1.0 Abstract

Title

Long-term Documentation of the Safety, Effectiveness, and Effects on Quality of Life and Work Productivity in Patients with Rheumatoid Arthritis during HUMIRA® (Adalimumab) Therapy in Routine Clinical Practice (AGIL) and Supplementary Documentation to Record Cardiovascular and Metabolic Risk Factors (AGIL-CV)

Keywords

Adalimumab, rheumatoid arthritis, work ability, effectiveness, safety, cardiovascular disease

Rationale and Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by progressive joint destruction, loss of physical function, and reduced quality of life and work productivity. Effective therapy with agents such as adalimumab, a tumor necrosis factor inhibitor, is associated with improvements in patient function and work productivity and, in some studies, reduced cardiovascular (CV) risk. The AGIL study was designed to evaluate the effectiveness and safety of adalimumab over 5 years in routine daily clinical practice in Germany, with a focus on the impact of therapy on employment-related outcomes. A substudy of AGIL, AGIL-CV, evaluated the effect of therapy on CV risk factors, including lipid profiles.

Research Question and Objectives

Primary employment-related objectives were to examine changes in:

- Number of missed working days due to sick leave
- Self-assessed work ability

Primary clinical objectives for this study were to examine changes in:

- Severity of clinical symptoms
- Levels of inflammatory markers
- Patient-reported function and health-related quality of life

The primary research questions for AGIL-CV were to evaluate:

- Changes from baseline in body measurements, vital signs, and lab chemistry blood parameters for glucose and lipid metabolism
- Differences in these parameters between treatment responders and non-responders
- Time point and frequency of CV events

Study Design

This study was a prospective, multicenter, observational study of adult patients with RA who initiated adalimumab therapy during routine clinical care. Patient data were recorded at Months 3, 6, 12, 24, 36, 48, and 60 months (recommended visit schedule). Patients continued in the study for a maximum of 60 months or until discontinuation from adalimumab therapy.

Setting

Patients were enrolled at 326 clinical centers in Germany and seen during regular visits for routine clinical care.

Subjects and Study Size, Including Dropouts

Four patient cohorts were evaluated (N values represent baseline numbers): employed patients (patients employed full- or part-time at baseline) (N = 3285), full analysis set (FAS; patients with sufficient data for effectiveness analyses) (N =4466), safety set (all enrolled patients who received at least one dose of adalimumab) (N = 7229), and the AGIL-CV substudy cohort (patients enrolled in AGIL-CV) (N = 260). At

Month 60, patient cohorts contained fewer than 20% of the baseline population. Study discontinuations were fairly evenly distributed between study withdrawals, most often due to lack of effectiveness, and patients lost to follow-up for unspecified reasons.

The study was stopped on 30 June 2017 after achieving the planned sample size for AGIL employment analyses (5000), and the number of patients needed for robust analyses of mean values at later time points (past the 24 month visit) was not attained.

Variables and Data Sources

Case report forms were the primary data source. Key variables included self-reported number of sick leave days and work ability, clinical symptoms, including the Disease Activity Score-28 joints (DAS28), tender and swollen joint counts, levels of inflammatory markers, and patient-reported function and health-related quality of life. The AGIL-CV substudy also included body measurements, vital signs, and lab chemistry parameters for glucose and lipid metabolism.

Results

During adalimumab therapy, mean sick leave days in the past 6 months decreased from 19.2 at baseline to 7.4 at Month 24 and remained near this level through Month 60 in patients who continued in the study. Because of asymmetric data distribution, the primary evaluation of sick leave days was a categorical analysis of patients with sick leave days within the normal range for the German population (0 to 5 days in the past 6 months) or higher than normal range (> 5 days in the past 6 months). At baseline, 55.3% of patients had sick leave days within the normal range; this figure significantly increased to 72.1% at Month 24 and was maintained at this level throughout the study. In patients with a higher than normal sick leave at baseline, 58.2% returned to normal values by Month 24 and 63.3% by Month 60. Improved work productivity was also observed during adalimumab therapy. Changes in employment-related outcomes were accompanied by significant improvements in clinical symptoms as assessed by objective assessments, including joint counts and

DAS28, and patient-reported evaluations, including function. Most improvements occurred by Month 6 and were maintained to Month 60 in patients remaining on therapy. No clear effect of adalimumab therapy on CV risk markers was observed, but AGIL-CV enrolled too few patients to allow valid conclusions. Over the 60-month period, 32.1% of patients reported an adverse event and 12.9% experienced a serious adverse event. Adverse events were consistent with the known adalimumab safety profile.

Discussion

Despite high discontinuation rates, the findings from AGIL indicate that long-term therapy with adalimumab results in significant improvements in employment-related outcomes and clinical outcomes for up to 60 months in adult patients with RA who remain on therapy. Continued improvements at later time points may have been influenced by responder bias. The findings of this observational study support the conclusion that adalimumab is effective and safe during long-term therapy of adult RA patients in Germany.

Marketing Authorisation Holder(s):

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