1.0 Abstract

Title

Prospective Multi-Center Observational Study to Assess Persistence, Adherence and Changes in Disease Activities in the Children Population of Juvenile Arthritis Patients Treated with adalimumab (HUMIRA) in the Routine Clinical Settings in the Russian Federation

Keywords

Adalimumab, juvenile arthritis, children, observational study

Rationale and Background

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood. The estimated incidence of JIA is 10–20 per 100,000 children up to 16 years of age [1]. Prevalence in Russian Federation for Juvenile Arthritis is estimated as 0.48 per 1000 children [15]. If not successfully treated, it can lead to severe disability [2]. According to national and international guidelines and recommendations, patients with JIA who are refractory to MTX treatment are eligible for treatment with biologic agents [3, 4]. Treatment of JIA includes nonsteroidal NSAIDs, systemic corticosteroids, and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate and hydroxychloroquine. The treatment paradigm for JIA has changed dramatically in recent years with the introduction of new biologic disease-modifying antirheumatic drugs (bDMARDs) such as tumor necrosis factor inhibitors (TNFis), interleukin inhibitors, and T-cell activation inhibitors [3-8].

Adherence to therapy is an important factor for influencing the efficacy of treatments [16]. Adherence is a complex term, reflects the active, voluntary collaborative involvement of the patient in a mutually acceptable course of behavior to produce a desired outcome [25]. Persistence (or drug survival) is an important measure that adds the dimension of time to understanding the patterns of use of pharmacotherapies, reflecting the duration of therapy from initiation to discontinuation of therapy, may also

be defined as the length of time that a patient continues on a prescribed course of medication, from initiation to discontinuation of therapy [16, 25]. Persistence is also often referred to as continuation rate or retention rate and is considered to be a measure of rates of drug discontinuation, and therefore directly connected both persistence and adherence [25, 26].

Limited data available in Russian Federation on retention rate [11, 25, 26] and no local data exist regarding persistence, and adherence of HUMIRA therapy in the treatment of JIA.

Research Question and Objectives

Primary Objective

To assess persistence in patients with polyarticular juvenile arthritis treated with HUMIRA over 48 weeks.

Secondary Objectives

1. To assess adherence in patients with polyarticular juvenile arthritis treated with HUMIRA over 48 weeks.

2. To assess change of disease activity using JADAS10 and ACR pedi 30-50-70 (and its components)* including extra-articular manifestations (EAMs), such as JIA-associated non inflectional uveitis, IBD, psoriasis) in patients with polyarticular juvenile arthritis of JIA treated with HUMIRA over 48 weeks.

*Information about disease activity based on JADAS10, ACR pedi 30-50-70 and CHAQ were collected from the medical charts if the site and physicians/investigators apply them in the routine medical practice. If physicians/investigators do not apply JADAS10, ACR pedi 30-50-70 and CHAQ in the routine medical practice then Unknown/Not Available/Not Applicable checkbox must be chosen. In this program AbbVie did not provide any license permission for using JADAS10, ACR pedi 30-50-70 and CHAQ to investigators as well as special training for correct usage of JADAS10, ACR pedi 30-50-70 and CHAQ. Only routine medical practice data were collected and further analyzed in this PMOS.

Study Design

This was a non-interventional, product-focused, longitudinal and multi-center study with no control group.

Setting

For purpose of this study, participants were recruited and observed in 16 national and regional hospital/outpatient services.

Subjects and Study Size, Including Dropouts

70 patients were included in this descriptive observational study without any priory sample size justification/calculation. Convenient sampling methods were used for enrollment of patients who attended routine outpatient visits, fulfilled the inclusion/exclusion criteria and had signed patient's informed consent form by the parent or guardian/and by the child (if applicable).

Variables and Data Sources

Primary Variables

- Humira persistence –

(1) Persistence was defined as the time (in days) between the start date of HUMIRA (adalimumab) treatment and the earliest date of discontinuation* of Humira (adalimumab) or drop out of study or lost to follow up. Patients did not discontinue after 48 weeks follow up period were censored at 48 weeks.

(2) Persistent rate – defined as the probability of patients that are ongoing on treatment at 48 weeks since they started on Humira (adalimumab) using Kaplan-Meier Method.

** Humira (adalimumab) discontinuation was defined as the interruption of continual adalimumab therapy for at least 28 days between doses (without prescription of an alternate bDMARD). Periods of less than 28 days between doses were defined as temporary dose delays, not meeting the criteria for a Humira (adalimumab) discontinuation. Also, discontinuation included stopping to participate in the*

study due to any reason (death, lost to follow-up, discontinuation due to Aes, switching to another treatment, physician decision, others).

Secondary Variables

- Medication adherence over observational study period – the extent to which a patient act in accordance with the prescribed interval and dose of a dosing. The cut-off for the adherence/non-adherence set up for this study at ≥ 80% of timely taking doses. The measure is based on patient or caregiver/legal representative reported data (patient or caregiver/legal representative diaries).

- Proportion of patients with 30%, 50% and 70% ACR pedi responses at 2, 3, 4 and 5 observational visits. The ACR Pediatric 30, 50, 70 are defined as 30%, 50%, and 70%, improvement respectively in a minimum of three core set criteria with worsening of one variable by no more than 30%.

- Change from baseline in physician overall disease activity measured by of 10 cm VAS – at 2, 3, 4 and 5 observational visits.

- Change from baseline in patient (if appropriate in age) or parent overall well-being measured by 10 cm VAS at 2, 3, 4 and 5 observational visits.

- Change from baseline in Childhood Health Assessment Questionnaire-Disability Index (CHAQ-DI) total score and subscales (disability, discomfort and pain) score at 2, 3, 4 and 5 observational visits.

- Change from baseline in number of joints with active arthritis at 2, 3, 4 and 5 observational visits.

- Change from baseline in number of joints with limited range of motion at 2, 3, 4 and 5 observational visits

- Change from baseline in ESR at 2, 3, 4 and 5 observational visits.

- Change from baseline in JADAS10 at 2, 3, 4 and 5 observational visits.

- Proportion of patient with low diseases activity (defined as a JADAS10 of 1.1 – 2) and moderate disease activity (defined as a JADAS10 of 2.1 – 4.2) based on JADAS10 at baseline, 2, 3, 4 and 5 observational visits.

- Proportion of patients with one, two and etc. missed dosed of HUMIRA and number of missed doses at 2, 3, 4 and 5 observational visits.

- Proportion of patients with any Extra-articular manifestations (EAMs) (JIA-associated non inflectional uveitis, IBD, psoriasis) at baseline, 2, 3, 4 and 5 observational visits.

- Proportion of patients with any comorbidity at baseline, 2, 3, 4 and 5 observational visits.

Results

A prospective multi-center observational study was conducted to assess persistence, adherence and changes in disease activity in the children population of juvenile arthritis patients treated with adalimumab (HUMIRA) in the routine clinical settings in the Russian Federation. 70 patients (from 2 to 17 years, the median age was 10 years) with polyarticular juvenile arthritis according to ILAR criteria (22 (31.4%) male and 48 (68.6%) female patients) from 16 clinical sites were included in this observational study. 59 patients fully completed participation in the clinical trial in accordance with the Protocol. Clinical characteristics of patients at baseline were the following: (1) all patients with available JADAS10 total score assessments (68) were with high diseases activity (>4,2 score), (2) JADAS10 mean total score was 22.6 (SD 5.7); (3) Impact on physical function using CHAQ-DI was considered significant (>1.6) in 34/69 (49%) patients moderate (0.64 to 1.6) in 24/69 (34.8%) and minimal (0.14 to 0.63) in 8/69 (11.6%); (4) mean disability index (CHAQ-DI) constituted 1.6 (SD 0.8); (5) proportion of patients with predefined EAMs constituted (a) with JIA-associated non-inflectional uveitis – 12/70 (17.1%), (b) with IBD – 4/70 (5.7%) and (c) with psoriasis – 2/70 (2.9%). In more details, please see Tables 10.1-3 – 10.1-7.

The median duration of therapy with HUMIRA (adalimumab) was 338.5 days in the total recruited patient population (70 patients). For patients with persistence (n = 59), the median duration of therapy was 343 days, for patients with discontinuation (n = 11) – 183 days. The most frequent duration of therapy in the study was 336 days (15 patients out of 70, 21.4 %). 59 patients (84.3%) continued therapy with HUMIRA (adalimumab) at 48 weeks of follow-up. According to the results of the study, high compliance of patients to therapy can be noted. Most patients continued therapy at the end of the study (48 weeks or 336 days). The most common category for discontinuation was more than 28 days between doses (5/70 enrolled patients, 7.1% or 5/11 discontinued patients, 45.5%). Most patients (64 patients (95.5%)) demonstrated high adherence to therapy (≥ 80% of timely taking doses). Thus, the treatment regimen with adalimumab (HUMIRA) appears acceptable, most patients did not stop taking adalimumab on their own without a doctor's recommendation. There were not patients who discontinued the study by physician decision according to completion form. This estimate is consistent with the results of the persistent rate calculations. The probability of patients that are ongoing on adalimumab at 48 weeks was 0.8 (0.7 – 0.9). The average number of missed doses demonstrates that patients follow the recommendations for the adalimumab (Humira) therapy regimen. The average number of missed doses in the study was 0.2.

These results allow us to highly evaluate the potential of using adalimumab (Humira) in routine clinical practice. High adherence and persistence of therapy positively characterizes adalimumab (Humira) for treatment of JIA and the convenience of its use.

By week 12, 58/58 (100%) of patients had achieved at least ACR Pedi 30, with 43/58 (74.1%) achieving ACR Pedi 50, and 18/58 (31.0%) achieving ACR70 Pedi 70. At week 48, the proportions of patients achieving ACR Pedi 30, 50, and 70 were 50/50 (100%), 47/50 (94.0%), and 46/50 (92.0%), respectively which is consistent with published data [30].

Evaluation using CHAQ-DI showed similar results for the manifestations of the disease. The study showed improvement in patients' condition that are shown as total score CHAQ-DI and the evaluation of the subscales. Treatment with adalimumab (Humira),

in children with juvenile arthritis was associated with decreases in pain and discomfort, and improvements in disability. Improvements in the condition of patients were noted after 12 weeks of therapy (Visit 2) with changes at later visits (after 24, 36 and 48 weeks of therapy), being further improved. During the study, the values of the Disability Index improved (the differences in scores on Visits 2, 3, 4 and 5 compared to the baseline level (Visit 1) were -0.9, -1.2, -1.2 and -1.4 points, respectively. The severity of discomfort and pain also decreased during the study, with the decrease in later visits being further improved: the differences in scores on Visits 2, 3, 4 and 5 compared to the baseline level (Visit 1) were -31.8, -43.8, -48.3 and -58.6 points, respectively. A decrease (improvement) in the CHAQ-DI score during the study was also registered for General Evaluation. Compared to the baseline level, a decrease in General Evaluation was observed on Visit 2 (-28.6 points), Visit 3 (-44.3 points), Visit 4 (-49.7 points) and Visit 5 (-59.2 points).

The positive effect of treatment with adalimumab (Humira) has been noted by both the attending physicians and the patients themselves or their parents. By the end of the follow-up period (48 weeks), the effects of therapy were most significant. At the same time, improvements were noted after 12 weeks of treatment. For Physician Overall Disease Activity Measured by 10 cm VAS, there was a decrease (improvement) compared to baseline. At Visit 2 (Week 12), the average changes were -2.6 cm compared to baseline, at Visit 3 (Week 24) -4.3 cm, at Visit 4 (Week 36) -5.2 cm and at Visit 5 (Week 48) -5.8. Changes from baseline in patient (if appropriate in age) or parent overall well-being measured by 10 cm VAS at 2, 3, 4 and 5 observational visits were -2.9 cm, -4.2 cm, -5.0 cm and -5.9 cm, respectively.

At week 48-week therapy with adalimumab (Humira) reduced the number of affected joints, up to the complete absence of affected joints. During the study, there was a decrease in the number of joints with active arthritis compared to baseline: on Visit 2, on average, the decrease was -5.4, on Visit 3 -7.2, on Visit 4 -7.8, on Visit 5 -8.6. By week 48 the number of joints with active arthritis was, on average, less than 1 (0.5). Similar results were obtained according to the evaluation number of joints with limited

range of motion. During the study, there was a decrease in the number of joints with limited range of motion: on Visits 2, 3, 4 and 5, the number of such joints compared to the baseline level was -4.1, -5.7, -6.4 and -7.6, respectively. By week 48 the number of joints with limited range of motion was, on average, less than 1 (0.9).

During the study, there was a decrease in ESR values: at Visit 2, the differences with the baseline level were -13.6 Mm/h, at Visit 3 -16.6 Mm/h, at Visit 4 -18.9 Mm/h, and at Visit 5 -21.0 Mm/h. After 48 weeks of follow-up, the average ESR values were 7.7 mm/h. 48-week therapy leads to decrease of ESR, which indicates a low level of the inflammatory process associated with the disease.

All patients had high disease activity at baseline (JADAS10>4.2). Number and proportion of patients with inactive disease (JADAS10 ≤1 score) at weeks 12, 24, 36 and 48 constituted 2/63 (3.2%), 3/64 (4.7%), 13/64 (20.3%) and 19/58 (32.8%) respectively. Number and proportion of patients with low diseases activity (JADAS10 1,1 – 2 score) at weeks 12, 24, 36 and 48 was 0/63 (0%), 6/64 (9.4%), 8/64 (12.5%) and 11/58 (19%) respectively. Cumulatively at weeks 12, 24, 36, and 48, the proportion of patients achieving at least low disease, defined as a JADAS10 ≤ 2.0 was 2/63 (3.2%), 9/64 (14.1%), 21/64 (32.8%), and 30/58 (51.7%), respectively. Number and proportion of patients with moderate diseases activity (2,1 – 4,2 score) at weeks 12, 24, 36 and 48 composed 9/63 (14.3%), 11/64 (17.2%), 14/64 (21.9%) and 13/58 (22.4%) consequently. Number and proportion of patients with high diseases activity (>4,2 score) was 52/63 (82.5%), 44/64 (68.8%), 29/64 (45.3%) and 15/58 (25.9%) accordingly.

The average JADAS10 total score decreased (improved) during the study, from 22.649 at baseline to 11.956, 7.556, 5.041 and 3.179 at weeks 12, 24 36 and 48, respectively. It is also important to note a decrease in the proportion of patients with high disease activity after 48 weeks of therapy (25.9% compared to 100% at baseline) and an increase in the proportion of patients with inactive disease (JADAS10≤1 score) - 32.8% compared to 0% at baseline.

The proportions of patients with extra-articular manifestations of juvenile idiopathic arthritis (JIA-associated non-inflectional uveitis, IBD, psoriasis) remained almost unchanged during the study. This study did not assess the impact of Humira on the severity of pre-existing EAMs. Proportions of patients with any comorbidity at baseline, 2, 3, 4 and 5 observational visits also remained almost unchanged..

Adalimumab (Humira) therapy appears to be well tolerated in this population of children with juvenile idiopathic arthritis. The study recorded a total of 4 serious AE's, all of which occurred in the same individual patient: 2 events were classes as severe (PT [redacted]Encephalitis and PT [redacted] Varicella and 2 classes as moderate (PT [redacted] Ataxia (ataxic syndrome) and PT [redacted] Meningeal disorder (meningeal symptoms). For all collected serious adverse events, there was no reasonable possible association by investigator opinion with the use of adalimumab (HUMIRA).

Discussion

The study demonstrated high compliance and persistence of therapy, which allows us to conclude that the drug is convenient to use in the pediatric population of patients with polyarticular juvenile arthritis. The results of this study regarding the effects of therapy on the manifestations of juvenile idiopathic arthritis in children are consistent with the published data. There are no new significant data on the safety of adalimumab (Humira) in this population.

Marketing Authorisation Holder(s)

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