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OUTCOMES OF TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS RELATED UVEITIS WITH TNF-ALPHA INHIBITORS

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Resume. The aim of the study was to evaluate the efficacy of two anti-TNF-alpha biological agents: Adalimumab (humanized monoclonal anti-TNF-alpha antibody) and Infliximab (chimeric monoclonal antibody that binds both circulating and membrane-bound TNF-alpha receptors) in treatment of Juvenile Idiopathic Arthritis related uveitis. 37 children (73% girls) with uveitis associated with aggressive forms of JIA who failed Methotrexate and topical treatment; Methotrexate and other immunosuppressive agents and systemic corticosteroids were included in the study. The age of patients at the beginning of biological therapies ranged 5–17 years. In ADA group the remission was observed in 61% of cases, in 18% we saw the reduction of flare-ups and in 14% of children we registered exacerbation of the disease which was caused in most cases by discontinuation of non-biological drug. In INF group we observed remission in 78% of the cases, no improvement in 22%. The speed of remission in JIA associated uveitis treated with ADA and INF depended on the severity of uveitis, the time between the beginning of the disease and administration of immunosuppressive therapy. Early administration of anti-TNF-alpha agents, when there is no results from standard immunosuppressive therapy, allowed us to achieve remission in a shorter period of time and also allowed as to decrease the severity of complications of uveitis, as well as reduce the side effects of immunosuppressive therapy, especially of corticosteroids. This study needs to be continued to enroll more patients and to increase the follow-up time to evaluate the long-term efficacy and safety of anti-TNF-alpha agents in JIA associated uveitis.

Key words: uveitis; juvenile idiopathic arthritis; inhibitors of TNF-α.

INTRODUCTION

As it is known uveitis is the inflammation of the uvea by definition, but for a rather long time the term "uveitis" was used to identify inflammation in any part of the eye (retinitis, chorioretinitis, scleritis, episcleritis) [1]. According to some authors [12] one of the most common causes of uveitis in childhood is Juvenile Idiopathic Arthritis (JIA). The incidence of eye involvement in JIA can be as high as 10–20% [3, 10, 11]. Oligoarthritis which contributes to 40–60% of all JIA cases is the most common pathology type associated with uveitis. Oligoarthritis is known to be more common among girls (ratio M:F=1:5) with the most common age of manifestation being around 2 years of age [6]. The second peak of the disease manifestation is during the puberty [7]. Young girls (<4 years of age) with oligoarthritis and antinuclear antibodies (ANA+) are at highest risk of developing chronic asymptomatic, nongranulomatous anterior uveitis. Patients with JIA associated uveitis are usually asymptomatic at early stages. In 20–30% of cases uveitis may occur a few years before joint manifestation. As the result of those two factors we often see the delay in the treatment or not adequate treatment [4]. As the sequela of this chain 30–40% of cases develop irreversible sight-threatening complications [5, 13, 16]. As the result of poor control of inflammation during the beginning of the disease, the complex surgical intervention is necessary to restore sight in older age [2, 8]. On the other hand early and aggressive treatment of JIA associated uveitis can help better control inflammation and can help to eliminate inflammation before development of irreversible ophthalmic pathology [9, 14, 15].

The goal of the study was to evaluate the efficacy of two anti-TNF-alpha biological agents: Adalimumab (ADA, humanized monoclonal anti-TNF-alpha antibody) and Infliximab (INF, chimeric monoclonal antibody that binds both circulating and membrane-bound TNF-alpha receptors) in the treatment of Juvenile idiopathic

MATERIALS AND METHODS

Thirty-seven children (73% of them girls) with aggressive forms of JIA with uveitis who failed Methotrexate and other immunosuppressive agents including systemic corticosteroids were enrolled in the study. In 8 children uveitis was in remission at the beginning of anti-TNF-alpha treatment, in others previous programs of systemic and topical treatment were ineffective. The age of the patients at the beginning of anti-TNF-alpha treatment ranged from 5 to 17 years. All patients were divided into two groups: one group (28 patients) was receiving ADA, and the other group (9 patients) was receiving INF. ADA was prescribed at

Table 1

Frequency of JIA subtypes in groups (P>0.30)

Type of arthritis	ADA (n=28)	INF (n=9)
Oligoarticular, n (%)	20 (71.4)	5 (55.5)
Polyarticular, n (%)	7 (25.0)	4 (44.5)
Psoriatic arthritis, n (%)	1 (3.6)	0 (0.0)

the dose of 40mg sq every 2 weeks. INF was used intravenously 5–6 mg/kg at week 0–2-6 and after it every 8 weeks. Duration of treatment was 3–48 months. In the first group (ADA) there were 67.9% of girls in the second group (INF) — 88.9% (p=0.39). The difference in number of subtypes of JIA between groups was not significant (tab. 1).

Both biological anti-TNF-alpha medications were used in combination with other therapy. The frequency of administration of non-biologics was the same in both groups (tab. 2).

The efficacy of treatment was assessed by reduction of flare-ups and by the reduction of activity of uveitis.

RESULTS

In ADA group the remission was observed in 61% of cases, reduction of number of flare-ups was registered in 18% and in 14% of children we saw worsening of the disease which was caused in most of the cases by discontinuation of non-biological drug. In 3,5% of cases after 29 months of treatment we needed to increase the dose or frequency of administration of the drug to achieve remission of arthritis and uveitis. In 3,5% treatment of JIA associated uveitis with ADA was ineffective.

In INF group we observed remission in 78% of the cases, no improvement in 22% of cases.

In the ADA group the average follow up period was 10 months (range 3–48 months). Six patients were treated with biologics prior to enrollment in the study: one child received INF and Abatacept, one child received Abatacept and three children were treated with INF alone. One child was on Etanercept. The treatment was ceased in all 6 children due to absence of efficacy. The child who was on Etanercept for arthritis developed the first episode of uveitis.

Six patients in ADA group had remission of uveitis at the beginning of anti-TNF-aplha treatment. During the 6 month period of follow-up we didn't register any flare-ups of uveitis in these patients.

The length of uveitis in ADA group ranged from 9 months to 10 years before starting ADA. Twenty two of 28 children in the ADA group had a clinical picture of iridocyclitis, 5 patients had a clinical picture of panuveitis, and one had a peripheral uveitis. Twenty one children had bilateral involvement and only 7 had unilateral uveitis. After administration of ADA 17 patients had a complete remission, 5 patients decreased the frequency of flare-ups, 3 had recurrence of uveitis after Methotrexate was abandoned. One patient had a flare-up of uveitis after ADA was ceased due to mononucleosis. In one patient after 29 months of treatment due to ongoing flare-ups the dose was increased to 80 mg for 4 months without any improvement, but after the increasing of frequency of drug injection to Qweek for 4 months a remission was achieved in 2 weeks and after 4 months of this treatment we were able to return to the regular protocol. In one patient we didn't achieve any improvement of chronic uveitis and arthritis. Therefore, ADA was ceased after 6 months and the child was switched to another drug.

Depending on the severity, we observed remission of uveitis in 0.5–4 months from the starting injection of ADA. After we added ADA topical Prednisone was tapered within 1.5–3 months and none of the patients required regional injections of steroids. Topical NSAIDs were stopped within 8 months after initiation of treatment with ADA.

Therapy with ADA gave us the chance to cease non-biological immunosuppressive agents, which was important especially in children who were receiving simultaneously 2 non-biological agents. Cyclosporine A was ceased in 3 cases: on week 2, month 5 and month 39 after starting ADA. No exacerbations of uveitis were revealed after cessation till the end of follow-up period.

In ADA group 17 patients achieved a stable remission of arthritis, 7 children with severe arthritis had improvement and 2 children had flare-ups of arthritis after Methotrexate had been ceased and 1 patient had ongoing exacerbation of arthritis.

Table 2

Frequency of non-biologics used in combination with biologics in groups (P>0.70)

Non biologics	ADA (28)	INF (n=9)
Methotrexate	21 (75.0)	7 (77.8)
Leflunomide	1 (3.6)	0 (0.0)
Methotrexate and Cyclosporine A	6 (21.4)	2 (22.2)

In 9 patients enrolled in the INF group the average follow up time was 12 months (range3–24 months).

Duration of uveitis before the beginning of treatment with INF was 9–14 years. Iridocyclitis was revealed in 66.6% of children of INF group, 33.3% of them had panuveitis. Bilateral involvement was obvious in 66.7% of cases. The range of severity of the disease was the same as in the ADA group.

In INF group we saw the remission in 78% of the cases. In one patient treatment was declared inefficient due to ongoing arthritis after 6 months of therapy. Two patients had active chronic uveitis and arthritis and we were to switch to ADA. Two children started INF while uveitis was in remission and stayed in remission for 6 months while they were under our care. Four patients had a total remission of arthritis, 2 — arthritis improvement, 2 had reactivation of arthritis after Methotrexate was discontinued and 1 had exacerbation of arthritis despite the therapy.

DISCUSSION/CONCLUSIONS

Our experience shows that switching to ADA in therapies of JIA associated uveitis in cases when the disease is resistant to treatment with common combination of different immunosuppressive agents, was effective in most cases. In 27 of 28 children of ADA group we registered improvement, remission or ongoing remission of uveitis. Of 9 children with JIA-associated uveitis in whom previous standard immunosuppressive therapies with different agents had no effect and which were enrolled in the INF group, switching to treatment with INF caused improvement in 7 cases. We did not see any major difference in the efficacy of treatment of JIA-associated uveitis in children with ADA or INF.

Our experience in ADA treatment of uveitis shows good result in control of uveitis independent from the severity of the disease and despite it was used as a first-, second- or third-line agent among the biologics. We observed improvement of uveitis in 5 children who failed treatment with INF and Abatacept prior to administration of ADA.

The speed of remission in patients with JIA associated uveitis treated with ADA and INF depends on the severity of uveitis, the time between the beginning of the disease and administration of immunosuppressive therapy. Early administration of anti-TNF-alpha agents, when we don't see positive results of the standard immunosuppressive therapies, allow us to achieve remission in a shorter period of time and also allow as to decrease the rate and the severity of complications of uveitis, as well as reduce the side effects of immunosuppressive therapy, especially of corticosteroids. This study needs to be continued to enroll more patients and to increase the follow-up time to evaluate the long-term efficacy and safety of anti-TNF-alpha agents in JIA associated uveitis.

REFERENCES

1. Moshetova L.K., Ermakova N.A. Oftal'mologiya: natsional'noe rukovodstvo [Ophthalmology: the national guide]. M.: GEOTAR-Media; 2013.
2. Acevedo S., Quinones K., Rao V., et al. Cataract surgery in children with juvenile idiopathic arthritis associated uveitis. Int Ophthalmol Clin. 2008; 48 (2): 1–7.
3. Boone M.I., Moore T.L., Cruz O.A. Screening for uveitis in juvenile rheumatoid arthritis. J Pediatr Ophthalmol Strabismus. 1998; 35 (1): 41–3.
4. Cassidy J.T., Petty R.E., Laxer R.M., Lindsley C. Textbook of Pediatric Rheumatology. 6th edition. Saunders; 2010.
5. Ceisler E.J., Foster C.S. Juvenile rheumatoid arthritis and uveitis: minimizing the blinding complications. Int Ophthalmol Clin. 1996; 36 (1): 91–107.
6. Gallagher K.T., Bernstein B. Juvenile rheumatoid arthritis. Curr Opin Rheumatol. 1999; 11 (5): 372–76.
7. Hoeve M., Kalinina Ayuso V., Schalij-Delfos N.E., Los L.I., Rothova A., de Boer J.H. The clinical course of juvenile idiopathic arthritis-associated uveitis in childhood and puberty. Br J Ophthalmol. 2012; 96 (6): 852–56.
8. Holland G.N. Intraocular lens implantation in patients with juvenile rheumatoid arthritis-associated uveitis: an unresolved management issue. Am J Ophthalmol. 1996; 122 (2): 255–57.
9. Imrie F.R., Dick A.D. Biologics in the treatment of uveitis. Curr Opin Ophthalmol. 2007; 18 (6): 481–86.
10. Kesen M.R., Setlur V., Goldstein D.A. Juvenile idiopathic arthritis-related uveitis. Int Ophthalmol Clin. 2008; 48 (3): 21–38.
11. Kotaniemi K., Kaipiainen-Seppanen O., Savolainen A., et al. A population-based study on uveitis in juvenile rheumatoid arthritis. Clin Exp Rheumatol. 1999; 17 (1): 119–22.
12. Päivönsalo-Hietanen T., Tuominen J., Saari K.M. Uveitis in children: population-based study in Finland. Acta Ophthalmol Scand. Feb 2000; 78 (1): 84–8.
13. Qian Y., Acharya N.R. Juvenile idiopathic arthritis-associated uveitis. Curr Opin Ophthalmol. 2010; 21 (6): 468–72.
14. Shetty A.K., Zganjar B.E., Ellis G.S. Jr., et al. Low-dose methotrexate in the treatment of associated chronic anterior uveitis. Rheumatology (Oxford). 2008; 47 (3): 339–44.
15. Tynjala P., Kotaniemi K., Lindahl P., et al. Adalimumab in juvenile idiopathic arthritis-associated chronic

anterior uveitis. Rheumatology (Oxford). 2008; 47 (3): 339–44.
16. Yu E.N., Meniconi M.E., Tufail F., et al. Outcomes of treatment with immunomodulatory therapy in patients with corticosteroid-resistant juvenile idiopathic arthritis-associated chronic iridocyclitis. Ocul Immunol Inflamm. 2005; 13 (5): 353–60.

РЕЗУЛЬТАТЫ ЛЕЧЕНИЯ УВЕИТА, АССОЦИИРОВАННОГО С ЮВЕНИЛЬНЫМ ИДИОПАТИЧЕСКИМ АРТРИТОМ, ИНГИБИТОРАМИ ФНО-АЛЬФА

Гайдар Е.В., Костик М.М., Снегирева Л.С., Дубко М.Ф., Масалова В.В., Серогодская Е.Д., Мациевская А.С., Хайнес А.

◆ **Resume.** Проанализирована эффективность применения генно-инженерной биологической терапии (ГИБТ) двумя препаратами, блокирующими фактор некроза опухолей-α (ФНОα), — адалимумаб (АДА) и инфлик-симаб (ИНФ) у детей, страдающих увеитом, ассоциированным с ювенильным идиопатическим артритом (ЮИА), резистентным к комбинированной терапии метотрексатом с топическим стероидами, а также к комбинации метотрексата с другими небиологическими болезнь-модифицирующими противоревматическими препаратами (БМПП) и системными кортикостероидами. В исследование включено 37 детей (73 % девочки). Возраст пациентов составил от 5 до 17 лет на момент начала ГИБТ. При применении АДА стойкая ремиссия увеита наступила в 61 % случаев, в 18 % снизилась частота рецидивов, у 14 % детей зарегистрированы обострения заболевания, которые, как правило, были связаны с отменой сопутствующей цитостатической терапии. На терапии ИНФ у 78 % детей зарегистрирована стойкая ремиссия, у 22 % детей лечение оказалось неэффективным. Сроки наступления ремиссии увеита на фоне терапии АДА, ИНФ зависят от тяжести поражения глаз, сроков назначения иммуносупрессивной терапии. Раннее назначение терапии ГИБТ при отсутсвии эффекта от стандартной терапии небиологическими БМПП позволяет достичь ремиссии в более короткие сроки, а также уменьшить частоту и степень выраженности осложнений, обусловленных как самим воспалительным процессом, так и побочными эффектами лекарственных препаратов, в частности кортикостероидов. Данное исследование требует продолжения в части увеличения численности выборки и продолжительности периода наблюдения для оценки долгосрочной эффективности и безопасности применения блокаторов ФНО-α в терапии ЮИА-ассоциированных увеитов.

◆ **Key words:** увеит; ювенильный идиопатический артрит; блокаторы фактора некроза опухолей-альфа.

ЛИТЕРАТУРА

1. Мошетова Л.К., Ермакова Н.А. Офтальмология: национальное руководство. М.: ГЭОТАР-Медиа; 2013.
2. Acevedo S., Quinones K., Rao V., et al. Cataract surgery in children with juvenile idiopathic arthritis associated uveitis. Int Ophthalmol Clin. 2008; 48 (2): 1–7.
3. Boone M.I., Moore T.L., Cruz O.A. Screening for uveitis in juvenile rheumatoid arthritis. J Pediatr Ophthalmol Strabismus. 1998; 35 (1): 41–3.
4. Cassidy J.T., Petty R.E., Laxer R.M., Lindsley C. Textbook of Pediatric Rheumatology. 6th edition. Saunders; 2010.
5. Ceisler E.J., Foster C.S. Juvenile rheumatoid arthritis and uveitis: minimizing the blinding complications. Int Ophthalmol Clin. 1996; 36 (1): 91–107.
6. Gallagher K.T., Bernstein B. Juvenile rheumatoid arthritis. Curr Opin Rheumatol. 1999; 11 (5): 372–76.
7. Hoeve M., Kalinina Ayuso V., Schalij-Delfos N.E., Los L.I., Rothova A., de Boer J.H. The clinical course of juvenile idiopathic arthritis-associated uveitis in childhood and puberty. Br J Ophthalmol. 2012; 96 (6): 852–56.
8. Holland G.N. Intraocular lens implantation in patients with juvenile rheumatoid arthritis-associated uveitis: an unresolved management issue. Am J Ophthalmol. 1996; 122 (2): 255–57.
9. Imrie F.R., Dick A.D. Biologics in the treatment of uveitis. Curr Opin Ophthalmol. 2007; 18 (6): 481–86.
10. Kesen M.R., Setlur V., Goldstein D.A. Juvenile idiopathic arthritis-related uveitis. Int Ophthalmol Clin. 2008; 48 (3): 21–38.
11. Kotaniemi K., Kaipiainen-Seppanen O., Savolainen A., et al. A population-based study on uveitis in juvenile rheumatoid arthritis. Clin Exp Rheumatol. 1999; 17 (1): 119–22.
12. Päivönsalo-Hietanen T., Tuominen J., Saari K.M. Uveitis in children: population-based study in Finland. Acta Ophthalmol Scand. Feb 2000; 78 (1): 84–8.
13. Qian Y., Acharya N.R. Juvenile idiopathic arthritis-associated uveitis. Curr Opin Ophthalmol. 2010; 21 (6): 468–72.
14. Shetty A.K., Zganjar B.E., Ellis G.S. Jr., et al. Low-dose methotrexate in the treatment of associated chronic anterior uveitis. Rheumatology (Oxford). 2008; 47 (3): 339–44.
15. Tynjala P., Kotaniemi K., Lindahl P., et al. Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis. Rheumatology (Oxford). 2008; 47 (3): 339–44.
16. Yu E.N., Meniconi M.E., Tufail F., et al. Outcomes of treatment with immunomodulatory therapy in patients with corticosteroid-resistant juvenile idiopath-

ic arthritis-associated chronic iridocyclitis. Ocul Immunol Inflamm. 2005; 13 (5): 353–60.

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