E.V. Gaidar, M.M. Kostik, M.F. Dubko, V.V. Masalova, L.S. Snegireva, E.A. Isupova, T.N. Nikitina, E.D. Serogodskaya, O.V. Kalashnikova, V.G. Chasnyk

St. Petersburg State Pediatric Medical University, St. Petersburg, Russia

The efficiency of adalimumab in cases of chronic methotrexate-resistant juvenile idiopathic arthritis-associated anterior uveitis – retrospective case series study.

Author affiliation:

Kostik Mikhail Mikhailovich, PhD, docent at the advanced therapy department of the St. Petersburg State Pediatric Medical University
Address: 2, Litovskaya Str., St. Petersburg, 194100; **tel.:** +7 (812) 416-52-98; **e-mail:** kost-mikhail@yandex.ru

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Background: *Juvenile idiopathic arthritis (JIA) associated uveitis may be the cause of not only visual acuity decrement, but also blindness. At the same time, in some patients therapy with methotrexate can not prevent the development of these complications.* ***Objective:*** *Our aim was to investigate the efficiency and safety of using a tumor necrosis factor inhibitor (adalimumab) in patients with JIA-associated uveitis.* ***Methods:*** *We conducted a retrospective single-arm study of a series of cases. The results of using adalimumab were evaluated in patients with JIA-associated chronic anterior uveitis, who have been under observation for no less than 1 year before and after starting using adalimumab. The latter was prescribed due to progressing and/or recidivous methotrexate-resistant uveitis.* ***Results:*** *We have analyzed clinical case records of 36 children with JIA-associated uveitis. At the start of therapy with adalimumab, actual uveitis was diagnosed in 30 (83%) patients. Remission was achieved in 29 of 30 cases in 2 (2; 12) weeks in patients with actual uveitis. 11 (31%) patients had a uveitis exacerbation 28 (13; 69) weeks after adalimumab therapy started. Adalimumab reduced the exacerbation frequency from 4 (1; 9) to 0 (0; 1) exacerbations per year for one patient ($p < 0,001$), and reduced the proportion of patients who were treated with topical glucocorticosteroids (from 83 to 8%). There were no differences (in achieving remission and reducing exacerbation frequency) with regard to patients' sex, involvement of one or both eyes in the disease onset, antinuclear factor seropositiveness, uveitis type and character of joints affection.* ***Conclusion:*** *Adalimumab promotes fast and long-lasting remission of JIA-associated methotrexate-resistant uveitis.*

Keywords*: juvenile idiopathic arthritis, uveitis, adalimumab.*

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RATIONALE

Juvenile idiopathic arthritis (JIA) is the most common cause of chronic anterior uveitis in childhood. In its turn, uveitis is the most common extra-articular manifestation of JIA diagnosed in every fifth child with this disease mainly in the first 2 years from the debut of the articular syndrome [1, 2], and this despite the fact that the onset of chronic anterior uveitis is often asymptomatic, one or both eyes may be affected. [3] Shorter interval between the onset of arthritis and uveitis' development is a predictive sign of severe course of uveitis. [4] Previous studies have established the main risk factors for uveitis: oligoarticular subtype of arthritis, early age of onset, antinuclear factor seropositivity, and high levels of C-reactive protein at the onset of the disease [5].

Uveitis is one of the most common causes of blindness in patients with JIA [3]. It is possible to prevent such variant of the disease by sequential therapy starting with topical glucocorticosteroids (GCS) application, subconjunctival, and para- and retrobulbar injections. In the absence of the effect of treatment with topical GCS, methotrexate therapy is prescribed, which can be enhanced by the addition of cyclosporin A and/or genetically engineered immune-biological preparations. In severe cases, it is possible to use systemic GCS [6]. It should be noted that GCS therapy can lead to such adverse events as metabolic disorders (hyperglycemia, dyslipidemia, obesity), arterial hypertension, osteoporosis, hypertrichosis, glaucoma and cataract [7].

Pro-inflammatory cytokines – tumor necrosis factor (TNF) α [8] – has a significant role in the basis of immune inflammation in the joints and the eyes of patients with JIA. It is known that TNF α stimulates production of a number of proinflammatory cytokines, such as interleukins 1, 6 and 8, thus maintaining the inflammation. Blockade of TNF α leads to suppression of monocytic cells (monocytes and macrophages) activity, reduction of the inflammatory response and, consequently, to prevention of tissue damage [9]. Application for blocking the activity of TNF α monoclonal antibodies (frequently of infliximab and adalimumab, less often — of golimumab and certolizumab) is the most promising type of therapy in patients resistant to therapy with non-biological disease modifying antirheumatic drugs such as methotrexate and cyclosporin A [10].

The purpose of this study was to investigate the efficacy and safety of adalimumab in patients with JIA-associated uveitis resistant to methotrexate therapy.

METHODS

Study design

A retrospective study of case series.

Eligibility Criteria

Inclusion criteria:

- patients with chronic progressive and/or relapsing in anterior uveitis associated with JIA;
- appointment of adalimumab because of resistance to methotrexate including therapy;
- availability of data on the course of the disease for at least 1 year before and 1 year after the appointment of adalimumab.

Non-inclusion criteria: patients with acute anterior (symptomatic) uveitis.

Data sources

Disease histories of patients with JIA hospitalized in the 3^{d} pediatric ward and eye microsurgery ward of Saint-Petersburg State Pediatric Medical University (St. Petersburg) were analyzed. Data accounting period is 2009-2016. JIA was diagnosed in accordance with the criteria of the International League of Associations for Rheumatology (ILAR) [11].

Ophthalmologic examination

To monitor the uveal activity, all patients regularly passed the ophthalmologic screening with biomicroscopy, which was performed by experienced ophthalmologists in decreed periods depending on the activity of uveitis. Assessment of the degree of activity and remission of uveitis was conducted based on the criteria of the Standardization of Uveitis Nomenclature Working Group terminology (Standardization of Uveitis Nomenclature Working Group, SUN) [12, 13]. In patients with continuous-recurrent uveitis, number of exacerbations per year was equated to 12.

Therapy effectiveness criteria

Periods of remission, dynamics of the uveitis exacerbations frequency, as well as changings in the current treatment with topical GCS during adalimumab therapy were assessed. The results of treatment in groups of patients of different sexes, in groups, separated based on involvement of one or both eyes in the disease debut, seropositivity for antinuclear factor, the uveitis type, the character of articular lesions (oligo-, polyarthritis), presence of concomitant cytotoxic therapy.

Ethical review

Study is approved by local ethics committee at the Saint-Petersburg State Pediatric Medical University (Minutes № 4 of 25.03.2013).

Statistical analysis

The sample size was not counted preliminarily. Statistical analysis was performed using the STATISTICA v. 6.0 (StatSoft Inc., USA) statistical software package. Description of the quantitative variables is presented as a median (25th, 75th percentiles). For comparison of the connected quantitative variables, the Wilcoxon test was used. In the analysis of risk factors of the uveitis remission and exacerbation, the Cox regression model with the calculation of the relative risk (RR) and 95% of confidence interval (CI) was used.

RESULTS

Sample characteristics

Results of treatment of 36 children (Table 1) were analyzed. Patients with oligoarthritis prevailed among children with JIA-associated uveitis. In most cases — in 27 (75%) patients — arthritis developed before the uveitis debut, while in other children uveitis preceded the development of articular syndrome. Positive antinuclear factor was detected in 19/33 (58%) children. 3 types of uveitis were revealed by the anatomical location of the inflammation in the eye: anterior — in 29 (81%), peripheral — in 2 (6%), and panuveitis — in 5 (14%) patients. In 3 (8%) patients, uveitis developed at the background of etanercept therapy. Active uveitis at the start of adalimumab therapy was diagnosed in 30 (83%) children. In 17 (47%) patients, in debut there was a monolateral damage of organ of vision, in 19 (52.8%) — bilateral. All patients were treated with methotrexate administered parenterally in a dose of 15-20 mg/m^2 per week, 11 (31%) patients received combination of methotrexate with cyclosporine A in a dose of 4-5 mg/kg of body weight. The starting dose of adalimumab in 15 (42%) children (weight <30 kg) was 20 mg, in 21 (58%) (weight > 30 kg) — 40 mg subcutaneously every 2 weeks.

Table 1. Characteristics of patients with JIA-associated uveitis

Index	**Value**
Girls, abs. (%)	25 (69)
Subtype of arthritis, abs. (%):	
• oligoarthritis	23 (64)
• polyarthritis	9 (25)
• enthesitis associated arthritis	4 (11)
Types of uveitis, abs. (%):	
• anterior	29 (81)
• peripheral	2 (5)
• panuveitis	5 (14)

Positive by antinuclear factor, abs. (%)	19/33 (58)
HLA-B27, n (%)	3/19 (16)
Age of the arthritis debut, years	2.9 (2.0; 6.0)
Age of the uveitis debut, years	5.0 (3.2; 7.7)
Bilateral eye damage	19 (52)
The number of exacerbations of uveitis (1 patient per year) until the appointment of adalimumab	4 (1; 9)
Uveitis *de novo* in the background of disease modifying antirheumatic drugs abs. (%)	14 (36)

Key findings

Remission of active uveitis on the background of adalimumab therapy has been achieved in 29 of 30 patients (97%) in 2 (2; 12) weeks from the start of treatment. A significant reduction in the frequency of the uveitis exacerbations was also noticed: from 4 (1; 9) exacerbations per patient per year prior to the appointment of adalimumab to 0 (0, 1) on the background of its application (p <0.001).

30 (83.3%) of patients received topical GCS prior to adalimumab therapy; by the end of the first year of the therapy, this number decreased to 3 (8.3%). Uveitis exacerbations occurred in 11 of 36 (30.6%) patients during the first year of treatment with adalimumab. The period before the escalation amounted to 28 (13; 69) weeks. Of these, 2 patients had an uveitis in inactive phase before starting the adalimumab therapy. In patients who got exacerbations, in case of the lack of effectiveness of topical GCS, appointed at the time of an exacerbation, or in case of steroid dependence, the dosing regimen was changed: in 4 patients adalimumab dose was increased from 20 to 40 mg, and in 1 child receiving 40 mg every 2 weeks, the interval between injections was reduced to 1 week.

Additional findings

Regression analysis showed no connection of the achievement of remission and the uveitis exacerbation development with patients' gender, involvement in the process of both eyes at the onset of uveitis, ANF seropositivity, type of uveitis, the character of articular lesions (Table 2).

Table 2. The results of the regression analysis of factors related to the achievement of remission and the development of uveitis exacerbation

Parameter	Remission achievement		Exacerbation of uveitis	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***
Uveitis type:				
• anterior *	1		1	
• peripheral	1,32 (0,87-2,11)	0.788	0,97 (0,43-1,26)	0.825
• panuveitis	1,08 (0,69-1,75)	0.742	0,53 (0,21-0,89)	0,264
Male	1,60 (0,92-1,95)	0.494	0,68 (0,41-0,98)	0.634
Bilateral eye damage	0,63 (0,23-0,95)	0.542	1,00 (0,67-1,82)	0.989
ANF seropositivity	0,62 (0,25-0,89)	0.543	0,48 (0,21-0,88)	0.287
Arthritis prior to uveitis	2,30 (1,73-3,42)	0.394	0,50 (0,19-0,83)	0.234
Subtype of arthritis:				
• oligoarthritis *				
• polyarthritis	1		1	
• enthesitis associated arthritis	1,24 (0,82-2,73)	0.601	1,01 (0,45-1,56)	0.991
	1,09 (0,67-1,92)	0.842	1,15 (0,83-1,73)	0.745

Note: * - Reference.

DISCUSSION

Summary of the key finding

Adalimumab therapy in children with chronic anterior uveitis associated with juvenile idiopathic arthritis and resistant to methotrexate therapy is highly effective and safe. Adalimumab treatment leads to the rapid development of the uveitis remission in most patients, reduces the incidence of recurrence of uveitis substantially, and reduces the need for systemic and local GCS therapy.

Key finding discussion

TNF α inhibitors are the most frequently used genetically engineered immune-biological drugs among ones that are used in the treatment of JIA-associated uveitis. Thus, according to a systematic review and meta-analysis data [14], it is presented that the most effective drugs were ones with the structure of monoclonal antibodies — adalimumab (87% of patients responded to the therapy) and infliximab (72%) compared with etanercept, belonging to the class of soluble receptors (33 %). Differences in efficacy may be related to features of the molecular structure. In particular, monoclonal antibodies, in addition to the TNF α soluble molecule binding, also have

the ability to complement- and antibody-dependent cytolysis of cell, receptors of which are linked with TNF α. This effect cannot be achieved using etanercept. Infliximab, unlike etanercept and adalimumab, also has the ability to induce the apoptosis of T lymphocytes and macrophages, which enhances its anti-inflammatory properties [15].

The most studied member of the group of TNF α inhibitors, used in the treatment of uveitis associated with autoimmune diseases, is adalimumab. For example, in one study, 17/18 patients treated with adalimumab in combination with GCS, showed positive effect after 2-16 weeks. It was possible to cancel GCS in 16 of 18 patients, and to reduce the dose in 1; there was no improvement only in 1 case. Thus, the effectiveness of the drug was at 88% [16]. In K. Kotaniemi et al. study, 94 patients JIA-associated uveitis in connection with active arthritis and/or uveitis received adalimumab. 54 out of 94 patients completed the study; 36 out of them had a good response to adalimumab (topical GCS therapy continued in 31%, the dose of topical GCS was reduced to 1-2 drops in one eye per day in 35%). In accordance with the SUN criteria [12, 13], in 28% of children there was a twofold decrease in the activity of uveitis, in 16 patients — moderate response, in 16 — no dynamics, and in 13 — deterioration, which was expressed in a twofold increase in the activity of uveitis. Also, during the observation period, it became possible to cancel systemic GCS completely in 22% of patients with uveitis. In 18/94 (19%) patients, adalimumab therapy was cancelled shortly after its inception due to inefficiency and/or the development of side effects [17].

According to the Italian national register, 55% among patients treated with infliximab or adalimumab achieved remission, 33% had recurrent uveitis, and 12% had chronic uveitis. The number of uveitis complications per patient decreased from 0.47 to 0.32 [18] on the background of therapy.

The second most commonly used in the treatment of JIA-associated uveitis drug is infliximab. However, the use of infliximab causes a number of difficulties associated with the fact that the drug has no official indications for use in patients with JIA in childhood. Thus, the appointment of the drug goes to the off-label regime. Moreover, the chimeric structure of infliximab molecule increases the risk of anti-drug-antibodies generation, which can lead to the development of infusion reactions and reduced efficiency (so-called escape effect). This, in turn, requires such changing in the dosing regimen as increased dosage of the drug and reduced interval between infusions, which results in essentially rise in price of therapy [19]. According to the Italian national register, in comparison of the effectiveness of adalimumab and infliximab, adalimumab was more effective (67 and 43% of patients receiving adalimumab and infliximab respectively responded to therapy), as well as more safe than infliximab (number of adverse events was almost 4 times lower) [18]. The study of G. Simonini et al. compared the efficacy of adalimumab as the first or second line therapy (in the latter case - after applying infliximab). The study found that the use of adalimumab as a first line drug is more effective than when it is administered after infliximab [20]. This can be explained by the ability to generate anti-drugs-antibodies when using the second blocker of TNF α after the first, which is a chimeric, especially if the out-turn of these drugs blockers has already occurred [21, 22].

Co-administration of methotrexate, as well as the use of adalimumab as first-line treatment (prior to infliximab) can reduce the risk of developing of anti-drugs-antibodies and thereby save the drug's effectiveness and increase the duration of its use [23]. The results obtained in this study confirm the relevance of further research on the long-term therapy with adalimumab assessment taking into account its high efficacy in all the analyzed subgroups.

Limitations of the study

The study has several limitations related to small sample size, sample's heterogeneity by subtype of arthritis, anatomical localization of uveitis, age composition of the group, as well as the nature of concomitant therapy. An important limitation is the lack of control patients group.

CONCLUSION

Adalimumab may contribute to the rapid and prolonged remission of uveitis associated with JIA and chronic anterior uveitis. Adalimumab therapy is a good treatment method for patients with uveitis resistant to cytotoxic therapy. Further randomized researches for possible determining the extended indications for adalimumab appointment at earlier stages of disease in patients with chronic anterior uveitis and uveitis associated with JIA are needed.

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Conflict of interest
The authors declared they have no competing interests to disclose.

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