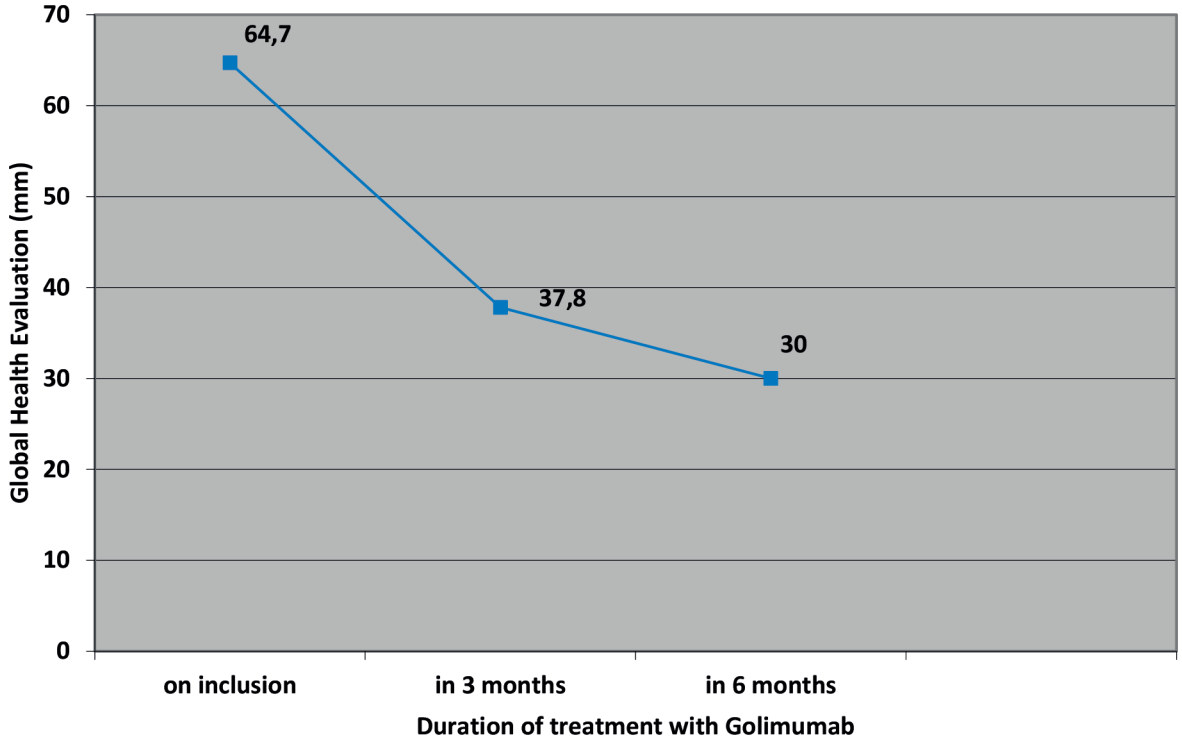

Figure 2. Dynamics of the global evaluation of the disease in patients with JIA treated with golimumab.

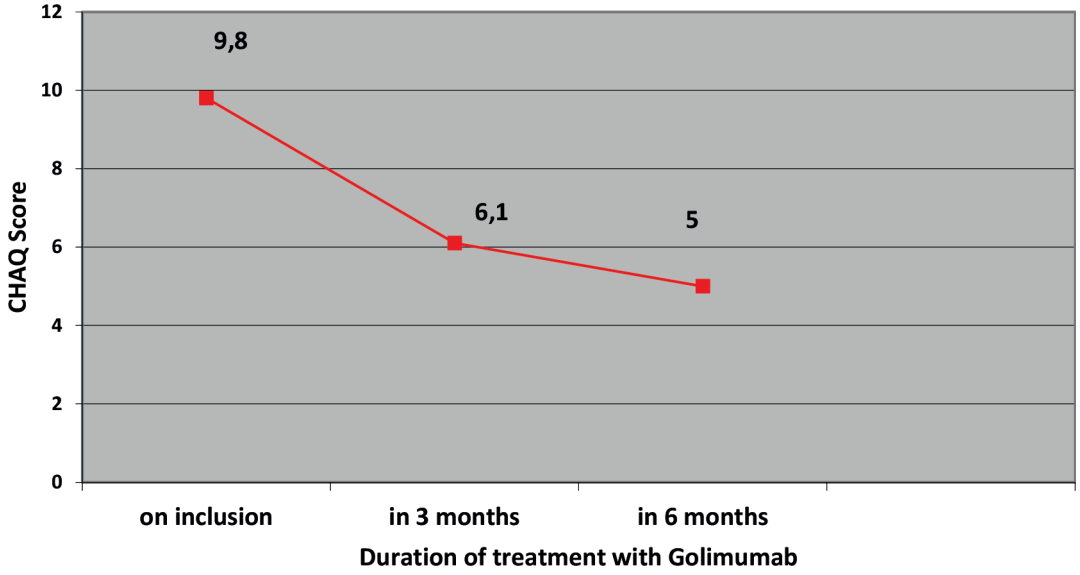

Figure 3. Dynamics of the Child Health Assessment Questionnaire (CHAQ) in patients with JIA treated with golimumab.

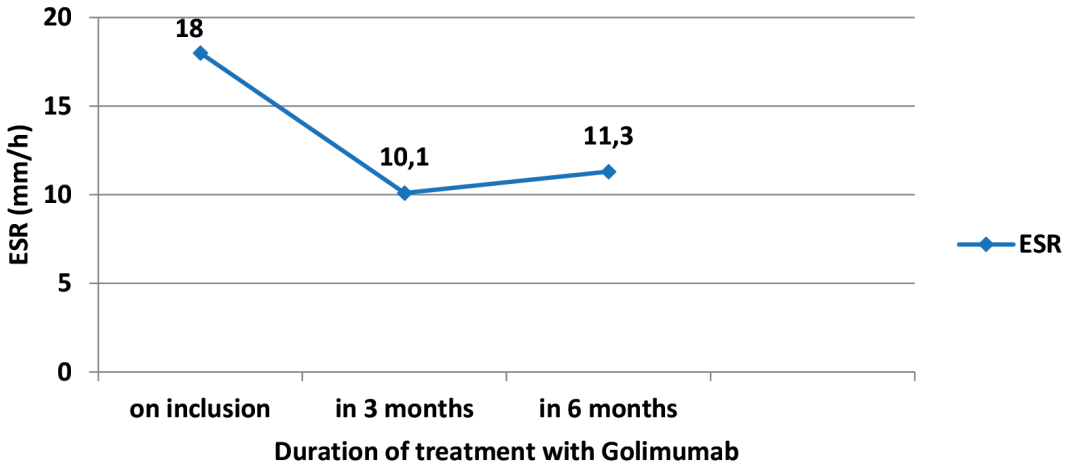

Figure 4. Dynamics of erythrocyte sedimentation rate (ESR) in patients with JIA treated with golimumab.

DAS28 at inclusion in the study showed moderate activity (average value 4.3), and decreased after six months of biological treatment, proving a drug-induced relapse (average value 2.4) (Figure 6).

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

Discussion

Juvenile idiopathic arthritis is a severe disease that leads to severe impairment of functional ability up to physical disability due to osteoarticular injuries, causing premature death due to systemic diseases, thus showing a great medical, social, and economic impact. To date, the underlying pathogenic mechanisms of JIA remain unclear or insufficiently highlighted.

In a randomized, double-blind, placebo-controlled study, all patients received golimumab (30 mg/m^2 body surface area; the highest dose: 50 mg/dose) every 4 weeks with weekly methotrexate therapy. Of 173 polyarticular JIA patients included within the study, 89.0% had an ACR30 response, 79.2% had an ACR50 response, 65.9% had an ACR70 response, and 36.4% had an ACR90 response. Golimumab resulted in a rapid and significant clinical improvement in children with active polyarticular JIA. Golimumab was well tolerated and no unexpected adverse effects occurred[13].

A single-centre, retrospective study included patients with JIA treated with golimumab for active uveitis after treatment failure with adalimumab. Ten female patients (17 eye impairment, mean age

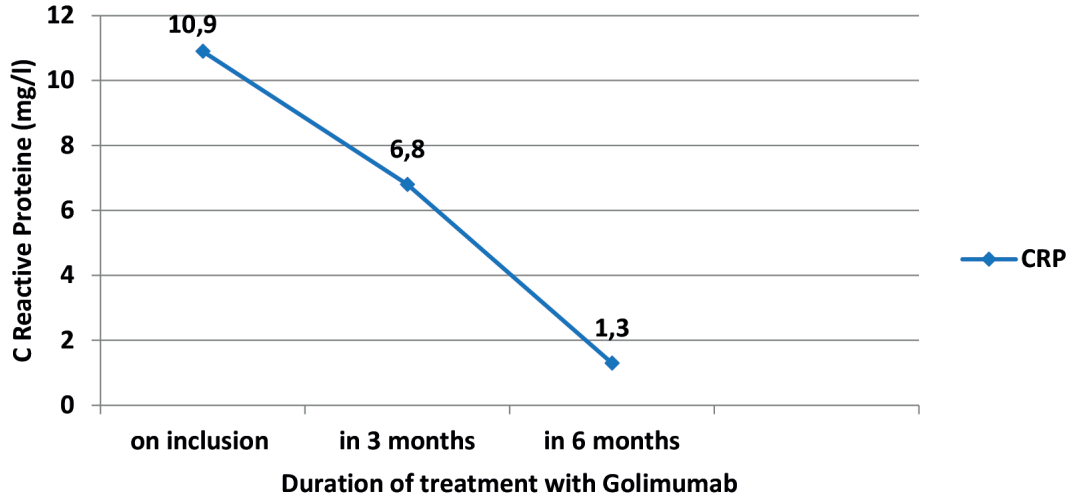

Figure 5. Dynamics of C-reactive protein (CRP) in patients with JIA treated with golimumab.

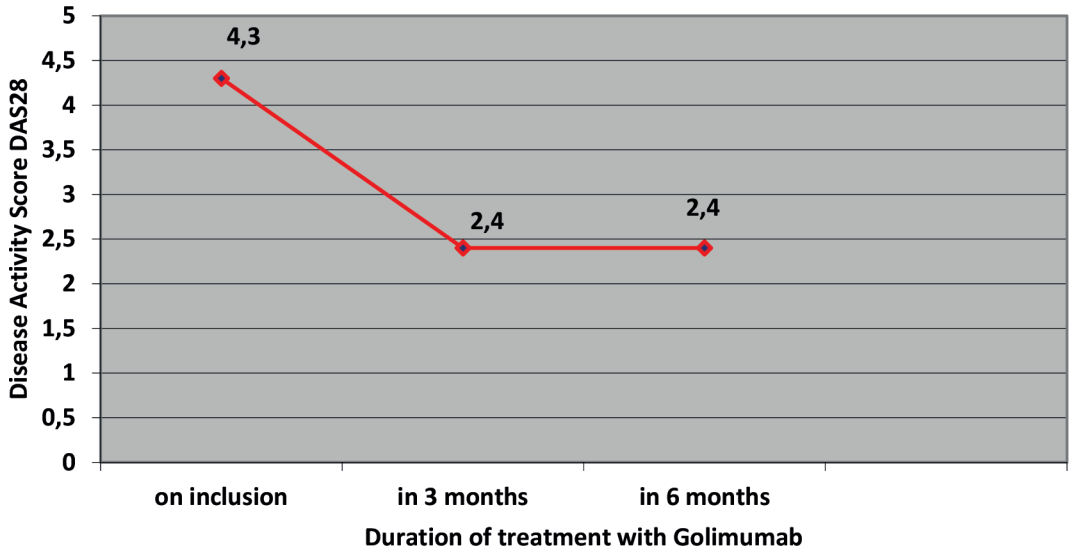

Figure 6. Dynamics of Disease Activity Score (DAS28) in patients with JIA treated with golimumab.

14.3±6.7 years) were examined. Two patients were switched to golimumab due to primary non-response to adalimumab, 8 children due to a response failure. Anti-adalimumab neutralizing antibodies were associated with 5 patients with a response failure. Golimumab-associated response was reported in 8 patients with a response failure, whereas 2 patients, with no primary response to adalimumab, experienced a response failure to golimumab, as well. Three out of 8 respondents had a response failure. At the end of the study, 4 of the remaining 5 respondents had a complete treatment response. One patient showed a partial response. Golimumab is an effective treatment option for patients, who have a response failure to adalimumab. Patients without a primary response to adalimumab should be switched to a biological agent with a different action mechanism instead of further blocking the TNF-alpha pathway[14].

In a study performed by Ruperto et al, 127 children aged 2-18 years with active polyarticular JIA, despite undergoing a 2-month methotrexate therapy, received 80 mg/m^2 golimumab at week 0, 4, then every 8 weeks until week 52 plus methotrexate therapy weekly until week 28. A total of 127 children were treated with Golimumab. Of these 127 patients, 113 (89%) remained within the study until week 52. The patients' mean age upon inclusion was 13 years, most patients being females (73%) with RF-negative (43%) and RF-positive (35%) polyarticular JIA. The most common previously used drugs included nonsteroidal anti-inflammatory drugs (94%) and systemic glucocorticoids (57%). Thus, 28 patients (22%) received

prior biological treatment. Of these, 25 patients underwent a prior anti-TNF therapy; the majority (80%) received etanercept. Upon inclusion in the study, 72% of patients were taking non-steroidal anti-inflammatory drugs, 37% were administering oral glucocorticoids, and 10% were taking DMARDs other than methotrexate. At weeks 28 and 52, the mean score improved up to 92% and 96% for the physician's global assessment (PGA) of disease activity, up to 63% and 70% for the patient's global assessment of disease activity (PtGA), 94% and 100% for the number of active joints, 89% and 85% for the number of joints with limited mobility, 57% and 63% for physical functioning assessed by CHAQ and 53% and 48% for C-reactive protein, respectively. ACR30, 50, 70 and 90 responses were reported as early as week 4. At week 28, 70% of patients showed at least an ACR70 response and almost half (47%) of them achieved ACR90, the response rates being maintained until week 52. The following response rates were recorded: ACR30 – 84%, ACR50 – 80%, ACR70 – 70% and ACR90 – 47% at week 28, being maintained until week 52. Golimumab was well tolerated and provided good clinical efficacy in children and adolescents with active polyarticular JIA[15].

Conclusions

Children with JIA treated with golimumab 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 golimumab treatment.

Author Contributions:

N.R., A.C., L.M.-N., S.F., R.E., V.I. 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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None

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