Early combination therapy with etanercept and methotrexate in JIA patients shortens the time to reach an inactive disease state and remission: Results of a double-blind placebo-controlled trial

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Abstract

Background Remission is the primary objective of treating juvenile idiopathic arthritis (JIA). It is still debatable whether early intensive treatment is superior in terms of earlier achievement of remission. The aim of this study was to evaluate the effectiveness of early etanercept+methotrexate (ETA+MTX) combination therapy versus step-up MTX monotherapy with ETA added in refractory disease.

Methods A multi-centre, double-blind, randomized study in active polyarticular JIA patients treated with either ETA+MTX (n=35) or placebo+MTX (n=33) for up to 24 weeks, followed by a 24-week open-label phase. The efficacy endpoints included pedACR30 criteria improvement at week 12, inactive disease at week 24, and remission at week 48. Patients who failed to achieve the endpoints at week 12 or at week 24 escaped to open-label ETA+MTX. Safety was assessed at each visit.

Results By intention-to-treat analysis, more patients in the ETA+MTX group reached the pedACR30 response at week 12 (33 (94.3%)) than in the placebo+MTX group (20 (60.6%); p=0.001). At week 24, comparable percentages of patients reached inactive disease (11 (31.4%) vs 11 (33.3%)). At week 48, 11 (31.4%) and eight (24.2%) patients achieved remission. The median (+/-IQR) times to achieve an inactive disease state in the ETA+MTX and placebo+MTX groups were 24 (14–32) and 32 (24–40) weeks, respectively. Forty-four (74/100 patient-years) adverse events (AEs) were reported, leading to treatment discontinuation in 6 patients.

Conclusions Early combination therapy with ETA+MTX proved to be highly effective compared to the standard step-up regimen. Compared to those treated with the standard regimen, more patients treated with a combination of ETA+MTX reached the pedACR30 response and achieved inactive disease and remission more rapidly.

Trial registration

The study was registered by the European Clinical Trials Database (EudraCT) as 2015-003384-11 on 07-21-2014.

Background

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease characterized by chronic arthritis with no further cause (1). It is a diagnosis of exclusion and embraces a rather heterogeneous patient cohort (2). Nevertheless, the most pronounced clinical and laboratory manifestations in these patients gave grounds for combining them into several JIA categories with respect to the ILAR criteria (3). For several JIA categories, own recommendations for patient management and treatment regimen exist (4). For patients with polyarticular JIA who have no systemic manifestations, they can be treated with either NSAIDs or intra-articular injections of glucocorticoids (GCs) as the first-line
therapy depending on the presence of poor prognosis features. Efficacy of Methotrexate (MTX) in polyarticular JIA has been demonstrated and thus it is recommended also in this cases as the first DMARD (4, 5). However, not all patients respond sufficiently to MTX, and some are intolerant of its side effects (6, 7). According to international guidelines and recommendations JIA patients refractory to MTX treatment are eligible for treatment with biologics (3). In most cases, biologics are prescribed after a patient already has been unsuccessfully treated with other drugs for several months. Approval of biologics such as Adalimumab, Etanercept, Golimumab and Tocilizumab is restricted to polyarticular patients who failed pretreatment with MTX. The current treatment strategies and the sequence of medication switches allow a considerable percentage of patients to achieve long-term remission (8). However, most questions related to the optimal treatment regimen still need to be solved. Some of them have been outlined in the project plan for new ACR guidelines (9) that will be issued in 2021. In particular, the question for anti-TNF drugs (the first-line biologics for treating arthritis without systemic manifestations) consists in choosing between the biologic monotherapy and biologic + non-biologic DMARD combination therapy if a biologic needs to be added to the treatment regimen. Identifying patient categories for the optimal treatment choice is also one of the high-priority tasks. Furthermore, according to the current clinical guidelines, anti-TNF agents can be prescribed only after the disease activity remains medium or high regardless of MTX treatment for 3–6 months (4). Such a delay prolongs the time with active arthritis and reduces the current quality of life for patients and their parents, as well as increases the risk of developing irreversible osteoarticular changes. Therefore, a very important issue is related to changing the timing of medication switching or identifying certain subgroups/cohorts of patients for whom early treatment with biologics or combination therapy will be the most effective option. Etanercept (ETA) remains to be one of the most frequently used anti-TNF drugs for JIA patients (10, 11). The development and spread of biosimilars also contribute to wider application (12, 13). Choosing the optimal regimen of ETA therapy is now very relevant for both issues mentioned above. Even for methotrexate as for basic therapy option, the relationship between the duration of the disease and the effectiveness of treatment has been demonstrated well known (14). One of the key questions is whether the strategy of waiting for 3–6 months to see that MTX monotherapy is ineffective before prescribing ETA is beneficial compared to simultaneous prescription of combination treatment at baseline in terms of the time to achieve remission and the long-term outcome. Wallace et al. (15) attempted to demonstrate that early aggressive therapy contributes to the earlier onset of clinical inactive disease. However, in this study, the control group received MTX monotherapy while the main group received combination MTX + ETA + GCs. That combination made it impossible to assess the efficacy of the biologic itself. In this connection, we planned and conducted a double-blind, placebo-controlled study to evaluate the effectiveness of two different treatment regimens: ETA + MTX combination therapy vs the standard MTX monotherapy with ETA added subsequently (not earlier than after 12 weeks of MTX monotherapy) in JIA patients without systemic manifestations of the disease.

**Methods**

**Patient selection and overall study design**
This multicenter, prospective, randomized, placebo-controlled study was conducted at seven pediatric rheumatology centers in the Russian Federation. Centralized randomization ensured that the patients were divided into two groups with a 1:1 allocation ratio using randomization envelopes. The study involved 3 phases. Phase 1 corresponded to 0–12 weeks (the double-blind phase); phase 2, to 12–24 weeks; and phase 3, to 24–48 weeks. The Initial Combination Scheme cohort was treated with ETA + MTX since baseline. The control therapy (Standard Consequent Scheme) group received placebo + MTX instead; unblinded treatment with ETA in both cohorts was performed as rescue therapy if the minimal clinical effectiveness criteria of PedACR30 had not been reached at 12 weeks. At 24 weeks, patients were assessed for the presence of inactive disease state according to the Wallace criteria and those who had not reach the target also received rescue therapy. Patients without rescue remained unblinded until study end. Final assessment was performed after 48 weeks. All patients were diagnosed with active polyarticular JIA (seronegative or seropositive), extended oligoarthritis, polyarticular course of psoriatic arthritis, and enthesitis-related arthritis as determined by the International League of Associations for Rheumatology (ILAR) criteria (3); disease duration was at least 6 weeks. Active disease was defined as the presence of at least 4 active joints, a physician's assessment of global disease severity of at least 3 of 10, a patient's or parent's global assessment of wellbeing of at least 3 of 10 on a visual analogue scale (VAS). Female or male patients aged 2 to 17 years diagnosed with rheumatoid factor (RF)-positive or RF-negative polyarticular or extended oligoarticular JIA, and disease durations of < 6 months were eligible. All patients had to have active JIA, i.e. > 3 joints with active arthritis, i.e. the presence of joint swelling or, in the absence of swelling, limitation of range of motion plus pain on motion and/or tenderness on palpation), and had to be naïve for treatment von conventional or biological disease modifying drugs. More detailed inclusion and exclusion criteria are listed in supplementary table 1.

The inclusion criteria were as follows:

- Patients aged 2-17 years;
- Male or female patients;
- A patient was currently not treated with disease-modifying antirheumatic drugs (DMARDs)
- Therapy with other DMARDs (leflunomide, azathioprine, hydroxychloroquine, chloroquine, etc.) must be stopped no later than 4 weeks prior to enrollment.

- Exception: the patient was allowed to receive stable doses of sulfasalazine provided that this treatment was received throughout the entire study, at baseline, and at least for four weeks prior to enrollment.

The patient was allowed to receive stable doses of NSAIDs and corticosteroids (≤ 0.2 mg/kg prednisolone per day, with the highest dose 10 mg/day) no later than 4 weeks before study initiation.

The exclusion criteria were as follows:

- active joint count < 4;
- Physician's assessment of disease severity: VAS score < 3 out of 10;
• Assessment of well-being by the patient or his/her parents: VAS score < 3 out of 10;
• Chronic or acute infection or severe infection episodes that required hospitalization or intravenous administration of antibiotics 30 days prior to study initiation;
• A previous history of malignancy;
• Pregnancy or lactation;
• Females who were unwilling to use proper methods of contraception or sexual abstinence;
• Ongoing active gastrointestinal disorders (e.g., inflammatory bowel disease);
• A previous history of tuberculosis or any opportunistic infection, including herpes zoster;
• A history of any chronic disease (except for JIA) that could influence the effectiveness or safety of the investigational medicinal product in investigator's opinion.

Treatment regimen

At treatment initiation, the Initial Combination Scheme cohort received ETA at a dose of 0.8 mg/kg per week (up to 50 mg/week) + MTX at a dose of 10–15 mg/week either orally or by subcutaneous injection as per standard of the center. The control cohort received placebo + MTX at a dose of 10–15 mg/week. If indicated, patients in both groups also were treated with NSAIDs, folic acid, and prednisolone at the investigator's discretion.

Primary outcome criteria

Primary outcome parameters of the study were improvement according to the pedACR30 criteria (3) at week 12. Secondary outcome parameters included inactive disease according to the Wallace criteria (16) at week 24 and remission defined as continuous inactive disease for at least 24 weeks at week 48.

Phases and time points

Patients in the initial combination scheme group were treated with ETA + MTX since the first day of treatment. Patients receiving the standard consequent scheme were treated with placebo + MTX since the first day of treatment. At week 12 visit, primary assessment of improvement according to the pedACR30 criteria was performed. The responders continued to receive the initial blinded therapy. The non-responders switched to the open-label phase and further received the ETA + MTX combination treatment. Secondary assessment of treatment effectiveness was performed at week 24 visit based on whether or not the patients had reached an inactive disease state according to the Wallace criteria. Patients who had reached the inactive disease state continued to receive the earlier therapy. Patients who had failed to reach an inactive disease state switched to the open-label ETA + MTX combination treatment. Final effectiveness and safety assessment was performed at week 48 visit. The patients were asked to make an additional follow-up study end visit 2–8 weeks after the study end. The intermediate points at which patients visited the study site and laboratory data were collected corresponded to 4, 8, 16, 42, and 40 weeks after study initiation.

Ethical considerations
The study protocol was approved by the ethical committee of the Scientific Center of Children's Health and registered with the European Clinical Trials Database (EudraCT) as 2015-003384-11. The study was conducted according to the Good Clinical Practice standards. These standards ensured that design, implementation, and communication of data were reliable, patients' rights were protected, and the integrity of subjects was maintained by the confidentiality of their data. 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 to be presented.

Protocol for collecting the effectiveness and safety data

Clinical and laboratory values were monitored at each visit for each patient. Parameters of disease activity and severity were evaluated, including: evaluation of joints (the swollen joint count, tender joint count, the number of joints with limitation of motion (LOM), physician's global assessment of disease activity, Patient's global assessment of wellbeing, the CHAQ (Childhood Health Assessment Questionnaire) score (17), the Juvenile Arthritis Disease Activity Score (JADAS 71) (18), inactive disease state according to the Wallace criteria (16), and pedACR 30/50/70/90/100 response (3). The primary objective of the study was to compare the effectiveness of combination treatment with etanercept/methotrexate as compared to the standard consequent scheme of treatment with methotrexate (MTX) according to the number of responders who reached an inactive disease state/remission at weeks 24 and 48 and time required to reach these parameters. The secondary objectives of the study consisted in evaluation and comparison of the effectiveness of MTX monotherapy and ETA + MTX combination therapy using the pedACR 30/50/70/90/100 criteria and evaluation of etanercept safety in JIA patients. All AEs were reported in compliance with the Common Terminology Criteria for Adverse Events and classified according to Medical Dictionary for Regulatory Activities (MedDRA).

Statistical Analysis

The calculations were performed using the R Statistical Package (http://www.r-project.org). Descriptive statistics were shown as absolute frequencies or medians with interquartile range. The Mann-Whitney U-test, or ANOVA, or Pearson's $\chi^2$ 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 analyzed data. 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.

Results

Baseline characteristics
The study involved 68 patients: 35 patients were randomized in the cohort receiving ETA + MTX combination therapy and 33 patients randomized to be treated with placebo + MTX. Patients’ characteristics at baseline are outlines in Table 1. Table 2 summarizes the data on arthritis severity and activity at initiation of current treatment. The patients were comparable in terms of sex, age and prior treatment. Several parameters however differ between the cohorts. Patients in the ETA-MTX combination cohort were older at disease onset and at diagnosis and had higher levels for CRP, JADAS-71 and physician's assessment of disease activity. Figure 1 outlines the patient disposition with information about patients switching and main outcomes during the study. 68 patients were enrolled and randomized: 33 received placebo + MTX and 35 received ETA + MTX (Fig. 1); of these, 2 patients discontinued the study before week 12, leaving 32 patients in the placebo + MTX group and 34 in the ETA + MTX eligible for analysis at week 12. 12 pedACR30 nonresponders of the placebo + MTX group and 1 nonresponder of the ETA + MTX group received open label ETA + MTX after week 12. Between week 12 and week 24 there were 3 further drop outs leaving 20 patients in the placebo + MTX group and 43 in the ETA + MTX group eligible for analysis at week 24. From 63 patients entering part 2, only 4 discontinued between week 24 and week 48.
Table 1
Baseline demographic and anamnestic characteristics of patients enrolled in the study.

| Parameter                                      | ETA + MTX (n = 35) | Placebo + MTX (n = 33) | p      |
|------------------------------------------------|--------------------|------------------------|--------|
| **Demographic characteristics**                |                    |                        |        |
| Female, n (%)                                  | 22 (64.71)         | 25 (75.76)             | 0.471  |
| Age at enrollment, years; median (IQR range)   | 9.8 (5.82–12.94)   | 6.62 (4.1-13.26)       | 0.11   |
| Disease duration, years; median (IQR range)    | 0.81 (0.29–1.68)   | 0.74 (0.32–3.48)       | 0.632  |
| Age at onset, years; median (IQR range)        | 7.2 (4.38–10.82)   | 4.7 (2.4–9.44)         | 0.032  |
| Age at diagnosis, years; median (IQR range)    | 9.16 (5.4-12.05)   | 4.86 (2.49–11.37)      | 0.035  |
| Disease duration, years; median (IQR range)    | 2.5 (1–9)          | 3 (2–16)               | 0.38   |
| **Prior treatment**                            |                    |                        |        |
| Conventional NSAIDs, n (%)                     | 31 (88.57)         | 27 (81.82)             | 0.507  |
| COX-2 inhibitors, n (%)                        | 11 (32.35)         | 13 (39.39)             | 0.729  |
| Sulfasalazine, n (%)                           | 6 (17.14)          | 9 (27.27)              | 0.475  |
| Leflunomide, n (%)                             | 1 (2.86)           | 0 (0)                  | > 0.999|
| Oral GCs, n (%)                                | 1 (2.86)           | 2 (6.06)               | 0.608  |
| Other GCs, n (%)                               | 11 (31.43)         | 8 (24.24)              | 0.697  |
PedACR response rates during the first 12 weeks of ETA + MTX combination therapy vs placebo + MTX

Response and kinetic of response according to the pedACR30/50/70/90/100 criteria and the JADAS-71 during the first 12 weeks of treatment are shown in Figs. 2–3. Differences between the cohorts were highly significant at all points of time favoring the early combination treatment.

The JADAS-71 significantly decreased in both groups during the first 12 weeks of treatment: median level reduced from 19 (17–24.3) at the baseline to 12 (9–19) at week 12 in placebo + MTX and from 24 (18.5–34) to 6 (3.25–9.75) in ETA + MTX group. The dynamics of reduction differed between the study groups: the decrease in JADAS-71 was more rapid and significant in the group treated with ETA + MTX. Reduction of JADAS-71 was 18.3 (12–26.2) in ETA + MTX group that was significantly higher as compared to 6 (2.5–10) in placebo + MTX group (p < 0.001). We additionally compared placebo + MTX responders with ETA + MTX responders. Among the patients treated with placebo + MTX, the subgroups of responders and nonresponders were also compared. In the group initially treated with ETA + MTX, 94% of patients responded to therapy within the first 12 weeks by reaching pedACR30. Meanwhile, only 60% of patients with a mild disease of JIA in the cohort responded to placebo + MTX therapy. The responders to placebo
+ MTX had a significantly milder course of the disease in terms of tender joint count, the number of joints with limitation of motion, as well as VAS and JADAS-71 disease activity scores as compared to both ETA + MTX responders and MTX non-responders (Table 3). Table 4 summarizes the patients who reached the clinical criteria of treatment effectiveness in this study.

Table 3
Comparison of baseline parameters in the subgroups of ACR30 responders and non-responders after 12-week treatment.

|                          | ETA + MTX, week 12 ACR30 responders (n = 33) | placebo + MTX, week 12 ACR30 responders (n = 20) | placebo + MTX, week 12 ACR30 non-responders (n = 12) | p      |
|-------------------------|---------------------------------------------|--------------------------------------------------|-------------------------------------------------------|--------|
| Number of joints with LOM | 8 (5–17)                                   | 6 (4-7.5)                                         | 5 (3.5–10.5)                                         | 0.030  |
| Tender joint count      | 10 (5–19)                                   | 6 (4–8)                                           | 6 (3.5–10.5)                                         | 0.023  |
| VAS assessment of disease activity | 8 (6–9)                                   | 6 (6–7)                                           | 6.5 (4.5-8)                                          | 0.036  |
| JADAS-71                | 24 (19–34)                                  | 19.3 (19-23.8)                                    | 17 (14–27)                                           | 0.020  |
| CRP                     | 3.6 (1–26)                                  | 1.6 (0.7–9.4)                                     | 1.1 (0.1–2.9)                                        | 0.031  |

Comparison of treatment regimens: the standard scheme including consequent addition of ETA to non-responders to MTX monotherapy vs the scheme with ETA + MTX combination therapy received during 48 weeks.
Table 4

Intention-to-treat and per protocol analysis of patients according to ACR30 response after 12-week treatment and reaching the Wallace inactive disease criteria after treatment for 24 and 48 weeks on the basis of the initial patient allocation into groups.

| Time-point | Efficacy parameter achieved | Intention-to-treat | Per protocol |
|------------|------------------------------|-------------------|--------------|
|            | initial combination scheme ETA + MTX | standard consequent scheme with MTX* | p | initial combination scheme ETA + MTX | standard consequent scheme with MTX* | p |
| 12 ACR30   | 33/35 (94.3%) | 20/33 (60.6%) | 0.001 | 33/34 (97.1%) | 20/32 (62.5%) | 0.001 |
| 24 Wallace inactive disease | 11/35 (31.4%) | 11/33 (33.3%) | > 0.999 | 11/33 (33.3%) | 11/30 (36.7%) | 0.798 |
| 48 Wallace inactive disease | 17/35 (48.6%) | 20/33 (60.6%) | 0.342 | 17/32 (53.1%) | 19/29 (65.5%) | 0.436 |
| 48 Remission | 11/35 (31.4%) | 8/33 (24.2%) | 0.594 | 11/32 (34.4%) | 8/29 (27.6%) | 0.593 |

*According to treatment regimen in this group, the non-responders were supposed to switch to open-label ETA + MTX combination therapy after 12- or 24-week treatment if they failed to reach the effectiveness parameter corresponding to the given week.

Adherence and reasons for discontinuation

Two patients were withdrawn from the study because of AEs during the first 12 weeks of treatment. One patient in the ETA + MTX group had an injection site reaction (arthralgia, myalgia, bone pain after injections) and one patient in the placebo + MTX group developed hepatotoxicity after 8-weeks of treatment. In the intention-to-treat analysis, these patients were regarded as non-responders after 12 weeks of treatment (according to the ACR30/Wallace criteria, respectively) and they were excluded from per protocol analysis. Three patients were withdrawn from the study between week 12 and week 24 of treatment. One of these patients was from the group receiving combination therapy since study initiation. This patient was lost to follow-up: the patient's data were taken into account in the Intention-to-treat analysis but not taken into account for the time points of 24 and 48 weeks in the per protocol analysis. Two patients who initially received placebo + MTX and switched to open-label treatment after 12 weeks were withdrawn because of AEs, each one with thrombocytopenia and hepatotoxicity. These patients were regarded as non-responders in both analyses. Four patients were withdrawn from the study between week 24 and week 48 of treatment. In the group receiving combination treatment since study initiation, one patient withdrew his/her consent. The patient was not taken into account at the time point "48 weeks" in the per protocol analysis. Two patients were withdrawn according to the investigator's decision due to poor efficacy which was regarded as secondary ineffectiveness. One patient receiving placebo + MTX was withdrawn because his diagnosis was changed to juvenile dermatomyositis. The patient was not taken into account for the time point "48 weeks" in the per protocol analysis. Median time to reach an
inactive disease state according to the Wallace criteria differed for the treatment groups: 24 (14–32) weeks in the ETA + MTX group and 32 (24–40) weeks in the placebo + MTX group. Time to achieve remission also differed between the groups. In all eight patients who had achieved remission in the standard consequent scheme with MTX, this time was 48 weeks. Meanwhile, in 5 of 11 patients who had achieved remission in the initial combination regimen ETA + MTX, this time was less than 48 weeks (after 32 weeks of treatment in 2 patients; after 36 weeks of treatment in 2 patients, and after 42 weeks of treatment in 1 patient). Thus, till the end of the study, patients had active arthritis for 32 (24–52) weeks and 6 (5–9) visits in ETA + MTX group and for 40 (24–50) weeks and 7 (5–9) visits in placebo + MTX group.

Safety analysis

Treatment safety was evaluated separately for each phase with allowance for therapy received by patients. At all phases, the frequency of AEs in the ETA + MTX group was 17% (6 AEs) / 11% (5 AEs) / 26% (3 AEs) during phases 1, 2, and 3, respectively (Table 5). Serious adverse events were reported only for the MTX group during phase 3 (2 SAEs): (1) uveitis and (2) patient’s diagnosis was changed to a different autoimmune disease. AEs which were not serious but still required additional actions and therapy included infections, gastrointestinal diseases and hepatic events. Infections were the most frequent AE (50%/40%/57% in the ETA + MTX group and 36%/100%/33% in the MTX group during phases 1, 2, and 3). The frequency of AEs classified as gastrointestinal diseases and hepatic events was rather high at initiation of MTX monotherapy (a total of 54% during phase 1 and 0% during phases 2 and 3). An opposite situation was observed in the ETA + MTX group, where these adverse events were reported after 12-week treatment (phases 2 and 3) rather than at treatment initiation.

| Group       | ETA + MTX | MTX |
|-------------|-----------|-----|
| Phase 1     | 4 patients (17%) (6 AEs) | 7 patients (33%) (11 AEs) |
| Phase 2     | 5 patients (11%) (5 AEs) | 3 patients (15%) (3 AEs) |
| Phase 3     | 9 patients (26%) (14 AEs) | 3 patients (33%) (3 AEs) |

Discussion
Our study revealed that initial therapy with ETA + MTX was very effective already at week 4 to 12 with nearly all patients responded according to the pedACR30 criteria and the response rate was significantly higher as compared to the placebo + MTX group. Although ETA has been studied in polyarticular JIA for 20 years, this is the first head to head placebo controlled trial with ETA in these patients. A different design has been used compared to the TREAT study, in which patients were receiving ETA + MTX + high dose steroids or MTX plus two placebos for steroids and ETA (15). The primary objective of our study was to investigate whether the ETA+MTX combination therapy is superior as compared to the treatment regimen recommended by current clinical guidelines (MTX only with subsequent addition of ETA if necessary). We have demonstrated that both treatment regimens are equally effective for achieving remission at week 48. Approximately 50% of patients reached an inactive disease state after 48-weeks of treatment. However, the effectiveness of these treatment regimens differed in terms of time required to reach an inactive disease state. It took in median 24 (IQR 14–32) weeks to reach an inactive disease state for patients treated with ETA + MTX combination. Patients who had been initially treated with placebo + MTX and then switched to combination therapy (at any time) reached an inactive disease state after a median of 32 (IQR 24–40) weeks. Time to reach an inactive disease state significantly affects quality of life for patients and their parents. Furthermore, the investigators believe that reaching an inactive disease state in the early stage of arthritis (up to 2 years after the onset) may prevent the development of irreversible osteoarticular changes and reduce the future risk of disability. In fact, the delay in identifying the optimal treatment at an early stage of disease can influence long-term joint damage (19). When preparing the novel clinical guidelines, the experts should take into account a number of questions related to identification of optimal administration of biologic (monotherapy versus combination with non-biologic DMARD). The subsequent questions should address the optimal use of each biologic taking into account that there might be cases when biologic monotherapy is acceptable due to adequate patient response, adverse events, or other aspects. In particular, the question 'should ETA monotherapy versus ETA + non-biologic DMARD be recommended for patients with polyarticular JIA?' is still open. Similar questions are also open for all anti-TNF drugs. Furthermore, a double-blind placebo-controlled study to compare the effectiveness of MTX vs ADA + MTX therapy has been published (20). Ramanan et al. demonstrated that adalimumab therapy controlled inflammation and was associated with a lower rate of treatment failure compared to placebo among children and adolescents with active JIA-associated uveitis who were taking a stable dose of methotrexate. Patients receiving adalimumab had a much higher incidence of adverse events and serious adverse events than those who received placebo. MTX is recommended as the first-line treatment in oligoarthritis persisting despite nonsteroidal anti-inflammatory drugs (NSAIDs) and intraarticular steroid therapy, and in all patients with active polyarticular disease (4). However, the question regarding shortening of the period before switching to biologics from MTX monotherapy in order to shorten the time to reach an inactive disease state and improve patient's quality of life is still open. Although MTX is the first-choice drug in JIA, about 50% of patients fail to respond to it and even in responders grade of remission activeness is low (21, 22). Given the time lag between MTX treatment initiation and the patient response (about 3 months), it would be particularly useful to determine a priori the probability of beneficial therapeutic response (19). According to the results of this study, ETA + MTX combination therapy allows patients to achieve remission sooner.
This fact makes it necessary to revise the timing of biologics treatment initiation in the current clinical guidelines. The potential responders and non-responders to MTX should also be identified for optimizing the treatment regimens. The first attempts to identify predictors of methotrexate response were made a rather long time ago. In 2010, Vilca et al. analyzed 563 patients from the PRINTO database (23). All patients received MTX monotherapy for 6 months. Authors demonstrated that the most important predictors of non-response were as follows: disease duration > 1.3 years, ANA negativity, higher CHAQ disability index, and the presence of right and left wrist activity. Hence, children with severe disease course and long disease duration exhibit the worst response even to long-term MTX monotherapy. In this study, we have confirmed these findings and additionally demonstrated that 94% of patients treated with ETA + MTX since treatment initiation responded to ETA treatment and achieved ACR30 during the first 12 weeks. However, only 60% of patients responded to the placebo + MTX treatment in the respective group, while the disease course was significantly milder in these patients according to joints with limited range of motion, tender joints, the VAS score, and JADAS). Hence, MTX quickly provides relief only to children with the mild course of JIA, while ETA + MTX can help all children, regardless of disease severity. Data from the German BIKER registry on an even larger patient population of 731 JIA polyarticular JIA patients treated with MTX showed that a minimal response of a pedACR30 was reached by 77.4% at month 3 and by 83.1% of patients at month 12 while 43.1% and 65.9% of patients had a PedACR 70 response at month 3 and at month 12 (24). Thus minimal response was frequently already reached at month 3 while a stronger response to MTX treatment took usually longer to achieve. In multivariate analysis determinants for reaching PedACR 70 at month 12 were disease duration below 1 year, a lower number of tender but a higher number of active joints and the presence of morning stiffness at baseline. Of importance, patients reaching pedACR30 response at month 3 have a 4 fold and thus significantly higher chance to reach pedACR70 at month 12. Patients, who do not have a pedACR30 at month 3, therefore, should not continue upon the same treatment. In this study, we have also collected the safety data for MTX treatment vs anti-TNF + MTX. During the first 12 weeks of combination therapy, adverse events were reported in 17% of patients, while 33% of patients treated with placebo + MTX developed adverse events. Infectious adverse events were the most frequent AEs in both treatment groups. The current clinical guidelines almost do not take into account the cost effectiveness of different treatment regimes. The first reason is that too few economic analyses of JIA exist to permit conclusions. The second reason is that the RAND/UCLA Appropriateness Method does not specifically consider cost implications (25). Nevertheless, the question regarding cost effectiveness of different treatment regimens remains one of the most topical issues in routine clinical practice. Cost-effectiveness analysis was conducted by Shepherd et al. (2016) upon the initiative of the National Institute for Health Research (26). The aim of their multiple technology appraisal was to assess the clinical effectiveness and cost-effectiveness of the biologic DMARDs etanercept, abatacept, adalimumab and tocilizumab, in combination with methotrexate, where permitted, in the treatment of JIA. The available cost-effectiveness analyses do not provide an unambiguous answer and require further research that would involve head-to-head comparison of treatment regimens. Development of biosimilars and launching them into clinical practice is one of promising approaches. However, clinical effectiveness of biosimilars is still an open question and is being actively studied (7, 8). In our study, 24/33 (72.7%) patients had to switch from using the placebo +
MTX regimen to the combination regimen because of poor response. In this case, the patients switched to the combination treatment regimen in compliance with the study protocol. Treatment was discontinued in three patients in the combination therapy group and one patient in the placebo + MTX group because of the development of adverse events. The rate of patients who did escape to combination therapy with ETA + MTX was higher than expected. With such a high percentage of patients required switching, the question must be raised of whether instead of first treating patients with placebo + MTX, primary combination of MTX + ETA must be recommended since this is more effective in quickly achieving an inactive disease and improving their quality of life. Our study has a number of limitations. The groups being compared differed significantly at baseline in terms of a number of parameters, including disease duration and disease severity according to the CHAQ score. Despite randomization, patients in ETA + MTX group had higher age of JIA debut than patients in Placebo + MTX group of initially combined therapy. As patients with younger debut usually perform better, this difference may have influence on response rate in Placebo + MTX group. However, even despite this possible advantage, the level of response in the first 12 weeks in Placebo + MTX group was significantly lower. All other differences (higher swollen joint count, higher CPR level and JADAS-71 level) were also in disadvantage for the primary combination group which did not prevent ETA + MTX patients from demonstrating a higher level of response. Nevertheless, we have performed unique comparison of two different treatment schemes in multicenter Russian prospective trial that can be compared to the data for patients from other countries.

Conclusion

Our findings demonstrate that ETA + MTX combination therapy is a universal treatment regimen that can be used for patients with both mild and severe disease course to quickly reduce inflammation and the articular syndrome already during the first 12 weeks of treatment. Only patients with mild disease course respond quickly to MTX monotherapy. Patients treated with ETA + MTX combination since treatment initiation sooner reached an inactive disease state and remission compared to patients for whom ETA was added only after they had failed to respond to MTX monotherapy. Hence, earlier addition of ETA to the treatment regimen shortens the time to achieve remission and improves patients' quality of life.

Abbreviations

AE, adverse event; CHAQ, Childhood Health Assessment Questionnaire; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; ETA, etanercept; GCs, glucocorticoids; ILAR, International League of Associations for Rheumatology; IQR, interquartile range; JADAS, Juvenile Arthritis Disease Activity Score; JIA, juvenile idiopathic arthritis; LOM, limitation of motion; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; pedACR, American College of Rheumatology pediatric < criteria>; RF, rheumatoid factor; TNF, tumor necrosis factor; VAS, visual analogue scale.

Declarations
Ethics approval and consent to participate

The study was conducted in accordance with the protocol, International Conference for Harmonization, Good Clinical Practice, Food and Drug Administration regulations governing clinical study conduct, ethical principles that have their origin in the Declaration of Helsinki, 1996 revision and 2000 revision with subsequent clarifications, and all applicable local regulations. Before the study was initiated, the study protocol, the informed consent form and subject information were submitted for review to the responsible independent local ethics committee of each research center. Parents/legal guardians signed the informed consent form before any study-related procedures occurred.

Consent for publication

Not applicable.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

Alexeeva has received research funds, advisory board membership and honorary fees from Novartis, Pfizer, Sanofi, MSD, AMGEN, Eli Lilly, and Roche.

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G. Santalova, I. Kriulin, A. Alshevskaya, and A. Moskalev declare that they have no competing interests.

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Authors' contributions

The manuscript has been read and approved by all of the authors. Any information from the article has not been published and is not under consideration for publication elsewhere. All authors contribute equally in the work of the manuscript preparation.

E. Alexeeva, G. Horneff, T. Dvoryakovskaya - conception and design of study, article drafting and revising;
R. Denisova, I. Nikishina, E. Zholobova, V. Malievskiy, G. Santalova, E. Stadler, L. Balykova, Y. Spivakovskiy - working with patients and their parents, acquisition of data, article drafting;
I. Kriulin, A. Alshevskaya, A. Moskalev – database preparation, analysis and interpretation of data, article drafting and revising.

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Figures
Figure 1

Study scheme with patient flow. AE = adverse events, LFU = lost to follow up, CWD = consent withdrawal, DC = diagnosis changed, CID = clinical inactive disease; ID=investigator decision. ETA= Etanercept, MTX=Methotrexate
**Figure 2**

The dynamics of patients' condition in the study groups evaluated using the ACR Pedi criteria. ETA=Etanercept; MTX=Methotrexate
Figure 3

The dynamics of JADAS-71 in treatment groups during the first 12 weeks of therapy. ETA= Etanercept; MTX=Methotrexate