1.0 Abstract

Title

A Prospective, Mono-Country, Multi-Center Study to observe the frequency of Extra-Axial symptoms in Korean Ankylosing Spondylitis patients on adalimumab therapy

Keywords

Ankylosing Spondylitis, adalimumab, Humira, Frequency of Extra-Axial symptoms, Korean, Prospective observational study

Rationale and Background

In addition to chronic inflammation of the spine, extra-axial manifestations (EAMs) are common features in patients with ankylosing spondylitis (AS). Although AS is primarily a disease of the axial skeleton, peripheral joint involvement occur in up to 70% of the patients.[1]. By the epidemiological study of 847 patients in Belgium, 42% of AS patients had one or more extra-articular manifestations.[2] According to a single center and cross-sectional study in Korea of 830 AS patients, cross-sectional study[3] revealed that Korean patients with AS have a higher frequency of peripheral arthritis and hip joint involvement. The incidence of peripheral arthritis was higher than that reported in Western countries,[14] but epidemiological data on the extra-axial manifestations of Korean AS patients are poor.

Adalimumab was approved for immune mediated inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis (AS), psoriatic arthritis, inflammatory bowel disease and psoriasis in Korea. In a large cohort of patients with active AS, adalimumab effectively reduced enthesitis and peripheral arthritis.[11, 12] However, there was no data on the effectiveness of adalimumab in extra-axial symptoms like peripheral arthritis, enthesitis or dactylitis in Korean AS patients.

This study was first prospective study of the frequency of EAMs in Korean AS patients being treated with adalimumab in routine clinical practice.

Research Question and Objectives

What are the frequency of EAMs in Korean AS patients and the effectiveness of adalimumab on EAMs?

Primary Objective:

To investigate the frequency of EAMs in AS patients on adalimumab therapy in routine clinical practice

Secondary Objectives:

- To observe the effectiveness of adalimumab on AS spinal disease activity in routine clinical practice
- To investigate the effectiveness of adalimumab on EAMs in routine clinical practice

Study Design

This was a prospective, mono-country, multi-center study in AS patients treated with adalimumab.

Setting

Based on case report forms (CRFs), total 201 patients enrolled the study from 31 Dec 2014 to 08 Aug 2017, at 13 institutions in Korea.

Subjects and Study Size, Including Dropouts

Planned: about 200 subjects (including 20% dropouts)
Enrolled: 201 subjects
ITT: 201 subjects
PP: 160 subjects

Variables and Data Sources

Variables and data sources included consisting of medical records containing demographic, previous AS-related medication (medication, dosage), concomitant medication, Bath Ankylosing Spondylitis Disease Activity Index(BASDAI), a 50% improvement of the initial BASDAI(BASDAI 50), extra-axial symptoms (Enthesitis, Peripheral arthritis and Dactylitis), extra-axial symptoms assessment (Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), enthesitis of the plantar fascia, Tender Joint Counts (TJC) and Swollen Joint Counts (SJC), Counts of dactylitic digits), adalimumab administration, extra-axial symptoms excluding Enthesitis, Peripheral arthritis and Dactylitis information.

Results

This study was conducted at 13 sites in South Korea, from 31 Dec 2014 to 8 Aug 2017, to assess the frequency of EAMs and the treatment effectiveness of adalimumab in AS patients on adalimumab therapy in routine clinical practice. Of the 201 subjects who enrolled in this study, 41 subjects were discontinued. A total of 201 subjects were considered for evaluation in ITT set. Among them, 41 subjects were excluded from PP set for reason of ‘study discontinuation’.

For the frequency of EAMs of interest at baseline in the ITT set, ‘peripheral arthritis’, ‘enthesitis’, and ‘dactylitis’ was 42.79% (86/201 subjects), 33.33% (67/201 subjects), and 2.99% (6/201 subjects), respectively. Similar results were obtained for frequency of EAMs of interest in PP set.

In ITT set, the mean BASDAI score at baseline and each follow up visit was 6.80±1.40 at baseline, 2.59±1.66 at week 12, 2.42±1.57 at week 28, 2.05± 1.34 at week 36, and 1.98±1.27 at week 52. The percentage of patients with 50% improvement of baseline BASDAI (BASDAI 50) at week 12, 28, 36, and 52 were 75.13% (142/189 subjects), 82.58% (128/155 subjects), 87.65% (142/162 subjects), and 90.28% (130/144 subjects) respectively.

In ITT set, the mean MASES score at baseline and each follow up visit was 2.67±1.88at baseline, 0.85±1.86 at week 12, 0.49±0.90 at week 28, 0.48±1.44 at week 36, and 0.34±1.02 at week 52. The mean change of MASES from baseline to week 12, 28, 36, 52 in patients who had enthesitis at baseline was -1.85±2.50, -2.31±2.03, -2.31±1.78, and -2.50±1.90 respectively.

In ITT set, the percentage of patients who have enthesitis of the plantar fascia at baseline and each follow up visit was 9.45% (19/201 subjects) at baseline, 5.18% (10/193 subjects) at week 12, 1.16% (2/173 subjects) at week 28, 2.37% (4/169 subjects) at week 36, and 4.38% (7/160 subjects) at week 52.

In ITT set, the mean dactylitis score at baseline and each follow up visit was 4.00±3.52 at baseline, 0.17±0.41 at week 12, 0.00±0.00 at week 28, 0.00±0.00 at week 36, and 0.00±0.00 at week 52. The mean change of dactylitis score from baseline to week 12, 28, 36, and 52 in patients who had dactylitis at baseline were -3.83±3.66, -4.40±3.78, -5.00±4.08, and -5.00±4.08 respectively.

In ITT set, the mean TJC at baseline and each follow up visit was 3.49±2.74 at baseline, 1.68±2.95 at week 12, 1.39±2.95 at week 28, 1.13±2.50 at week 36, and 0.92±1.71 at week 52. The mean SJC at baseline and each follow up visit was 2.58±2.11 at baseline, 0.80±1.71 at week 12, 0.55±2.14 at week 28, 0.57±1.97 at week 36, and 0.20±0.76 at week 52. The mean change of TJC from baseline to each follow up visit in patients, who had peripheral arthritis (≥1 swollen joint) at baseline, was -1.82±3.43 at week 12, -2.05±3.03 at week 28, -2.38±3.13 at week 36, and -2.60±2.87 at week 52. The mean change of SJC from baseline to each follow up visit in patients, who had peripheral arthritis (≥1 swollen joint) at baseline, was -1.80±2.25 at week 12, -1.98±2.79 at week 28, -2.04±2.86 at week 36, and -2.40±2.30 at week 52.

In same analyses for PP set, the results were similar to results obtained for all items in ITT set.

During this study period, the incidence of AEs and ADRs was 8.96% (18/201 subjects, 22 cases) and 6.97% (14/201 subjects, 17 cases), respectively. Among all AEs reported

during this study, the incidence of SAEs was 3.98% (8/201 subjects, 11 cases). The incidence of AEs leading to discontinue adalimumab was 5.97% (12/201 subjects, 13 cases).

Within AEs collected during this study period, SAEs and AEs leading to adalimumab discontinuation were used as safety variables. Among all AEs reported during this study, the incidence of SAEs was 3.98% (8/201 subjects, 11 cases). The incidence of AEs leading to discontinue adalimumab was 5.97% (12/201 subjects, 13 cases).

Discussion

In this study, for the frequency of EAMs of interest at baseline in the ITT set, 'enthesitis', 'peripheral arthritis', and 'dactylitis' was 46.27% (93/201 subjects), 33.33% (67/201 subjects), and 2.99% (6/201 subjects). For the frequency of EAMs of interest at baseline in the PP set, 'enthesitis', 'peripheral arthritis' and 'dactylitis' was 45.63% (73/160 subjects), 31.25% (50/160 subjects) and 2.50% (4/160 subjects). When compared, the frequency of EAMs of this study to similar open-label, uncontrolled, multi-center study in Europe, enthesitis was lower (46.27% vs. 54.88%) and peripheral arthritis was higher (33.33% vs. 22.48%) in Korean patients.[11] In study of Szanto et al with 566 subjects in Europe, 403 subjects were AS patients. In frequency of EAMs in AS patients, the frequency of patients who had enthesitis was lower than this study with Korean AS patients (23.1% vs. 42.79%).[18]

For observing the effectiveness of adalimumab on AS spinal disease activity in routine clinical practice, the mean BASDAI score at baseline and BASDAI 50 was observed.

In ITT set, the mean BASDAI score at baseline and each follow up visit was 6.80±1.40 at baseline, 2.59±1.66 at week 12, 2.42±1.57 at week 28, 2.05± 1.34 at week 36, and 1.98±1.27 at week 52. In PP set, the mean BASDAI score at baseline and each follow up visit was 6.75±1.39 at baseline, 2.42±1.39 at week 12, 2.35±1.50 at week 28, 1.99±1.23 at week 36, and 1.98±1.27 at week 52.

In ITT set, the percentage of patients with BASDAI 50 at each follow up visit was 75.13% (142/189 subjects) at week 12, 82.58% (128/155 subjects) at week 28, 87.65%

(142/162 subjects) at week 36, and 90.28% (130/144 subjects) at week 52. In PP set, the percentage of patients with BASDAI 50 at each follow up visit was 76.92% (120/156 subjects) at week 12, 84.29% (118/140 subjects) at week 28, 88.24% (135/153 subjects) at week 36, and 90.28% (130/144 subjects) at week 52. The mean BASDAI score decreased significantly from week 12 and keep decreased over time. The percentage of patients with BASDAI 50 increased with time, and clinical response was observed in about 90% of patients at 52 weeks.

For investigating the effectiveness of adalimumab on EAMs in routine clinical practice, following data was collected: the change of MASES at each follow up visit in patients who had enthesitis at baseline, the change of dactylitis score at each follow up visit in patients who had dactylitis at baseline and the change of TJC and SJC at each follow up visit in patients who had peripheral arthritis (≥1 swollen joint) at baseline.

The mean change of MASES from baseline to each follow up visit in patients, who had enthesitis at baseline, was -1.85±2.50 at week 12, -2.31±2.03 at week 28, -2.31±1.78 at week 36, and -2.50±1.90 at week 52. In general, MASES showed a tendency to decrease in patients who had enthesitis at baseline.

The mean change of dactylitis score from baseline to each follow up visit in patients, who had dactylitis at baseline, was -3.83±3.66 at week 12, -4.40±3.78 at week 28, -5.00±4.08 at week 36, and -5.00±4.08 at week 52. In general, dactylitis showed a tendency to decrease in patients who had dactylitis at baseline.

The mean change of TJC from baseline to each follow up visit in patients, who had peripheral arthritis (≥1 swollen joint) at baseline, was -1.82±3.43 at week 12, -2.05±3.03 at week 28, -2.38±3.13 at week 36, and -2.60±2.87 at week 52. The mean change of SJC from baseline to each follow up visit in patients, who had peripheral arthritis (≥1 swollen joint) at baseline, was -1.80±2.25 at week 12, -1.98±2.79 at week 28, -2.04±2.86 at week 36, and -2.40±2.30 at week 52. In general, TJC and SJC showed a tendency to decrease in patients who had peripheral arthritis (≥1 swollen joint) at baseline.

In conclusion, based on the findings of the study, the effectiveness of adalimumab in Korean clinical practice turned out to be effective in two aspects. Firstly, to observe the effectiveness of adalimumab on AS spinal disease activity in routine clinical practice; the mean BASDAI score decreased significantly from week 12 and decreased over time. The percentage of patients with BASDAI 50 increased with time, and clinical response was observed in about 90% of patients at 52 weeks. Secondly, to observe the effectiveness of adalimumab on EAMs; the MASES, dactylitis score, TJC and SJC decreased from baseline to week 12 with greatest change, and maintained or gradually decreased until the end of last follow up visit. As a result, adalimumab proved to be effective in AS patients and patients who have EAMs. With safety assessment, any different tendency in safety from the approved label of adalimumab was not observed.

Marketing Authorization Holder(s)

AbbVie Korea

Names and Affiliations of Principal Investigators

Refer to section 3.0 Investigators