1.0 Abstract

Title: Real Life Evaluation of Rheumatoid Arthritis in Canadians taking HUMIRA

Keywords

Rationale and Background:

This abbreviated clinical study report is based on a clinical surveillance evaluation protocol that was launched post adalimumab NOC in Canada in 2005, and as such the protocol utilized standards that have since changed. The original protocol of less than 30 pages stipulated the following in July 2005 amendment: Since the survey is observational in nature, adverse events will be monitored and reported by the investigator as per the regular practice. Therefore the study did not mandate the systematic collection of AEs until the safety section was updated in an amendment in August 2013. The limited safety data of 55 SAEs collected with the amendment did not differ from data we have seen in our large safety database of patients across indications, Burmester et al., 2012. Regardless of the limited safety data, this study represents real-life Canadian data for patients naïve to adalimumab therapy. Enrollment (Week 0) took place to include patients that had been receiving therapy for less than 4 months. Consequently there was no witnessed dose at Visit 1 and the data shown in this report are stratified based on pre- and post-starts to the baseline visit.

Although the efficacy profile of adalimumab has been established in controlled clinical trials, in Canada, data are still lacking with regards to the long-term effectiveness of adalimumab in the setting of usual care. Moreover, the association between long-term effectiveness of adalimumab and patients' functional status has not been shown in this population. Consequently, using the DAS28, the present observational survey provided information on the long-term clinical effectiveness of adalimumab in the setting of usual care. Using the HAQ, this survey also provided information on the effects of adalimumab on patients' functional status. In addition, the present survey generated data to evaluate the association between the long-term effectiveness of adalimumab and patients' functional status.

Because there is no information available with regards to the effects of adalimumab on patients' assessment of RA disease activity, patient's assessment of disease activity was measured using the RADAI. Thus, the present survey also provided data to evaluate the association between the effects of adalimumab on patients' assessments of disease activity and patients' functional status.

To further evaluate the long-term safety profile of adalimumab in the setting of usual care, serious adverse events were also collected and analyzed.

Research Question and Objectives

Primary Objective:

To describe the clinical effectiveness of adalimumab, as measured by the proportion of patients reaching a DAS28 of less than 2.6, in subjects with moderately to severely active RA that are receiving anti-rheumatic treatments including adalimumab.

Secondary Objectives:

1. To evaluate the sustainability of the clinical response, as measured by the duration of time that a DAS28 of less than 2.6 will be maintained, in subjects with moderately to severely active RA receiving anti-rheumatic treatments including adalimumab.

2. To describe the impact of adalimumab on patients' functional status, as measured by the change in HAQ, in subjects with moderately to severely active RA receiving anti-rheumatic treatments including adalimumab.

3. To evaluate the association between clinical effectiveness measured by changes in the DAS28 and patients' functional status measured by the HAQ, in subjects with moderately to severely active RA receiving anti-rheumatic treatments including adalimumab.

4. To describe the effects of adalimumab on patients' perception of RA disease activity, as measured by the change in the RADAI, in subjects with moderately to severely active RA receiving anti-rheumatic treatments including adalimumab.

5. To evaluate the association between patients' perception of disease activity as measured by the RADAI and functional status as measured by the HAQ, in subjects

with moderately to severely active RA receiving anti-rheumatic treatments including adalimumab.

Tertiary Objective:

To describe the long-term safety profile of adalimumab, as measured by investigator-reported serious adverse events, in subjects with moderately to severely active RA receiving anti-rheumatic treatments including adalimumab.

Study Design

This was a multi-center, open-label observational survey resulting from the regular utilization of adalimumab (HUMIRA®). All potentially eligible patients were asked to participate in the survey by the investigator who explained the survey and requirements for participation (Figure 1). Patients that fulfill the inclusion and exclusion criteria have signed the survey-specific informed consent.

Setting

Eligible patients were enrolled by investigators. The selection criteria were as follows:

Inclusion Criteria: The following inclusion criteria have been applied:

- Patient is eligible to take part in the registry as per the product monograph.
- Patients that are naïve to adalimumab therapy / or patients that have been receiving adalimumab therapy for less than 4 months.
- Patient is 18 years of age or older.
- Patient has moderately to severely active RA.
- Patient who has had an inadequate response to one or more DMARDs.
- Patient received provincial or private (insurance companies)

approval for adalimumab.

- Patient is able to give written informed consent and to understand the survey requirements.

Exclusion Criteria: The following exclusion criteria have been applied:

- Patient to whom a traditional DMARD had never been tried.
- Patient with a known hypersensitivity to adalimumab, or any of its components.
- Patient is receiving free adalimumab as part of a compassionate program or an early access drug distribution program.
- Patient with clinically significant concurrent medical or psychiatric disorders that may influence survey outcomes.
- Patient with any condition that would prevent participation in the survey and completion of the survey procedures including language limitation or possibility that the patient was not going to be available for a period of time (> 12 months) while being enrolled in the survey.

Subjects and Study Size, Including Dropouts

Given that this was an observational survey with primarily descriptive objectives, sample size estimates are based on the precision of the estimates that were obtained. In addition, sufficient patients have been recruited to ensure that sub-group analyses had enough power to produce estimates with acceptable precision.

A total of 1,013 patients were recruited for the current survey. Approximately 5 subgroups of patients were identified. With approximately 200 patients per sub-group, we were able to produce estimates of the proportion reaching the target DAS28 of less than 2.6 within ± 6 % in each end of the 95% confidence interval.

Variables and Data Sources

Data Analysis Plan:

Descriptive statistics have been produced for all variables. This included frequency distributions for all categorical variables. For continuous variables the mean, median, standard deviation and 95% confidence intervals of the mean were reported. Descriptive statistics were produced for the entire sample and for clinically relevant subgroups based on age, gender, co-morbidity, duration of adalimumab therapy, concomitant anti-rheumatic medication, and baseline disease activity and functional status. The primary objective of the study was to describe effectiveness of treatment with adalimumab as measured by the proportion of patients that achieve a DAS score < 2.6. The results from previous studies have shown that approximately 20% of patients achieve this therapeutic target. Ninety five percent confidence intervals around the point estimate of this rate in the sample was used to determine whether the rates observed in the study sample and in the study sub-samples are consistent with this expectation.

For the secondary objectives, the changes in the HAQ and the RADAI were evaluated for statistical significance with the Student's t-test for paired observations. The null hypothesis tested is that the mean change was less or equal to zero. This allowed us to determine whether patients treated with adalimumab were either stable or improved with respects to these outcome measures.

The association between objective measures of clinical effectiveness and patient based outcomes including functional status and disease activity has been evaluated with the Pearson's correlation coefficient and the Intra-Class Correlation Coefficient. Simple and Multi-Variable linear Regression analysis were used to test the adjusted associations between measures of clinical effectiveness and subjective outcome measures. Patient characteristics including age, gender, duration of disease, duration of adalimumab therapy, concomitant anti-rheumatic medications and co-morbidity were among the covariates that were included in the multi-variable models.

All of the above analyses were repeated for clinically relevant patient subgroups based on age, gender, concomitant medications, duration of adalimumab therapy, and baseline disease duration and activity. Moreover, the above analysis was repeated for sub- groups of patients defined according to the baseline (pre-treatment) ranges of DAS28 and HAQ scores.

Results

A total of 985 patients were included in the overall ITT population. At baseline, these patients demonstrated moderate to severe disease activity (DAS28=5.14, RADAI=5.4) and moderate disability (HAQ=1.39). By 24 months of adalimumab therapy, significant changes ($p<0.001$) in patients' functional status and disease activity were observed. Mean changes in the DAS28, HAQ, and RADAI were -1.34 +/-1.72, -0.37 +/-0.65, and -1.93 +/-2.39, respectively. A total of 55% of patients had achieved a EULAR response of good or moderate, 43% had achieved low disease activity (DAS28 $\leq$ 3.2), and 31% were in clinical remission (DAS28 <2.6). Moreover, 72.6% maintained clinical remission from their 12 month assessment. Concomitant mean DMARD use decreased from 1.26 DMARDs at baseline to 1.0 DMARDs after 24 months of adalimumab use. There were 442 withdrawals from the survey; primary reasons were lack of efficacy (33%), drug discontinued/other (20%), adverse event (17%), lost to follow-up/moved away (15%), and withdrawal of consent (13%). There a total of 76 AE's reported, of which 43 were Serious, including 9 deaths. Among the 9 deaths, 3 were considered possibly related, 1 probable, 2 not related and 3 did not report causality.

Discussion

Clinical improvements in disease activity and physical function were observed for the overall ITT population after 6, 12, 18 and 24 months of adalimumab therapy. Significant changes in the DAS28 illustrate how adalimumab provides long-term effectiveness in the setting of usual care. Patients responded positively to

adalimumab therapy, as evidenced by clinical changes in their functional status as scored by the HAQ and by their assessment of disease activity, as measured by the RADAI. More importantly, these clinical improvements were maintained over the 24 months of adalimumab use. Patients who started adalimumab therapy >1 month before their baseline assessment showed less improvement at 24 months. These patients may have already experienced clinical response by the time they were enrolled. Improvements from baseline were generally similar between patients who were naive to biologic therapy and those who had previous biologic use
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