1.0 Abstract

Title

P13-562

Assessment of Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Plaque Psoriasis, Crohn's Disease and Ulcerative Colitis patients`adherence attitudes to maintenance therapy with a scheduled Adalimumab treatment in routine clinical practice.

Keywords

Adalimumab, Adherence, Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Psoriasis

Rationale and Background

In chronic diseases adherence to therapy is a critical factor for outcomes and may be influenced by patient's beliefs (Horne R et al., 2013). In consequence of an insufficient adherence clinical outcomes will deteriorate and may prompt a physician to further diagnostic procedures and eventually to an unnecessary change in medication (Koncz T et al., 2010).

The aim of this non-interventional post-marketing observational study (PMOS) was to assess rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), psoriasis (PS), Crohn`s disease (CD) and ulcerative colitis (UC) patients` adherence attitudes (beliefs), being managed in a specialist rheumatology, dermatology or gastroenterology practice or respective hospital department, to maintenance therapy with a scheduled originator adalimumab (Humira®), monotherapy or a combination therapy with methotrexate (for patients with RA) and to investigate whether there are correlations between such beliefs and adherence to maintenance treatment. Furthermore, because the degree of disease activity has

certainly a significant impact of treatment adherence, different scores for disease activity were assessed. It should be noted, that no CD and UC patients were assessed and are thus not included in this final report.

Research Question and Objectives

The aim of this non-interventional post-marketing observational study (PMOS) is to assess RA, PsA, AS and PS patients` adherence attitudes (beliefs) to maintenance therapy with a scheduled originator adalimumab (Humira®), monotherapy or a combination therapy with methotrexate (for RA) and to investigate whether there are correlations between such beliefs and adherence to maintenance treatment.

Main objectives

The main purpose of this study is to assess patients` adherence attitudes (beliefs) to maintenance of the therapy with a scheduled originator adalimumab (Humira®) monotherapy or a combination therapy with methotrexate (for RA) and to investigate whether there are correlations between such beliefs and adherence to maintenance treatment. In order to measure such beliefs the following questionnaire is used:

- Changes in the Beliefs about Medicines Questionnaire (BMQ) at 12 months compared to baseline. In addition, the correlations between beliefs and adherence to treatment will be done at baseline and at 12 months

Secondary objectives

- Changes in the Morisky Medication Adherence Scale (MMAS) at 12 months compared to month 3
- Changes of the Treatment Satisfaction Questionnaire for Medication (TSQM) over time

- Changes in Rheumatoid Arthritis Disease Activity Index (RADAI) in patients with RA and if reasonable in patients with PsA
- Changes in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in patients with AS
- Changes of the C-reactive protein (CRP) over time
- Changes of the Erythrocyte sedimentation rate (ESR) over time
- Changes in Psoriasis Area and Severity index (PASI) over time in patients with PS

Study Design

This is a non-interventional, observational study in a prospective, single-country, multicenter format.

Setting

The investigational sites were centers with experience in the treatment of RA, PsA, AS and PS patients. For the investigators it is not mandatory to have any clinical research (i.e. PMOS) experience but it may be beneficial. 13 centers participated in the study.

Subjects and Study Size, Including Dropouts

In 13 centers 96 patients were recruited. The median age of patients was 50 years, 36 (37,5%) patients were male and 60 (62,5%) were female.

22 (22,9%) patients discontinued the study before the end time point projected by protocol. Reasons for early study termination are shown in the following table.

		Gender					
		male		female		Total	
		N	%	N	%	N	%
Reason for Discontinuation	Serious Adverse Event	0	0%	1/60	1,7%	1/96	1,0%
	Lost to follow-up	1/36	2,8%	8/60	13,3%	9/96	9,4%
	Lack of Efficacy	2/36	5,6%	6/60	10%	8/96	8,3%
	Other	2/36	5,6%	2/60	3,3%	4/96	4,2%

Table 1.0_2: Reasons for discontinuation

The specifications for "Other" reasons were "Patient moved to Germany" and "aggravation of NYHA 3 (New York Hear Association Classification), p" for the male patients and "exanthema" and "non vult" (patients`wish) for the two female patients.

Inclusion Criteria

- Patients aged ≥ 18 years with RA, PsA, AS, PS
- Patients must fulfill international and national guidelines for the use of a BDMARD in RA, PsA, AS (Chest X-ray and IGRA interferon gamma release assay or PPD-skin test negative for tuberculosis).
- unsatisfactory DMARD response defined as failure to treatment with at least two DMARDs including Methotrexate in patients with RA or PsA
- unsatisfactory NSAID response in patients with AS or unsatisfactory response to prior BDMARDs in patients with RA or PsA or AS.

Exclusion Criteria

- Patients who are not covered in the latest version of the Humira syringe® SPC and Humira Pen® SPC
- Patients participating in another study program or clinical trial.
- Patients who have been treated with originator adalimumab (Humira®) before

Variables and Data Sources

Examinations, diagnostic measures, findings and observations routinely performed in patients included in this PMOS were entered by the investigator or staff according to the protocol in the data report forms provided by AbbVie. AbbVie Austria documented data in electronic data report forms (eCRF). Completed eCRF visit modules were sent electronically immediately after completion to the contracted statistician and contract research organization (CRO).

Patients were documented according to the following procedure: demographics (year of birth, gender, disease and disease duration, results of Chest X-ray and a highly specific interferon-γ-release assay [IGRA] or PPD-test for Tb-screening and RA, PsA and AS treatment in the past), ESR, CRP; Beliefs about Medicines Questionnaire (BMQ), concomitant treatment other medication or supplement, start of originator adalimumab (Humira®) application was documented in the appropriate eCRF.

Results

Demographics

In 13 centers 96 patients were recruited. The median age of patients was 50 years, 36 (37,5%) patients were male and 60 (62,5%) were female. Median follow-up duration was 12,1 months and median duration of originator adalimumab (Humira®) therapy was 11,7 months.

Median duration of disease was 4 years.

Four subgroups of patients were defined by their disease. 42 (43,8%) patients were of the Rheumatoid Arthritis (RA) group, 12 (12,5%) patients were of the Psoriatic Arthritis (PsA) group, 29 (30,2%) patients were of the Ankylosing Spondylitis (AS) group, and 13 (13,5%) patients were of the Psoriasis (PS) group.

Pre-treatment

72 (75%) patients were biological naive. In the non-naive group (n=24; 25%) the most frequent documented BDMARD was etanercept (n=10).

TB screening

Chest x-ray was performed for 67,7% of the patients with no abnormal findings.

Interferon gamma test was performed on 58,3% of the patients with three positive findings. PPD skin test was performed on 39 (40,6%) patients with two positive findings.

Primary Objectives - Beliefs about Medicines Questionnaire (BMQ)

BMQ scores were on average statistically significantly reduced from baseline (Visit 1) to 12 months (Visit 5) (WSR p = 0,015). The 95% CI for the mean change was [-2,574; -0,203].

BMQ scores were on average not statistically significantly reduced from baseline (Visit 1) to 12 months (Visit 5) (WSR p = 0,079) for female patients. The 95% CI for the mean change was [-2,865; 0,168].

BMQ scores did not change statistically significantly from baseline (Visit 1) to 12 months (Visit 5) (WSR p = 0,081) for male patients. The 95% CI for the mean change was [-3,465; 0,569].

Primary Objectives - Correlation between Beliefs about Medicines Questionnaire (BMQ) and Morisky Medication Adherence Scale (MMAS)

No substantial correlation was observed between BMQ and MMAS at any time point. No substantial correlation was observed between the changes of BMQ and MMAS until 12 months (Visit 5).

Secondary Objectives - Morisky Medication Adherence Scale (MMAS)

MMAS scores at month 12 were on average statistically significantly higher than at month 3 (WSR p = 0,047). The 95% CI for the mean change was [0,008; 0,407].

MMAS scores did not change statistically significantly from month 3 to month 12 (WSR p = 0,755) for female patients. The 95% CI for the mean change was [-0,162; 0,336].

MMAS scores were on average statistically significantly increased from month 3 to month 12(WSR p = 0,020) for male patients. The 95% CI for the mean change was [0,050; 0,724].

Secondary Objectives - Treatment Satisfaction Questionnaire for Medication (TSQM)

TSQM Efficacy (Eff)

TSQM Eff scores were on average statistically significantly increased at month 12 (Visit 5) compared to month 3 (Visit 2) (WSR p = 0,005). The 95% CI for the mean change was [1,423; 12,172].

TSQM Eff scores did not change statistically significantly from month 3 (Visit 2) to month 12 (Visit 5) (WSR p = 0,145) for female patients. The 95% CI for the mean change was [-4,071; 10,736].

TSQM Eff scores were on average statistically significantly increased from month 3 (Visit 2) to month 12 (Visit 5) (WSR p = 0,008) for male patients. The 95% CI for the mean change was [4,063; 19,590].

TSQM Side Effects (SE)

TSQM SE scores did not change statistically significantly from month 3 (Visit 2) to month 12 (Visit 5) (WSR p = 0,506). The 95% CI for the mean change was [-2,075; 5,971].

TSQM SE scores did not change statistically significantly from month 3 (Visit 2) to month 12 (Visit 5) (WSR p = 0,362) for female patients. The 95% CI for the mean change was [-2,879; 6,864].

TSQM SE scores did not change statistically significantly from month 3 (Visit 2) to month 12 (Visit 5) (WSR p = 0,937) for male patients. The 95% CI for the mean change was [-5,382; 9,147].

TSQM Convenience (Conv)

TSQM Conv scores were on average statistically significantly increased from month 3 (Visit 2) to month 12 (Visit 5) (WSR p = 0,025). The 95% CI for the mean change was [-0,281; 7,207].

TSQM Conv scores did not change statistically significantly from month 3 (Visit 2) to month 12 (Visit 5) (WSR p = 0,249) for female patients. The 95% CI for the mean change was [-3,210; 5,866].

TSQM Conv scores were on average statistically significantly increased from month 3 (Visit 2) to month 12 (Visit 5) (WSR p = 0,040) for male patients. The 95% CI for the mean change was [0,050; 13,210].

TSQM Global Satisfaction (Global)

TSQM Global scores did not change statistically significantly from month 3 (Visit 2) to month 12 (Visit 5) (WSR p = 0,097). The 95% CI for the mean change was [-1,840; 9,173].

TSQM Global scores did not change statistically significantly from month3 (Visit 2) to month 12 (Visit 5) (WSR p = 0,129) for female patients. The 95% CI for the mean change was [-4,126; 8,292].

TSQM Global scores did not change statistically significantly from month3 (Visit 2) to month 12 (Visit 5) (WSR p = 0,345) for male patients. The 95% CI for the mean change was [-4,503; 16,329].

Secondary Objectives - C-reactive protein (CRP)

CRP levels were on average statistically significantly lower at month 12 compared to baseline (Visit 1) (WSR p < 0,001). The 95% CI for the mean change was [-1,605; -0,523].

CRP levels were on average statistically significantly lower at month 12 compared to baseline (Visit 1) (WSR p = 0,002) for female patients. The 95% CI for the mean change was [-1,632; -0,175].

CRP levels were on average statistically significantly lower at month 12 compared to baseline (Visit 1) (WSR p < 0,001) for male patients. The 95% CI for the mean change was [-2,357; -0,491].

Secondary Objectives - Erythrocyte sedimentation rate (ESR)

ESR levels were on average statistically significantly lower at month 12 compared to baseline (Visit 1) (WSR p < 0,001). The 95% CI for the mean change was [-19,269; -9,989].

ESR levels were on average statistically significantly lower at month 12 compared to baseline (Visit 1) (WSR p < 0,001) for female patients. The 95% CI for the mean change was [-21,833; -8,983].

ESR levels were on average statistically significantly lower at month 12 compared to baseline (Visit 1) (WSR p < 0,001) for male patients. The 95% CI for the mean change was [-19,413; -6,910].

Secondary Objectives - Rheumatoid Arthritis Disease Activity Index (RADAI)

RADAI scores were on average statistically significantly lower at month 12 compared to baseline (Visit 1) (WSR p < 0,001). The 95% CI for the mean change was [-4,661; -2,993].

RADAI scores significantly improved from baseline (Visit 1) to 12 months (Visit 5) (WSR p < 0,001) for female patients. The 95% CI for the mean change was [-5,141; -3,108].

RADAI scores statistically significantly improved from baseline (Visit 1) to month 12 (Visit 5) (WSR p = 0,005) for male patients. The 95% CI for the mean change was [-4,851; -1,611].

Secondary Objectives - Bath Ankylosing Activity Index (BASDAI)

BASDAI scores were on average statistically significantly lower at month 12 compared to baseline (Visit 1) (WSR p < 0,001). The 95% CI for the mean change was [-4,17; -1,937].

BASDAI scores on average statistically improved from baseline (Visit 1) to month 12 (Visit 5) (WSR p = 0,016) for female patients. The 95% CI for the mean change was [-4,370; -0,753].

BASDAI scores on average statistically significantly improved from baseline (Visit 1) to month 12 (Visit 5) (WSR p = 0,006) for male patients. The 95% CI for the mean change was [-5,054; -2,322].

Discontinuation of study drug

Among 96 enrolled patients, 74 (77,1%) patients completed the study and 22 (22,9%) patients discontinued the study. Most frequently observed reasons for discontinuation were “Lost to follow-up” (9 patients) and “Lack of Efficacy” (8 patients).

For 74 (84,1%) patients therapy with originator adalimumab (Humira®) was ongoing after the end of the study.

Serious Adverse Events (SAE)

There was only 1 SAE documented for 1 (1/96 = 1%) patient [redacted]. The SAE was described as Cephalea (headache) and assessed as severe. Therapy with originator adalimumab (Humira®) was discontinued, the patient recovered, the duration was rated as nonrecurring, and investigator’s opinion of causal relationship was probable.

Discussion

Primary objective

A statistically significant average reduction of Beliefs about Medicines Questionnaire (BMQ) score until the end of the study could be seen. However no significant correlation between MMAS (as measurement for adherence) and BMQ at any time point of the study could be seen. Results in literature indicate that there is a correlation between BMQ specific concern sores and adherence (Michetti P et al., 2017, Horne et al. 2013, Zwicker HE et al., 2014, van den Bemt BJ et al, 2009). Data from meta-analyses suggest that necessity beliefs about medication are a prerequisite for taking medicines, and that necessity beliefs seem to outweigh concerns about the medication (Horne R et al., 2013, Michetti P et al. 2017). Our results would need to be further

investigated in a broader patient population and in correlation to specific BMQ concern and necessity scores.

Secondary objective - Self reported adherence

Adherence to therapy, measured by MMAS, increased significantly over time. Reports in literature about adherence-rates to medication for the treatment of conditions of immune-mediated inflammatory diseases (IMIDs) are widely ranging with few studies examining longitudinal patterns of adherence (Calip GS et al., 2017). Various parameters, like age, type of treatment, disease severity and duration or beliefs in medication might have an influence on adherence to medication. Older age, greater treatment necessity beliefs, and TNF inhibitor therapy seem to be associated with high self-reported medication adherence across all IMIDs (Michetti P et al., 2017). In this study 72,9 % of patients reported quite high adherence with an MMAS of 4 at visit 5, which is in line with previous data (Michetti P et al., 2017).

Secondary Objectives - Treatment Satisfaction Questionaire for Medication (TSQM)

Satisfaction with treatment in regards to effectivity satisfaction (TSQM eff), convenience satisfaction (TSQM conv) and side effects (TSQM side effect scale) increased over time. Treatment satisfaction did not increase over time for the female population. There was no change in global treatment satisfaction over time.

Secondary Objectives – Disease Parameters

A significant reduction in disease activity, measured by various methods over the different indications could be seen in the whole patient population. According to previous reports in RA clinical parameters are not necessarily associated with higher medication beliefs or adherence (Zwicker HE et al., 2014; van den Bemt BJ et al., 2009). In this study disease parameters as well as adherence improved over time, however the study was not designed to identify a correlation of these parameters.