

EVALUATION OF PEDIATRIC PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS TREATED WITH BIOLOGICAL THERAPY TOCILIZUMAB (ACTEMRA)

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Abstract

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Juvenile idiopathic arthritis (JIA) is the most common chronic disease in childhood. It manifests a heterogenic group of symptoms of arthritis, lasting at least 6 weeks and it appears before the age of 16. Patients who had no good therapeutic response to conventional therapy with Methotrexate were treated with biological therapy. The aim of this paper was to evaluate 9 patients who were receiving Tocilizumab at the Department of Rheumatology, University Clinic of Pediatric Diseases in Skopje. Materials and methods: Our study included 9 patients treated at our Department with biological therapy with Tocilizumab. Prior to initiation of the biological therapy, all patients underwent laboratory investigations, purified protein derivative (PPD) skin test for tuberculosis, X ray of the lungs and heart, and analysis of hepatitis markers. All patients were treated with amp. Actemra (tocilizumab) 8 mg/kg/12 h i.v. Two of the patients had a severe form of the disease (one with severe systemic form and one with severe oligoarticular form of JIA). All presented patients had clinical remission of the disease. Conclusion: Therapy with tocilizumab in patients with juvenile idiopathic arthritis is a good therapeutic choice. The results obtained in our study have shown a significant therapeutic effect of tocilizumab even in severe forms of the disease.

Клинички испитувања

ЕВАЛУАЦИЈА НА ПЕДИЈАТРИСКИ ПАЦИЕНТИ СО ЈУВЕНИЛЕН ИДИОПАТСКИ АРТРИТ ТРЕТИРАНИ СО БИОЛОШКА ТЕРАПИЈА ТОЦИЛИЗУМАБ (АСТЕМРА)

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Извадок

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Печатарски права: ©2021 Марија Нешковска-Шуменковска, Аспазија Софијанова, Розана Кацарска, Констандина Кузевска-Манева, Бети Ѓуркова-Ангеловска, Валентина Јовановска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Јувенилниот идиопатски артрит е најчеста форма на хронично заболување во детската возраст, кое се манифестира со хетерогена група на симптоми на артрит коишто траат најмалку 6 недели, а се појавиле пред 16-годишна возраст. Пациентите кои не дадоа добар тераписки одговор на конвенционалната терапија со Метотрексат, беа префрлени на биолошка терапија. Целта на оваа студија беше да изврши евалуација на 9 пациенти кои примаа тоцилизумаб на Одделот за реуматологија на Универзитетската клиника за детски болести во Скопје. Материјали и методи: Во нашата студија беа вклучени 9 пациенти третирани на нашиот Оддел со Тоцилизумаб во период од 2010-2020 година. Кај сите пациенти пред започнување на терапијата беа направени лабораториски иследувања, прочистен протеински деривативен кожен тест за туберкулоза (ППД), РДГ на градите, и маркери за хепатит. Сите пациенти беа третирани со амп. Актемра 8мг/кг/12 и.в. Два пациента имаа тешка клиничка презентација на јувенилен идиопатски артрит (првиот со тешка системска форма на болеста, а вториот со тешка олигоартикуларна форма). Кај сите третирани пациенти настана ремисија на клиничката слика по спроведување на терапијата. Заклучок: Биолошката терапија со тоцилизумаб кај пациентите со јувенилен идиопатски артрит е добар тераписки избор. Резултатите покажаа сигнификантен тераписки ефект дури и кај потешките облици на болеста.

Introduction

Juvenile idiopathic arthritis is the most common chronic disease in childhood. It is manifested with a heterogenic group of symptoms of arthritis, lasting at least 6 weeks, which appear before the age of 16^{1,2}. Juvenile idiopathic arthritis is divided in 7 subgroups according to ILAR classification:

1. Oligoarticular arthritis - arthritis of one to four joints in the first 6 months from the beginning of the disease (there are persistent and extended forms of this type),
2. Rheumatoid factor (RF) positive polyarticular arthritis - arthritis of five or more joints in the first 6 months from the beginning of the disease; RF is positive in the last three months.
3. RF negative polyarticular arthritis - arthritis of five or more joints in the first 6 months from the beginning of the disease; RF is negative.
4. Systemic juvenile idiopathic arthritis (sJIA) - fever, rash on the body, hepatosplenomegaly in duration of 2 weeks at least.
5. Arthritis with enthesitis - sacroiliitis, lumbosacral pain, HLA B27 genotyping, ankylosing spondylitis,
6. Psoriatic juvenile arthritis - psoriasis and arthritis,
7. Undefined JIA - extra-articular manifestations of the disease are: chronic uveitis, hepato/splenomegaly, pleuritis, pericarditis. These manifestations are often part of a systemic form of juvenile idiopathic arthritis³. Therapeutic procedures include basal therapy with NSAID,

and tabl. Methotrexate as DMARD (disease-modified antirheumatic drug)^{4,5}. Patients who have had no good response to therapy with Methotrexate are candidates for biological therapy (Biological DMARDS). Components of biological therapy have endogen proteins who specifically induced the immune response in the body, especially through the cytokine pathway^{6,7,8}.

The aim of this paper was to evaluate pediatric patients who received biological therapy with Tocilizumab.

Material and methods

In the period of 10 years (2010 - 2020), a total of 115 patients with diagnosis of juvenile idiopathic arthritis were followed-up and treated at the Department for Rheumocardiology. Of all these patients 97 received Methotrexate therapy, 9 patients received biological therapy with Adalimumab (Humira) and with Tocilizumab (Actemra). All 9 patients received 8 mg/kg i.v. every four weeks. All patients were treated according to the International League of Associations for Rheumatology (ILAR) classification criteria. Of the 9 evaluated patients, 5 were males and 4 females. Patients were aged from 7 - 19 years (mean age 14 years). Prior to initiation of the biological therapy with Tocilizumab in all 9 patients, they underwent laboratory analysis (blood count, CRP, hepatic transaminases, lipids), PPD, X-ray of the lungs and the heart, rheumatoid antibody (RF, ANA, ADNA, anti-ccp, anti-ssa, anti-ssb, lupus cells). Patients were classified according to the ILAR classifications of patients with systemic form of juvenile idiopathic arthritis, monoarticular, oligoarticular, polyarticular (RF positive), polyarticular (RF negative), arthritis with

enthesitis (sacroiliitis), psoriatic form and undefined form. HLA genotyping was also made. According to their place of birth, our patients were divided in two groups (patients from town and patients from village). Osteodensitometry was performed in two of our patients because of suspicion for osteoporosis.

Results

According to gender, of 9 patients 5 were male (55%) and 4 female (44%). We evaluated our patients according to duration of therapy with Tocilizumab.

Table 1. Patients treated with biological therapy Tocilizumab (Actemra) according to duration of therapy.

Duration of therapy with Tocilizumab	5 years	4 years	3 years	1 year
Number of patients	4	1	2	2
Percentage (%)	44%	11%	22%	22%

Table 1. shows that according to duration of therapy 4 patients of our 9 patients were treated with Tocilizumab for 5 years; therapy lasted 4 years in 1 patient, 3-year-therapy re-

ceived 2 patients and 1-year-therapy received 2 patients. Thus, most of the patients received therapy with Tocilizumab in a period of 5 years.

Table 2. Patients treated with Tocilizumab (Actemra) therapy according to ILAR classification

Systemic	Monoarticular	Oligoarticular	RF positive Polyarticular	RF negative Polyarticular	Sacroiliitis	Undefined arthritis
1	0	3	1	3	1	0

Table 2. shows that according to the ILAR classification, 1 patient was with a systemic form of the disease, 1 with sacroiliitis, 3 patients were with oligoarticular form, 4 patients were with polyarticular form of the disease. Table 2 shows that most of the patients were with oligoarticular juvenile idiopathic arthritis and RF negative polyarticular form of juvenile idiopathic arthritis (33%).

Two patients were with severe clinical presentation of juvenile idio-

pathic arthritis (one with systemic form presented with tachycardia, chest pain and signs for pericarditis, treated with Verapamil, and the other patient was with severe oligoarthritis presented with pericarditis, contractures of the joints, and was treated with diuretics and anti-inflammatory drugs). Both patients continued with biological therapy with Tocilizumab (amp. Actemra) and presented with a good therapeutic effect.

In the other 7 patients, therapy with Tocilizumab showed a good therapeutic effect resulting in a reduced number of inflamed joints and better quality of life.

We evaluated our patients according to allergic manifestations while they were receiving therapy with Tocilizumab.

Table 3 Allergic manifestation in patients treated with Tocilizumab

Allergic manifestations	Number of patients
Urticaria (rash)	2
Severe abdominal cramps	1
No allergy manifestation	6

Allergic manifestations appeared in 3 of our patients, two of them manifested urticaria, and one had severe abdominal cramps (Table 3). Thus, therapy was discontinued for a short period, and after that they all completed the biological therapy.

Regarding rheumatoid antibody, 3 of our 9 patients had negative rheumatoid antibodies, two had positive ANA (antinuclear antibodies) 1:160, the other antibodies were negative. Osteoporosis was registered in 2 of our patients, which was detected with osteodensitometry. HLA genotyping was realized in 3 of our patients. One patient with sacroiliitis had HLA B27, and the same genotyping had two of the patients (monozygotic twins) with oligoarticular form of the disease. From 9 patients treated at our Clinic after 14 years, 6 patients were transferred to the University Clinic for Adult Rheumatology; of these, 4 were males and 2 were females, the other patients continued to be followed at our Clinic.

Discussion

Immunological system has a central role in maintaining identity and in-

tegrity of the body. Basal immunological reactions based on the ability of the immunological system to recognize strange molecules and antigens, and to have a good response, and, on the other side, to recognize its own molecules. Reaction of the body to pathogens can be nonspecific and specific. In rheumatology, this reaction is nonspecific presented by cytokines like IL-1, IL-6 and TNF α .

In 2014, our Department published a study presenting 4 patients who received biological therapy. Patients had different forms of the disease. In a patient with arthritis with enthesitis, HLA B27 was found by using HLA typing test. In a patient with systemic form and oligoarticular form with chronic eye inflammation of anterior eye segment, positive ANA antibodies were found. All patients were treated according to the ILAR criteria, and had good therapeutic response (ACR Pedi 70-90%)¹⁰. After completion of this study, we have continued to evaluate patients who received biological therapy and we published the results obtained in other studies. In our series of patients, all showed a good response to therapy with Actemra in combina-

tion with Methotrexate. One patient received a combination of Tocilizumab and Leflunomide (ARAVA), but he also showed a good response to therapy. Therapeutic effect was good in a patient with severe systemic form and severe oligoarticular form of the disease^{4,5,11}.

Osteoporosis is a typical systemic manifestation of rheumatic arthritis. There were 2 patients in our study who had osteoporosis detected with osteodensitometry. One of these patients received bisphosphonates (Pamidronate) in addition to the biological therapy, other patient was given Ca and vit. D and he is a candidate for bisphosphonate therapy¹³. Tocilizumab is a recombinant human anti-IL-6 antibody. In clinical trials realized in three phases in patients with RA in Japan, Tocilizumab monotherapy at a dose of 8 mg/kg showed clinical efficacy equaling that of tumor necrosis factor (TNF) inhibitor in combination with Methotrexate. This combination is also used in pediatric population with a success. The safety profile of Tocilizumab appears to be satisfactory. However, several serious infections have been reported in different studies and therefore, careful monitoring is important during the use of this therapy. In 3 of our patients allergic reactions appeared after one application, and hence, after this, the patients were given Tocilizumab therapy^{7,8,9}.

The University Clinic for Rheumatology published 2 studies about safety of treatment with Actemra in a patient with early, and severe rheumatoid arthritis in 2017 and 2020. The studies were multicenter open-label. Both studies proved the safety of using biological therapy with Tocilizumab and with a very good

therapeutic response. The effect of the clinical response to Tocilizumab was fast and seen after just two weeks of application. Moreover, the magnitude of the effect increased in the studies with the increase of the duration of treatment^{14,15}.

Many studies have confirmed benefits from the biological therapy with Tocilizumab: CHARISMA study, CHERIS study (studies show best results in patients with oligoarticular form of disease), TENDER study (evaluated efficacy of Tocilizumab in patients with systemic form of disease), which showed reducing of fever episodes after 12 weeks of therapy⁶.

HLA B27 genotyping is often associated with JIA with enthesitis (sacroiliitis) and in children with oligoarthritis or polyarthritis. With regard to this, our results are similar to those published by some other authors. HLA typing is also a good predictive factor in patients with juvenile idiopathic arthritis^{16,17,18}.

In pediatric population, the combination of Tocilizumab (Actemra) and Methotrexate has shown better results. In patients who are unable to tolerate Methotrexate, a combination of Tocilizumab and Leflunomid (Arava) can be used⁷.

The goal of the therapy with Tocilizumab is to prevent joint erosions, maintenance of their function and control of the pain⁹. Therapeutic approach is multidisciplinary. The team included in the treatment of these patients consists of pediatric rheumatologist, adult rheumatologist, ophthalmology specialist, physical therapy and psychological support of the family.

Conclusion

In summary, the use of the biological therapy with Tocilizumab in combination with Methotrexate in pediatric population is safe and patients have good therapeutic responses. Tocilizumab prevents joint erosions, and maintains their function. Tocilizumab is a good therapeutic choice in treatment of juvenile idiopathic arthritis. In this study we have presented our experience in treatment of patients with biological therapy (Tocilizumab).

References

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet* 2007;369:767-778.
2. Martini A, Lovell DJ. Juvenile idiopathic arthritis: state of the art and future perspectives. *Ann Rheum Dis* 2010;69:1260-1263.
3. Petty RE, Southwood TR, Manners P et al. International League of Associations for rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004; 31:390-2
4. Ravelli A, Martini A. Methotrexate in juvenile idiopathic arthritis: answers and questions. *J Rheumatol* 2000;27:1830-3
5. Silverman E, Mouy R, Spiegel L, et al. Leflunomide or methotrexate for juvenile rheumatoid arthritis. *N Engl J Med* 2000; 342:763-9
6. Maini RN, Taylor PC, Szechinski J, Pavelka K, Brolj, BalintG, et al. CHARISMA Study Group Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had incomplete response to methotrexate. *Arthritis Rheum* 2006; 54(9):2817-29.
7. Brunner HI, Ruperto N, Zuber Z et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from phase 3, randomised, double-blind withdrawal trial. *Ann Rheum Dis* 2015;74:1110-1117.
8. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008; 67(11):1516-23.
9. Fleischmann R, Burgos-Vargas R, Ambs P, Alecock E, Kremer J. LITHE:tocilizumab inhibits radiographic progression and improves physical function in rheumatoid arthritis (RA) patients (Pts)at 2 Yrs with increasing clinical efficacy over time. *Arthritis Rheum* 2009; 60(10): S238-S239.
10. Gjurkova-Angelovska B, Kacarska R, Kuzevska-Maneva K, Jovanovska V, Neskovska Sumenkovska M. Juvenile idiopathic arthritis - case reports and modern therapeutic treatment. *Arch Pub Health* 2014; 6(1): 30-33
11. Yokota S, Imagawa T, Mori M, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo controlled, withdrawal phase III trial. *Lancet* 2008;371:998-1006.

12. Macaubas C, Nguyen K, Milojevic D, et al. Oligoarticular and polyarticular JIA: epidemiology and pathogenesis. *Nat Rev Rheumatol* 2009;5:616-26
13. Al-Matar MJ, Petty RE, Tucker LB, Malleson PN, Schroeder ML, Cabral DA. The early pattern of joint involvement predicts disease progression in children with oligoarticular (pauciarticular) juvenile arthritis. *Arthritis Rheum* 2002;46:2708-2715.
14. Kafedziska I, Mishevskaja Perchinkova S, Antova D, Kotevska Nikolova M, Stojanovska A, Guchev F. ML28133- A Multicenter, Open-Label, Long-term extensions study of Wa19926 to describe safety during treatment with Tocilizumab in patients with early, moderate to severe Rheumatoid arthritis *Mac Med Review* 2017;71(2):83-90
15. Kafedziska I, Mishevskaja Perchinkova S, Antova D, Kotevska Nikolova M, Stojanovska A, Guchev F. Multicenter, Open-Label, Long-term Extension to Describe the safety of Tocilizumab in Patients with early, moderate to severe rheumatoid arthritis. *American Journal of Internal Medicine* 2020;8(3):125-132.
16. Sonkar GK, Usha U, Singhs. Is HLAB27 a useful test in the diagnosis of juvenile spondyloarthropathies? *Singapore Med J* 2008;49:795-799
17. Angeles-Han ST, McCracken C, Yeh S, Jang SR, Jenkins K, Cope S, et al. HLA associations in a cohort of children with juvenile idiopathic arthritis with and without uveitis. *Invest Ophthalmol Vis Sci* 2015;56(10):6043-8.-6048
18. Watts R, Clunie G, Hall F, Marshall T. *Rheumatology: Oxford University Press* 2009.