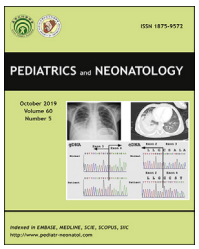
Pediatrics and Neonatology (2019) 60, 549—555

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.pediatr-neonatol.com



Original Article

Dynamics of concomitant therapy in children with juvenile idiopathic arthritis treated with etanercept and methotrexate

Ekaterina Alexeeva [a,b,*], Tatyana Dvoryakovskaya [a,b], Rina Denisova [a], Tatyana Sleptsova [a], Kseniya Isaeva [a], Alexandra Chomahidze [a], Anna Fetisova [a], Anna Mamutova [a], Alina Alshevskaya [c], Victor Gladkikh [c], Andrey Moskalev [c]

[a] *Federal State Autonomous Institution "National Medical Research Center of Children's Health" of the Ministry of Health of the Russian Federation, Moscow, Russia*
[b] *Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation, Russia*
[c] *Biostatistics and Clinical Trials Center, Novosibirsk, Russia*

Received Jun 21, 2018; received in revised form Dec 6, 2018; accepted Feb 18, 2019
Available online 22 February 2019

Key Words
concomitant treatment;
etanercept;
juvenile idiopathic arthritis;
NSAID

Background: Both the steroid- and NSAID-sparing effects of biologics in juvenile idiopathic arthritis (JIA) treatment are key aspects of the dynamics of patient's condition. The proper selection of biologics enables maximum treatment effectiveness and reduction of the dosage of concomitant therapy. Our aim was to study the dynamics of concomitant therapy during etanercept (ETA) and methotrexate (MTX) treatment in patients with JIA.
Methods: This analysis included 215 JIA patients (63.3% females) showing sufficient response to main therapy. One hundred patients received MTX as main therapy, 24 received ETA monotherapy, and 91 received ETA þ MTX combination therapy. The dynamics of concomitant therapy were analyzed after 1 month, every 3 months during the first year, and every 6 months during the long-term follow-up (up to 5 years).
Results: At the baseline, 24 (11.2%) patients received concomitant oral glucocorticoids (orGCs) and NSAIDs; the remaining 191 (88.8%) patients were treated with concomitant NSAIDs only. Within 1-year treatment, NSAIDs were discontinued in 162 (75.3%) patients. There were no significant differences in the dynamics of withdrawal of NSAIDs in patients who received and did not receive concomitant MTX. However, the percentage of treatment discontinuation in the MTX group was significantly lower compared to the other two groups ($p < 0.001$). Oral GCs were discontinued completely in 4 children (16.7%), and the dose of

* Corresponding author. Federal State Autonomous Institution "National Medical Research Center of Children's Health" of the Ministry of Health of the Russian Federation, Lomonosovsky prospekt, 2, b.1, 119991, Moscow, Russia.
E-mail address: ekaterina.i.alekseeva@mail.ru (E. Alexeeva).

https://doi.org/10.1016/j.pedneo.2019.02.003

oral GCs was reduced in another 4 patients (16.7%). By the end of the follow-up period, 44 of 115 patients (38.3%) treated with ETA in combination with any concomitant therapy could switch to ETA monotherapy.
Conclusion: Therapy with ETA makes it possible to reduce the dosage or completely discontinue most concomitant medications (orGCs, NSAIDs, MTX) in a significant percentage of patients. This reduces the risk of development of NSAID- and GC-induced pathological conditions, while the effectiveness of therapy of the underlying condition remains high.

1. Introduction

Juvenile idiopathic arthritis (JIA) belongs to the heterogeneous group of chronic arthritides. JIA is characterized by persistent joint inflammation lasting longer than 6 weeks, begins before the age of 16, and is of unknown cause. Before the era of biological therapy, patients with JIA at 5 years after onset had severe irreversible damage significantly worsening their quality of life.[1] Some of the unfavorable sequelae were caused by adverse events (AEs) accompanying the long-term therapy with standard drugs (glucocorticoids (GCs) and nonsteroidal anti-inflammatory drugs (NSAIDs)).

Therapy with biologics, and anti-TNF drugs in particular, has made it possible to significantly improve patients' quality of life as it quickly reduces the disease activity score and the number of joints affected within 4—12 weeks. Furthermore, the dosage of concomitant medications can potentially be reduced or they even can be completely discontinued in patients with rheumatic diseases treated with biologics.[2]

However, some children show an insufficient response to biologics and require multiple concomitant treatments even after anti-TNF therapy was started. The combination of a large number of drugs substantially elevates the risk of adverse effects. NSAIDs, GCs, and DMARDs cause serious adverse effects in some patients. NSAID-induced gastropathy and adverse effects on the cardiovascular system and the gastrointestinal tract pose a common serious problem in treatment of rheumatoid arthritis in adults,[3] being also typical in pediatric patients.[4,5] In some cases, long-term administration of NSAIDs requires prescription of adjuvant medications (gastroprotectors and cardioprotectors) to eliminate the adverse sequelae. This increases the total pill burden, which is especially important in medically compromised patients and among them children with JIA. Long-term glucocorticoid therapy in pediatric patients with different forms of arthritis leads to serious unfavorable alterations in the growing organism, with effects on the endocrine profile, growth, and development being the critical ones.[6—8] Although biologics per se have the potential for recovering normal function of the organism (e.g., they contribute to restoration of normal growth)[9—11] or may protect against NSAID-induced small intestinal damage,[12] it is equally important to assess their ability to have a therapeutic effect that would be sufficient to discontinue concomitant therapy.

Therefore, the steroid-sparing and NSAID-sparing effects of biologics are the crucial aspects of therapy. Our study aimed to assess the dynamics of concomitant therapy using the real-world data obtained for the cohort of JIA patients treated with etanercept (ETA) and methotrexate (MTX) at the Department of Rheumatology of the Scientific Center for Children's Health, one of the largest research centers for pediatric rheumatology in Russia.

2. Methods

2.1. Patients

This analysis was performed using the data obtained in the open-label, prospective study conducted at the Department of Rheumatology of the Scientific Center for Children's Health (Russian Academy of Medical Sciences, Russia). The study was approved by the local ethics committee of the Scientific Center of Children's Health (protocol no. 36, dated October 16, 2008). All patients and their parents provided written informed consent in accordance with the Declaration of Helsinki, which included their consent for using their data in analyses and for the data to be presented.

The analysis included children who received ETA and/or MTX treatment and complied with the following requirements: they met the International League of Associations for Rheumatology (ILAR) criteria for JIA, had no systemic symptoms, had no signs of tuberculosis, and were etanercept-naïve. The patients were subdivided into 3 groups: patients receiving ETA monotherapy (ETA group, without MTX treatment in anamnesis, n = 35); those receiving MTX monotherapy (n = 200); and those receiving ETA + MTX combination therapy (ETA + MTX group, continued MTX treatment, n = 163).

2.2. Drug administration

Etanercept was administered subcutaneously, 0.4 mg per kg of body weight (maximum single dose, 25 mg), 2 times a week. One or several concomitant drugs could be prescribed at start of ETA treatment depending on patient's

individual tolerance, past medical history, and current disease activity. GCs were prescribed only in the oral form (orGC); the dose ranged from 0.1 mg/kg per day to 2 mg/kg per day and depended on prior dose of GCs and patient status. NSAIDs were prescribed in the standard dose: meloxicam 0.125 mg/kg per day, nimesulide 3–5 mg/kg per day. In patients receiving MTX or other DMARDs prior to therapy initiation, these drugs were not discontinued. The MTX dose was selected for each individual patient and ranged from 5 to 50 mg/m^2 per week.

2.3. The dynamics of concomitant treatment if the main therapy was effective

The effectiveness of the main therapy and the dynamics of concomitant therapy were analyzed one month after treatment initiation, every 3 months during the first year, and every 6 months during the long-term follow-up. The total treatment duration with main therapy was 697 patient-years in 215 patients (34.5 patient-years in the ETA group, 176.75 years in the ETA + MTX group and 485.75 in the MTX group). The median treatment duration was 12 months (IQR 12:24) in the ETA group, 24 months (IQR 12: 36) in the ETA + MTX group, and 60 months (IQR 60: 60) in the MTX group, respectively.

The effectiveness of main therapy of JIA was assessed using the dynamics of laboratory and clinical signs and the scale scores. The percentage of patients who had reached better ACR Pedi response, minimal disease activity (MDA), and remission according to the Wallace criteria was calculated.

The dynamics of long-term concomitant therapy with DMARDs, orGCs or NSAIDs were assessed in patients who initially received any of the variants of concomitant treatment and showed a sufficient response to main therapy. The reasons for each dose adjustment, therapy discontinuation, or drug rechallenge were recorded. The reasons for dose reduction and subsequence discontinuation of concomitant treatment were as follows: effectiveness of main therapy at least ACR50, absence of pained joints and morning stiffness (for NSAIDs); inactive disease (by Wallace criteria or JADAS-71 cut-off point), normal level of CRP and ESR level (for orGC). The steroid-sparing effect of main therapy was assessed as the percentage of patients who had totally discontinued GC therapy and were receiving a reduced dose of orGCs. The NSAID-sparing effect of main therapy was assessed as the percentage of patients who had totally discontinued concomitant NSAIDs.

2.4. Statistical analysis

Descriptive statistics were provided as absolute frequencies or medians with interquartile range. The Mann–Whitney U-test, or Pearson's χ^2 test, or Fisher's exact test and non-parametric Kruskal–Wallis test by rank and median multiple comparisons were used depending on type of the data processed. All the reported p-values were based on two-tailed tests of significance; the p-values < 0.05 were regarded as statistically significant. The STATISTICA 7.0 software (StatSoft, USA) and RStudio software version 1.0.136 (Free Software Foundation, Inc., USA) with R packages version 3.3.1 (R Foundation for Statistical Computing, Austria) were used for the analyses.

3. Results

3.1. Baseline characteristics

The data for 397 patients from the registry of the Scientific Center for Children's Health who had received ETA and/or MTX as main therapy of JIA were analyzed. The patients were divided into subgroups in order to assess the dynamics of concomitant therapy in the groups showing a sufficient response to main treatment (Fig. 1). The main study group involved the cohort of patients who showed a sufficiently high response to main therapy and met the eligibility criteria for concomitant therapy discontinuation. These criteria were as follows: progressive improvement in well-being, no joints affected by active arthritis, pain reduction, and reaching an at least ACR30. Patients who had been withdrawn for any reason from main therapy before being eligible for concomitant therapy discontinuation were excluded from analysis. This group (n = 100) involved the patients showing insufficient primary response to main therapy, the patients showing a latent low response to treatment, and the patients who showed no positive dynamics of clinical and laboratory signs over the period of $\geq$3 months after the primary response to therapy had been achieved.

Hence, the main study group consisted of 215 patients. Of those, 24 patients received ETA monotherapy; 100 patients received MTX monotherapy; and 91 patients received ETA + MTX combination.

Persistent oligoarthritis and RF-negative polyarthritis were the predominant diagnoses in all three groups (Table 1). Children in the ETA + MTX group were older and had a longer history of the disease than those in monotherapy groups. The condition of the patients receiving MTX monotherapy was less severe at baseline with respect to a number of parameters. The CHAQ ($p = 0.033$) and JADAS71 scores ($p < 0.001$) were lower in the group of patients receiving MTX therapy.

None of the patients in the ETA group required concomitant therapy with GCs; all patients in this group received concomitant NSAIDs at start of ETA therapy. All patients received NSAIDs; 10 (11%) patients in the ETA + MTX group and 14 (14%) patients in MTX group also received or GCs.

3.2. Intergroup differences in effectiveness of main therapy

Although only the primary responders to main therapy were included in the study, the subgroups differed in terms of time it took them to achieve improvement. Five patients discontinued main treatment during first year for administrative reasons (one in ETA group, 2 in ETA + MTX group, 2 in MTX group). In groups treated with ETA, patients' condition improved much faster assessed using the ACR Pedi criteria. The percentage of patients who had achieved ACR70 in the ETA and ETA + MTX groups after 3-month therapy was 87.5 and 65.9%, respectively (Table 2).

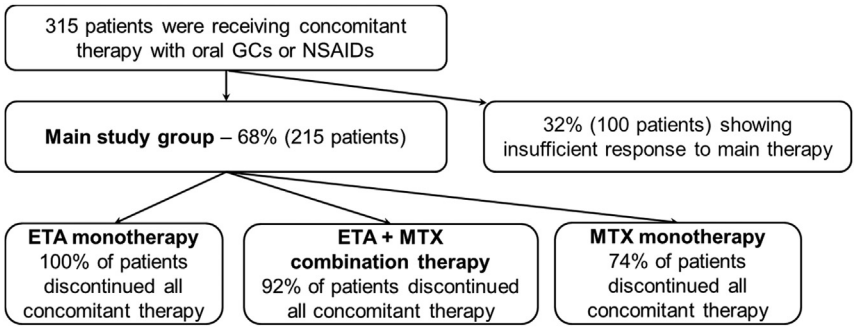


Figure 1 Study scheme.

Response to methotrexate therapy developed much slower. Nevertheless, the response levels according to the ACR criteria were comparable within the groups by the end of the follow-up period.

3.3. Effectiveness of dose reduction and discontinuation of concomitant therapy

The high effectiveness of the main therapy of JIA made it possible to reduce the dose and/or discontinue concomitant therapy. Fig. 2 shows the intragroup dynamics of NSAID discontinuation. After three-month therapy, NSAIDs were completely discontinued in 22 (91.7%) patients in the ETA group, in 79 (86.8%) patients in the ETA + MTX group, and in only 17 (17%) patients in the MTX group. During the first year/the entire follow-up of therapy, NSAIDs were completely discontinued in 24/24 (100%/100%) patients in the ETA group, in 90/90 (98.9%/98%) patients in the ETA + MTX group, and in 48/85 (48%/85%) patients in the MTX group.

In our study, only a small percentage of patients received concomitant glucocorticoid therapy: 10 (11%) patients in the ETA + MTX group and 14 (14%) patients in the MTX group. None of the patients receiving ETA monotherapy needed concomitant treatment with glucocorticoids at study start. The combination therapy made it possible to reduce the dose or completely discontinue glucocorticoid therapy in 8 (80%) patients. In all patients, the dose was reduced for the first time within the first 3 months of therapy. However, neither dose reduction nor treatment discontinuation was reported for the 14 patients receiving GC therapy in the MTX group. In the group receiving ETA as monotherapy or in combination with DMARDs, we assessed whether it was necessary to add MTX to biologic therapy. We followed up the patients who had initially been treated with ETA + MTX combination and later switched to ETA monotherapy and, contrariwise, the patients who had initially received ETA monotherapy and switched to ETA + MTX combination therapy. It turned out that in the first case, MTX treatment was discontinued in 21 out of 91 (23.1%) children. In more than half of those patients (62%), MTX therapy was discontinued after three months of treatment. Only 2 out of 24 (8.3%) patients in the ETA monotherapy group required addition of MTX to the treatment schedule after the 6-month therapy because of persistent joint pain, although the overall well-being was significantly improved (one patient achieved ACR50 and the other one achieved ACR70 at the moment when MTX was added to the treatment schedule).

3.4. The differences in effectiveness of JIA therapy depending on concomitant treatment and/or its dynamics

Concomitant treatment with NSAIDs was discontinued if patient's condition was significantly improved according to the ACR Pedi criteria. After discontinuation, child's condition was monitored to reveal any possible worsening related to concomitant therapy discontinuation. In the ETA group, none of the 24 patients who had discontinued concomitant NSAID therapy showed poorer response to therapy within the subsequent 3 months. In 3 patients in the ETA + MTX group (3.3% of all the patients who had discontinued NSAIDs in this group) and in one (1.1%) patient in the MTX group, the response was worse by one level according to the ACR Pedi criteria. Nevertheless, the final response to therapy of ACR90 was reached in all these patients without any additional adjustment of concomitant treatment.

4. Discussion

This study focused on pediatric patients with JIA provides unique data on the dynamics of concomitant ETA therapy. The findings demonstrate that long-term ETA treatment both as monotherapy and in combination with MTX therapy made it possible to reduce dose or completely discontinue most concomitant drugs in most patients. Therapy effectiveness in the ETA and ETA + MTX groups was not lower than in the MTX group, so the concomitant therapy could be discontinued more quickly and in more patients, while the effect of therapy was retained.

Although clinicians anticipated that the development of novel classes of highly efficient drugs would reduce the use of concomitant drugs in pediatric rheumatology patients, this is not always so in practice. The schedules used to treat early rheumatoid arthritis in patients with the disease onset in the 1990s and after 2006 were compared, showing no differences in administration of oral glucocorticoids (52% versus 61%, $p = 0.267$) and the number of intra-articular injections of GCs ($p = 0.269$).[13] There is a tendency towards reduction of NSAID dose; nevertheless, half of patients (28 out of 56 patients treated with NSAIDs at the first

Table 1 Demographic and clinical characteristics of patients at study initiation.

Characteristic	MTX (n = 100)	ETA (n = 24)	ETA + MTX (n = 91)	p-value
Sex:				
female, n [%]	58 [58%]	14 [58.33%]	64 [70.33%]	0.183
male, n [%]	42 [42%]	10 [41.67%]	27 [29.67%]	
ILAR subclass, n [%]:				
Persistent oligoarticular	32 [32%]	10 [41.7%]	51 [56%]	0.344
Extended oligoarticular	13 [13%]	2 [8.3%]	10 [11%]	
Polyarticular RF negative	34 [34%]	6 [25%]	26 [28.6%]	
Polyarticular RF positive	1 [1%]	0 [0%]	1 [1.1%]	
Enthesitis-related	11 [11%]	6 [25%]	12 [13.2%]	
Age at JIA onset, years, median (IQR)	2.5 (2: 5)	3 (1.7: 9.5)	2.7 (2: 6)	0.718
Disease duration, years, median (IQR)	**1.5 (0.6: 5)**	**0.75 (0.5: 1.38)**	**3.8 (1.2: 6.4)**	**0.022**
Age at study start, years, median (IQR)	**5.75 (2.9: 10.75)**	**4.35 (2.38: 13.2)**	**8.5 (4.75: 12.05)**	**0.014**
Previous therapy with oral GC, n [%]	14 [14%]	4 [16.7%]	23 [25.3%]	0.134
Previous therapy with intra-joint GC, n [%]	47 [47%]	6 [5%]	43 [47.3%]	0.126
Previous therapy with NSAIDs, n [%]	100 [100%]	24 [100%]	89 [97.8%]	0.253
Erythrocyte sedimentation rate, mm/h, median (IQR)	28 (9.25: 45)	25 (16.25: 33.75)	25 (13: 41)	0.926
C-reactive protein level, mg/l, median (IQR)	7 (1.05: 11.03)	8.5 (0.75: 17.79)	9 (2.55: 22.73)	0.225
Duration of morning stiffness, min, median (IQR)	45 (20: 60)	60 (30: 90)	60 (5: 85)	0.132
Painful joint count, median (IQR)	**3 (2: 7)**	**5 (2: 9.25)**	**5 (2: 16)**	**0.001**
Swollen joint count, median (IQR)	**3 (2: 6)**	**4.5 (2: 7.25)**	**5 (2.5: 12.5)**	**0.001**
Limited joint count, median (IQR)	**3.5 (2: 8.25)**	**5 (2: 9.25)**	**6 (3: 18)**	**<0.001**
Active joint count, median (IQR)	**3 (2: 6)**	**6 (2: 9.25)**	**6 (3: 16)**	**<0.001**
Physician global assessment of disease activity (0—100 mm), median (IQR)	58 (45: 80)	58 (47.25: 76)	65 (47.5: 80)	0.155
Parent/patient's global assessment of well-being (0—100 mm), median (IQR)	68.5 (50: 80)	70 (59.5: 90)	70 (58: 86)	0.071
Childhood health assessment questionnaire (0—3), median (IQR)	**1 (0.3: 1.5)**	**1.5 (0.75: 1.91)**	**1.25 (0.5: 2)**	**0.033**
Juvenile arthritis disease activity score-71, median (IQR)	**17.55 (13.97: 22)**	**20.5 (15.25: 25.7)**	**20 (15.85: 33.85)**	**<0.001**

Characteristics and outcomes which differ significantly ($p < 0.005$) are in bold.

Table 2 The dynamics of clinical response to main therapy in subgroup.

Outcomes	ETA (n = 24)	ETA + MTX (n = 91)	MTX (n = 100)	p-value
Therapy effectiveness 3 months *after treatment*				
ACR30	24 (100%)	89 (97.8%)	64 (64%)	
ACR50	24 (100%)	78 (85.7%)	49 (49%)	
ACR70	21 (87.5%)	60 (65.9%)	20 (20%)	**<0.001**
ACR90	14 (58.3%)	41 (45.1%)	11 (11%)	
Inactive disease (Wallace)	14 (58.3%)	29 (31.9%)	0 (0%)	**<0.001**
Therapy effectiveness 6 months *after treatment*				
ACR30	24 (100%)	90 (98.9%)	85 (85%)	
ACR50	24 (100%)	86 (94.5%)	81 (81%)	
ACR70	23 (95.8%)	78 (85.7%)	69 (69%)	**0.004**
ACR90	20 (83.3%)	55 (60.4%)	54 (54%)	
Inactive disease (Wallace)	18 (75%)	48 (52.7%)	22 (22%)	**<0.001**
Therapy effectiveness 12 months *after treatment*				
ACR30	23 (95.8%)	89 (97.8%)	98 (98%)	
ACR50	23 (95.8%)	86 (94.5%)	94 (94%)	0.343
ACR70	23 (95.8%)	81 (89%)	89 (89%)	
ACR90	19 (79.2%)	67 (73.6%)	84 (84%)	
Inactive disease (Wallace)	20 (83.3%)	50 (54.9%)	72 (72%)	**0.029**

Characteristics and outcomes which differ significantly ($p < 0.005$) are in bold.

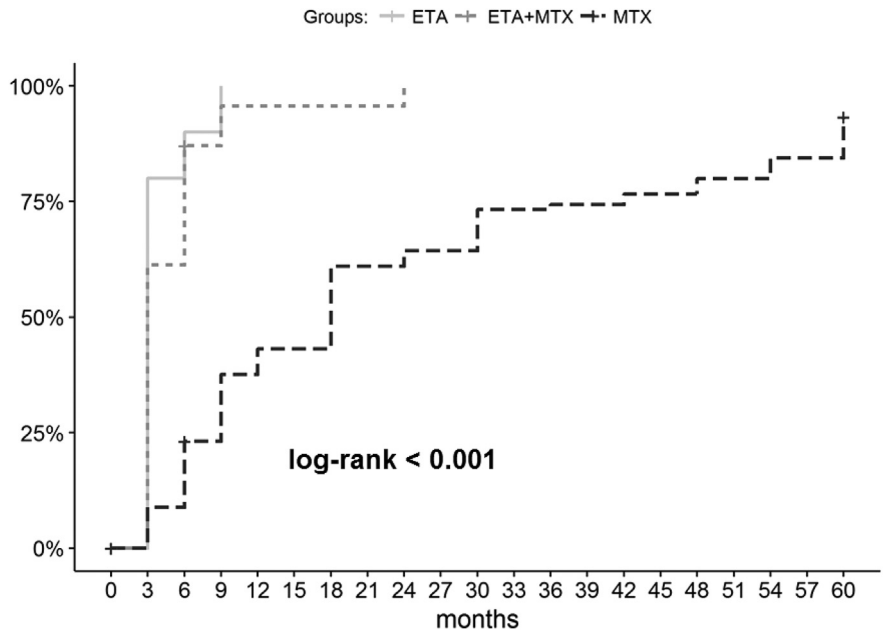


Figure 2 The probability of discontinuing concomitant NSAIDs in patient groups showing a sufficient response to main therapy.

visit) continue administration of NSAIDs as anti-inflammatory treatment even after follow-up.[14] Our study has demonstrated that when patients show a good response to main biological therapy, there is no need for concomitant treatment with NSAIDs in most cases. Since ETA therapy causes improvement in patients' well-being and symptom relief rather quickly, it is safe to discontinue concomitant NSAIDs as early as 3 months after the therapy without any risk of disease aggravation. Meanwhile, effective MTX monotherapy allows discontinuation of concomitant NSAIDs less quickly; the median duration of treatment prior to discontinuation in our study was 18 months for this group. Among the 199 patients who had discontinued concomitant NSAID treatment, a slight decrease in effectiveness of JIA therapy within the subsequent 3 months requiring no main therapy adjustment was observed in only 4 patients (2%; one patient receiving MTX and 3 patients receiving the combination therapy). In the ETA and ETA + MTX groups, concomitant NSAID therapy was discontinued in 100 and 98.9% of patients, respectively, while concomitant NSAID therapy in the monotherapy group was discontinued in only 85% of patients ($p < 0.001$). During the first year of therapy, concomitant NSAIDs were discontinued in 87.5% of ETA patients, in 98.9% of ETA + MTX patients, and in only 48% of MTX patients ($p < 0.001$), thus indicating that ETA treatment (both as monotherapy and in combination with MTX) has a much stronger NSAID-sparing effect than MTX monotherapy. This makes it possible to reduce the risk of NSAID-induced pathologies (e.g., NSAID-induced gastropathy), while the effectiveness of main treatment remains high.

The planned frequency of data collection was higher during the first year, so we have revealed a number of additional trends in the dynamics of patients' indicators. This allowed us to adjust the doses of concomitant drugs in accordance with the current status of patients. Among 114 children who discontinued NSAIDs while receiving ETA or ETA + MTX treatment, 88.6% children stopped administering NSAIDs within the first 3 months. The criteria for NSAID discontinuation were met sufficiently early. Once patients have reached the ACR50 (or better) response after a 4—8-week therapy, it is reasonable to discontinue NSAID therapy. Our findings may differ from the practice of other pediatric rheumatologists as each individual case depends on several factors: economic, insurance, and demographic ones. Furthermore, the approaches used to treat JIA may vary depending on rheumatologist experience and education.

Administration of methotrexate is another important aspect of the therapy analyzed in the present study. Our findings lead us to believe that a more thorough follow-up of patients' condition during the first 3 months of therapy is required: this will allow prompt readjustment of the therapy to meet patients' individual needs and also discontinuation of concomitant therapy with drugs that are no longer required as the main therapy is sufficiently effective.

Although the variants of concomitant therapy at follow-up initiation and prescription trends have been described widely,[15,16] few studies have assessed the steroid-sparing and NSAID-sparing effects of therapies with DMARDs and biologics[2,17] and the data in these studies are very heterogeneous. However, this aspect is the most important one with respect to therapy effectiveness as long-term steroid treatment has a significant effect on child's growth and development. In our study, ETA + MTX combination therapy made it possible to significantly reduce the dose of oral GCs administered as compared to MTX monotherapy. This fact indicates that ETA has a greater steroid-sparing effect than the conventional DMARDs.

In their multicenter study involving 130 patients, Fortunet et al. demonstrated that tocilizumab therapy in patients with rheumatoid arthritis allowed quick reduction of the dose of oral glucocorticoids without lowering effectiveness of the main therapy.[2] In turn, we have shown this possibility for etanercept therapy, although the absolute

number of patients treated with glucocorticoids at study initiation is rather small in our cohort. Verazza et al. reported that etanercept therapy reduced the use of concomitant therapy with MTX (from 73.7 to 47.4% of patients) and GCs (from 22 to 4.7%) in a cohort consisting of 422 patients who had been treated with ETA for at least 6 months.[17] According to the German and Austrian etanercept registries, glucocorticoid therapy was discontinued in 25% of 199 children receiving ETA + oral GC combination therapy (such patients were not included in our study). Among 235 patients receiving ETA + MTX combination therapy, methotrexate was discontinued in 10.6% of patients; this percentage is significantly lower than that in our study (23.1%, $p = 0.007$).[18] The potential reason for this may lie in the difference in key characteristics at baseline between our cohort and the cohort studied by Horneff et al., including disease duration and the fact that the baseline condition of patients in the German cohort was more severe. The researchers also reported that the groups receiving ETA monotherapy and ETA + MTX combination therapy did not differ in terms of frequency and time required to achieve improvement, which is consistent with our findings.

5. Conclusion

Our results demonstrate that therapy with ETA makes it possible to reduce the dosage or completely discontinue most concomitant medications (orGCs, NSAIDs, MTX) in a significant percentage of patients. Our experience of NSAID discontinuation and long-term follow-up of a large patient cohort with quality of life not being worsened gives grounds for stating that discontinuation of NSAIDs and orGCs is not accompanied by loss of effectiveness of the main therapy. This reduces the risk of developing NSAID- and GC-associated pathological conditions, while the effectiveness of main therapy remains high.

Conflict of interest statement

The authors have no conflicts of interest relevant to this article.

References

1. Gerloni V, Pontikaki I, Gattinara M, Fantini F. Focus on adverse events of tumour necrosis factor α blockade in juvenile idiopathic arthritis in an open monocentric long-term prospective study of 163 patients. *Ann Rheum Dis* 2008;**67**:1145—52.
2. Fortunet C, Pers YM, Lambert J, Godfrin-Valnet M, Constant E, Devilliers H, et al. Tocilizumab induces corticosteroid sparing in rheumatoid arthritis patients in clinical practice. *Rheumatology (Oxford)* 2015;**54**:672—7.
3. Galarraga B, Ho M, Youssef HM, Hill A, McMahon H, Hall C, et al. Cod liver oil (n-3 fatty acids) as an non-steroidal anti-inflammatory drug sparing agent in rheumatoid arthritis. *Rheumatology (Oxford)* 2008;**47**:665—9.
4. Eccleston C, Cooper TE, Fisher E, Anderson B, Wilkinson NM. Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev* 2017;**8**:CD012537.
5. Sobel RE, Lovell DJ, Brunner HI, Weiss JE, Morris PW, Gottlieb BS, et al. Safety of celecoxib and nonselective nonsteroidal anti-inflammatory drugs in juvenile idiopathic arthritis: results of the phase 4 registry. *Pediatr Rheumatol Online J* 2014;**12**:29.
6. Miyamae T, Yokoya S, Yamanaka H, Yokota S. Effect of Tocilizumab on growth impairment in systemic juvenile idiopathic arthritis with long-term corticosteroid therapy. *Mod Rheumatol* 2014;**24**:567—71.
7. Gaspari S, Marcovecchio ML, Breda L, Chiarelli F. Growth in juvenile idiopathic arthritis: the role of inflammation. *Clin Exp Rheumatol* 2011;**29**:104—10.
8. Bechtold S, Simon D. Growth abnormalities in children and adolescents with juvenile idiopathic arthritis. *Rheumatol Int* 2014;**34**:1483—8.
9. Billiau AD, Loop M, Le PQ, Berthet F, Philippet P, Kasran A, et al. Etanercept improves linear growth and bone mass acquisition in MTX-resistant polyarticular-course juvenile idiopathic arthritis. *Rheumatology (Oxford)* 2010;**49**:1550—8.
10. De Benedetti F, Brunner H, Ruperto N, Schneider R, Xavier R, Allen R, et al. Catch-up growth during tocilizumab therapy for systemic juvenile idiopathic arthritis: results from a phase III trial. *Arthritis Rheumatol* 2015;**67**:840—8.
11. Giannini EH, Ilowite NT, Lovell DJ, Wallace CA, Rabinovich CE, Reiff A, et al. Effects of long-term etanercept treatment on growth in children with selected categories of juvenile idiopathic arthritis. *Arthritis Rheum* 2010;**62**:3259—64.
12. Watanabe T, Tanigawa T, Shiba M, Nadatani Y, Nagami Y, Sugimori S, et al. Anti-tumour necrosis factor agents reduce non-steroidal anti-inflammatory drug-induced small bowel injury in rheumatoid arthritis patients. *Gut* 2014;**63**:409—14.
13. Weitoft T, Øberg K. Does modern treatment of early rheumatoid arthritis reduce the need for intra-articular glucocorticoids? *Scand J Rheumatol* 2013;**42**:163—4.
14. Kochar R, Walsh KM, Jain A, Spalding SJ, Hashkes PJ. Decreased use of non-steroidal anti-inflammatory drugs for the treatment of juvenile idiopathic arthritis in the era of modern aggressive treatment. *Rheumatol Int* 2012;**32**:3055—60.
15. Al-hemairi MH, Albokhari SM, Muzaffer MA. The pattern of juvenile idiopathic arthritis in a single tertiary center in Saudi Arabia. *Int J Inflam* 2016;**2016**:7802957.
16. Hugle B, Haas JP, Benseler SM. Treatment preferences in juvenile idiopathic arthritis — a comparative analysis in two health care systems. *Pediatr Rheumatol Online J* 2013;**11**:3.
17. Verazza S, Davì S, Consolaro A, Bovis F, Insalaco A, Magni-Manzoni S, et al. Disease status, reasons for discontinuation and adverse events in 1038 Italian children with juvenile idiopathic arthritis treated with etanercept. *Pediatr Rheumatol Online J* 2016;**14**:68.
18. Horneff G, Schmeling H, Biedermann T, Foeldvari I, Ganser G, Girschick HJ, et al. The German etanercept registry for treatment of juvenile idiopathic arthritis. *Ann Rheum Dis* 2004;**63**:1638—44.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2019.02.003.