
1.0 Abstract

Title

Prospective, Multi-Center, Observational, Program to Assess Retention Rate, Persistence and Adherence in the Population of Spondylarthritis (Ankylosing Spondylitis and Psoriatic Arthritis) Patients Treated with Adalimumab (Humira®) in the Routine Clinical Settings in the Russian Federation

Keywords

Adherence, biologics, persistence, rheumatoid arthritis

Rationale and Background

Ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are two major subtypes of a rheumatic disease group called spondyloarthritis (SpA). SpA is characterized by enthesitis and joint involvement of the spine and/or peripheral joints. The management of SpA has advanced greatly in recent years. Especially biologics such as anti-tumor necrosis factor a (anti-TNF-a) agents have the potential of improving the signs and symptoms of SpA as measured by commonly used outcome parameters.

To achieve long-term optimal patient outcomes with regards to disease activity, health-related function and quality of life, the appropriate use of medication is central to the successful management of long-term conditions. However, many patients do not take their medications as prescribed, and non-adherence is perceived a major problem in healthcare. [Thier SL et al. (2008); Sabaté E (2003); Harrold LR et al. (2009)] Treatment adherence is of importance in chronic inflammatory disorders as SpA as these are characterized by fluctuating and usually progressive disease courses and a need for lifetime management. Suboptimal adherence to therapy, as observed in patients with may contribute to the unsatisfactory therapeutic response or to treatment failure.

Retention rate, persistence, and adherence to therapy are the important factors influencing effectiveness of treatment. [Lie E et al. (2015)] Medication persistence refers to the act of continuing the treatment for the prescribed duration. It may be defined as ‘the duration of time from initiation to discontinuation of therapy.’ Medication persistence is an important measure that adds the dimension of time to understanding the patterns of use of pharmacotherapies. [Blum MA et al. (2011)] Medication compliance (synonym: adherence) refers to the degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency. It may be defined as ‘the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen.’ Medication adherence also helps to capture whether a patient takes a medication sporadically during a defined time and hence is also an important dimension for understanding medication-use patterns. [Blum MA et al. (2011)] Retention rate is the number of individuals who remained in the study at the end of data collection as a proportion of the total number of participants recruited at the baseline assessment. Retention rate reflects duration of patient’s staying on therapy and directly connects both persistence and adherence.

No local data available in Russian Federation on retention rate, persistence, adherence of adalimumab (Humira®) treatment in SpA patients in real-world setting.

Research Question and Objectives

Primary Objective:

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- To assess retention rate in SpA (AS and PsA) patients treated with adalimumab (Humira®) over 48 weeks.

Secondary Objectives:

- To assess persistence in SpA (AS and PsA) patients treated with adalimumab (Humira®) over 48 weeks.
- To assess adherence in SpA (AS and PsA) patients treated with adalimumab (Humira®) over 48 weeks.
- To assess change of disease activity in (Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in AS and Disease Activity Score—28 joints (DAS28) in PsA) patients treated with adalimumab (Humira®) over 48 weeks.

Study Design

This was a multi-center, mono-country, single-arm longitudinal post-marketing study. The program comprised 5 observational visits, which were scheduled over the 48-week treatment period. Patients visited the study site approximately every 3 months, which was in accordance with the routine clinical practice. Evaluations were to be conducted at baseline (Visit 1 (Enrollment)), and then at 3 months (Visit 2), 6 months (Visit 3), 9 months (Visit 4) and 12 months (Visit 5). Failure to observe these 3-month intervals was not considered a breach or violation of the protocol. All enrolled patients were to be followed by a personal or telephone contact at 30 days after their last dose in the program.

Setting

For purpose of this study participants were recruited and observed in approximately 15 national and regional hospital/outpatient services in the Russian Federation.

Patients and Study Size, Including Dropouts

The source population in this program comprised patients diagnosed with spondylarthritis (ankylosing spondylitis and psoriatic arthritis) and treated with adalimumab (Humira®) in routine clinical practice.

Eligible patients were adults aged 18 years old and above with a confirmed diagnosis of AS or PsA who were eligible for adalimumab (Humira®) treatment or who were prescribed adalimumab (Humira®) within a maximum of 1 month prior to study enrolment (and independent of study inclusion). At the moment of start of treatment with adalimumab (Humira®) patients had to have moderate/severe AS or PsA (BASDAI > 4 for AS; DAS28 >3,2 for PsA). Patients had to either have a negative test result for tuberculosis (TB) and TB specialist permission to start biologic therapy. Patients had to be willing to authorize use and disclosure of personal and health data, and to provide written informed consent to participate in the study.

Patients with contraindications for adalimumab (Humira®) treatment, as well as those unable to walk and perform basic self-care activities either due to SpA or a comorbid condition, who had any biologic drugs

taken over before 3 months of enrolment to the study, or who had previously participated in this program, were excluded from the study.

Based on data of a prospective, observational program [Heiberg M.S. *et al.*, 2008], unadjusted 1-year retention rates of anti-tumor necrosis factor (anti-TNF) medications were 77.3% and 77.5% for PsA, and AS groups, respectively. Therefore, for this program, it was assumed that about 77.0% of the participants would remain on the therapy with adalimumab (Humira®) in routine clinical settings. The sample size calculation was performed in order to obtain assessments of qualitative features with a normal approximation two-sided 95% confidence interval for a single proportion. The half-width of this two-sided 95% confidence interval should not have exceeded $\pm 7\%$ (i.e. width 14%, where the low limit was 70% and the upper limit was 84%). Thus, it was concluded that 139 participants would be sufficient.

Variables and Data Sources

Primary Variable:

- Number and proportion (%) vs baseline of patients on the therapy at 48 weeks of the program (retention rate) for the total study population of patients with SpA (AS and PsA).

Secondary Variables:

- Medication adherence over observational program period, defined as ‘the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen’. The cut-off for the adherence was set up for this program at $\geq 80\%$ of timely administered doses. According to label injections of adalimumab (Humira®) should be administered every two weeks. To be considered ‘timely administered’ an injection should have been administered within a ± 3 -day window of the recommended dosing schedule.
- Medication persistence as expressed by the duration of time (in weeks) from initiation to discontinuation of therapy.
- BASDAI total score (changes from baseline) for AS.
- DAS28-ESR total score (changes from baseline) for PsA.

A secure web-based electronic data capture (EDC) system was utilized for data collection, monitoring, and quality control. Data validation was programmed in the EDC system to automate data queries. Electronic case report forms (eCRF) were designed to gather the data needed for the program that were collected as part of local standard of care of the program patients. Data for the program were collected during clinical interview with the patient and from the source documents at the center. Source documents were original documents, data, and records. Those included hospital records, clinical and office charts, laboratory data/information, pharmacy dispensing and other records, recorded data from automated instruments, patients’ diaries, etc.

Baseline information regarding patient demographics, social status, relevant medical history (current rheumatological diagnosis, duration of symptoms and disease duration), pharmacological treatment (past and present) of SpA, extra-articular manifestations, laboratory parameters (erythrocyte sedimentation

rate [ESR] and/or C-reactive protein [CRP]), and scores on the following indices: BASDAI and DAS28 was collected at each investigational site at the time of patient enrollment (Visit 1). Where available, baseline information was collected from the medical records of all enrolled subjects and entered into the eCRF by the investigator or designated site staff at each respective investigational site. Collection of the information about prior diseases was not planned in this program.

Composite score values on BASDAI and DAS28 indices and laboratory parameters (CRP and ESR) were assessed at visits 2, 3, 4 and 5 (if part of the normal routine). Additional documentation recorded throughout the observation period included concomitant medication, and serious adverse events (SAEs). SAEs were reported based on current version (21.0 or later) of Medical Dictionary for Regulatory Activities (MedDRA).

Data pertaining to self-administration of adalimumab (Humira[®]) was self-reported by the patient in the patient's diary. These data were then transferred to the eCRF by the investigator or designated site staff during observational visits 2,3,4 and 5.

The evaluation of retention rate, medication persistence, and medication adherence was based on the information from the “ADALIMUMAB (HUMIRA[®]) THERAPY ADMINISTRATION” eCRF form, which corresponded to the information from patient's diary about self-administration of adalimumab (Humira[®]). BASDAI total score in AS patients and DAS28-ESR total score in PsA patients were evaluated based on the information from the “LABORATORY DATA, BASDAI, DAS 28” eCRF forms, which corresponded to that of the medical records.

Because the “RELEVANT MEDICAL HISTORY” form might have contained partial date of onset of the first symptoms and the date of confirmed diagnosis, day was to be imputed before calculations performing — it was to be defined as the first day of the reporting month. If only year was recorded the date was to be imputed as January 1st of the corresponding year. This imputation was to be used only for calculations and was not to be reported in the corresponding listing.

No other imputations for missing data were performed.

Considering the observational design of the program and its objectives, the statistical analysis was descriptive in nature. Quantitative (continuous) variables were summarized with n (the number of patients with no missing data), mean, standard deviation, median, 1st quartile, 3rd quartile, minimum and maximum values. 95% CIs for mean and median were computed (except for laboratory data analysis results).

Qualitative (categorical) variables were summarized with n (the number of patients with no missing data), frequencies and percentages. In addition, 95% confidence intervals were generated (except laboratory data analysis results).

For the laboratory data analysis results, percentages by categories were calculated based on the number of patients with no missing data. For all other cases, percentages were computed from the number of all patients in the analysis set.

All analyses were based on the All Enrolled set, which included all the patients who signed Authorization (Consent) for Use/Disclosure of Data form to participate in the program and had any collected data.

The following arrangements were applied: all tests were two-sided with the default significant level 5%; all confidence intervals (CIs) were two-sided with 95% confidence level.

The duration of therapy (in weeks) was computed as the difference between the first and the last adalimumab (Humira[®]) administration in days +1 divided by 7. After these calculations, the number and proportion of patients on the therapy at 48th week of the program (retention rate) were defined as the number and proportion of patients with therapy duration greater than 47 weeks.

Patient adherence were calculated as:

$$100\% \times \left(\frac{\text{number of timely administered injections}}{\text{number of all administered injections}} \right)$$

A patient was considered adherent if $\geq 80\%$ of doses he/she took were timely administered. The number and proportion of adherent patients were computed.

The calculation of the duration of time from initiation to discontinuation of therapy (medication persistence) was similar to that described above for the retention rate.

Changes in BASDAI total score were to be tested using paired Student's t-test or Wilcoxon signed-rank test: values on visit 5 were compared with the baseline values. Non-parametric test was to be used if data distribution deviate appreciably from normality. As a primary analysis, all patients who completed visit 5 were analyzed. As a sensitivity analysis, patients who started adalimumab (Humira[®]) treatment more than 14 days before the baseline BASDAI evaluation were to be excluded from the comparison.

Frequency tables with the number and percentages of patients with improvement (decreasing) level for BASDAI total score, determined on each appropriate program visit, were presented. Clinically significant improvement was defined as the total score decrease by ≥ 2 points comparing with the baseline value. If the total score decreased by < 2 points, it was considered a not significant improvement. [*van der Heijde D et al. (2017)*]

Changes in DAS28 total score were to be tested using paired Student's t-test or Wilcoxon signed-rank test: values on visit 5 were compared with the baseline values. Non-parametric test was to be used if data distribution deviated appreciably from normality. As a primary analysis, all patients who completed visit 5 were analyzed. As a sensitivity analysis, patients who started adalimumab (Humira[®]) treatment more than 14 days before the baseline DAS28 evaluation were to be excluded from the comparison.

Frequency tables with the number and percentages of patients with improvement (decreasing) level for DAS28 total score, determined on each appropriate program visit, were presented. Additionally, frequency tables were presented only for patients with spondyloarthritis who started adalimumab (Humira®) treatment not more than 14 days before the baseline DAS28 assessment.

Improvement was determined according to the European League Against Rheumatism (EULAR) improvement criteria. [*van Gestel AM et al. (1999)*]

Results

A total of 139 patients were enrolled into the program in 14 national and regional hospital/outpatient services in the Russian Federation. The current rheumatological diagnosis in majority 95 (68.3%) of all enrolled patients was formulated as “ankylosing spondylitis”. The rest 44 (31.7%) patients were diagnosed with psoriatic arthritis.

The majority of patients in the All Enrolled set were white, high school educated, middle-aged men, currently working. Most of the patients never smoked, neither had any alcohol use disorders.

The patients were almost equally distributed according to their disability status: 70 (50.4%) patients reported having had disability, while 69 (49.6%) patients did not report disability. Rheumatologic diseases were the reason for disability in 68 (48.9%) patients. In 2 (1.4%) patients the disability was due to other diseases.

Of 48 (34.5%) patients who reported their occupational status as “not working”, 27 (19.4%) were not working due to disability.

According to the data presented, 110 (79.1%) patients were still on the therapy at 48th week of the program.

The median proportion of timely administered adalimumab (Humira®) doses (medication adherence) was 100%. In 25% of participants (Q1) the medication adherence was less than 95.83%; in 75% of participants (Q3) the medication adherence was less than 100.00%. Of 139 enrolled patients 131 (94.2%) patient was adherent, since $\geq 80\%$ of adalimumab (Humira®) doses they took were timely administered.

The duration between the first and the last dose administration (medication persistence) ranged from 0.1 week to 66.7 weeks. The median medication persistence was 50.43 weeks. In 25% of participants (Q1) the medication persistence was shorter than 48.14 weeks; in 75% of participants (Q3) the medication persistence was shorter than 52.57 weeks.

Of 95 patients with ankylosing spondylitis enrolled in the program, 77 patients completed visit 5 which corresponds to 81.0% retention rate. The BASDAI total score at visit 1 ranged from 4.1 to 9.5 points, with the mean (SD) of 6.35 (1.406) points, which signified high disease activity, according to *Garrett S*

et al. (1994). The BASDAI total score at visit 5 ranged from 0.2 to 8.6 points, with the mean (SD) of 3.08 (1.792) points. The mean (SD) BASDAI total score change from baseline at visits 2, 3, 4 and 5, which were conducted approximately every 3 months, were -2.29 (1.591), -2.97 (1.713), -3.20 (1.949) and -3.31 (2.174), respectively. The change in disease activity was statistically significant — p-value (Student's paired t-test) for visit 1 — visit 5 comparison was <0.0001. Clinically significant BASDAI improvement was seen in 59 (76.6%) patients at visit 5, while at visit 2 clinically significant BASDAI improvement was seen in 48 (53.9%) patients. Not significant BASDAI improvement was seen in 15 (19.5%) patients at visit 5, while at visit 2 not significant BASDAI improvement was seen in 36 (40.4%) patients. The number of patients (3 (3.9%)) who reported “no improvement” at visit 5 was less than the number of patients (5 (5.6%)) who reported “no improvement” at visit 2. The difference was due to the shift of patients during the program from categories with lower improvement to categories with higher improvement, and due to dropouts of no responders.

Of 44 patients with psoriatic arthritis enrolled in the program, 41 patients completed visit 5 which corresponds to 93.2% retention rate. The mean (SD) of DAS28-ESR total score at baseline (Visit 1) was 5.529 (0.9984) points, which corresponded to high disease activity, according to *Singh JA et al. (2016)*. The mean (SD) of DAS28-ESR total score at Visit 5 was 2.974 (1.1693) points. The mean (SD) DAS28-ESR total score changes from baseline at visits 2, 3, 4 and 5, which were conducted approximately every 3 months, were -1.762 (1.0099), -2.155 (1.1322), -2.472 (1.3373) and -2.555 (1.5078), respectively. The change in disease activity was statistically significant — p-value for visit 1 — visit 5 comparison was <0.0001. Good EULAR response was seen in 24 (58.5%) patients at visit 5, while at visit 2 good EULAR improvement was seen in 10 (25.0%) patients. Moderate EULAR DAS28 response in comparison with the baseline values was seen in 15 (36.6%) patients at visit 5, while at visit 2 moderate EULAR DAS28 response in comparison with the baseline values was seen in 26 (65.0%) patients. The number of patients (2 (4.9%)) who reported “no improvement” at visit 5 was less than the number of patients (4 (10.0%)) who reported “no improvement” at visit 2. The difference was due to the shift of patients during the program from categories with lower improvement to categories with higher improvement, and due to dropouts of no responders.

Conclusion

Based on the available data presented, adalimumab (Humira®) was shown to be an effective, with favorable safety profile, treatment for adults with spondylarthritis (ankylosing spondylitis and psoriatic arthritis) in routine clinical practice in Russian Federation. The retention rate, that was primary objective of the study, over 48-weeks observational period constituted 79,1%. Only 12 patients experienced 20 AEs during the program, including 7 SAEs experienced by 3 (2.2%) patients. The ability of adalimumab (Humira®) to offer satisfactory disease control in the majority of adult patients with spondylarthritis (ankylosing spondylitis and psoriatic arthritis) was demonstrated.

Marketing Authorisation Holder

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Names and Affiliations of Principal Investigators

The information on principal investigators of centers which enrolled patients in the present program, with detailed contact information is presented in Annex 3. A list of registry physicians with detailed contact information.