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ORIGINAL RESEARCH

Impact of adalimumab on clinical outcomes, healthcare resource utilization, and sick leave in patients with ankylosing spondylitis: an observational study from five Central and Eastern European countries

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Abstract

Background: Patients with ankylosing spondylitis (AS) are substantial users of healthcare resources due to chronic and potentially disabling disease. This study assessed the impact of adalimumab on clinical outcomes, healthcare resource utilization, and sick leave in patients with AS in five Central and Eastern Europe (CEE) countries.

Methods: This was an observational study in the routine clinical setting. Patients diagnosed with AS and starting treatment with originator adalimumab were followed for 12 months by assessing disease activity (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] and Ankylosing Spondylitis Disease Activity Score [ASDAS]) and physical function (Bath Ankylosing Spondylitis Functional Index [BASFI]). Data on healthcare resource utilization and sick leave were collected prospectively and compared with historical data before adalimumab initiation, as well as between treatment responders and non-responders defined by BASDAI-50.

Results: The total effectiveness population comprised 450 patients with on average long-standing AS, high disease activity, and functional impairment. At 12 months of adalimumab therapy, mean ASDAS and BASFI scores were in the range of low disease activity and normal physical function, respectively. The mean number of hospital admissions, hospital inpatient days, and healthcare provider visits were decreased by 67.9, 83.0, and 46.3%, respectively. The number and length of sick leaves were decreased by 65.6 and 81.4%, respectively. Reductions were higher in treatment responders than non-responders.

Conclusion: Originator adalimumab in routine clinical practice in five CEE countries produced clinically meaningful improvements in disease activity and physical function, and it was associated with reductions in healthcare resource utilization and sick leave.

Keywords: adalimumab, ankylosing spondylitis, disease activity, healthcare resource utilization, physical function, work outcomes.

Citation

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Introduction

Ankylosing spondylitis (AS) is the prototype of axial spondyloarthritis (SpA),[1,2] characterized by advanced structural changes in the sacroiliac joints, which, together with persistent inflammatory disease activity and progressive structural damage in the spine, can lead to severe functional disability.

Inflammation may also affect peripheral joints and entheses, and extra-articular manifestations (EAMs) such as uveitis, inflammatory bowel disease, and psoriasis are frequently present.[3,4] Similar to individuals with other inflammatory musculoskeletal disorders, AS patients have a reduced health-related quality of life (HRQoL) compared with the general population.[5]

Due to the chronic, disabling nature of the disease and average young age at onset, AS is associated with substantial direct medical and indirect societal costs.[6,7] AS patients are substantial users of disease-related healthcare resources, with higher disease activity and worse physical functioning being major determinants of these costs.[6,7] Moreover, patients with AS have significant sick leave and may experience reduced productivity while at work due to limitations imposed by impaired physical functioning.[7–9] Thus, interventions that maintain or improve patients' functional ability have the greatest potential to reduce the total costs of the disease.[9]

Originator adalimumab (HUMIRA®; AbbVie Inc., North Chicago, IL, USA) is a fully human anti-tumour necrosis factor (TNF) monoclonal antibody that effectively reduces the long-term signs and symptoms of AS,[10–14] and EAMs such as uveitis flares.[14] Treatment with adalimumab has also been shown to improve patients' HRQoL and work outcomes such as work productivity,[13,15–18] and it was cost effective based on a UK health economic assessment.[19] However, health economic data cannot be generalized across countries due to differences in healthcare systems and health insurance schemes. At present, there is limited available evidence on clinical effectiveness and health economic outcomes in patients with AS treated with adalimumab in the routine clinical setting in Central and Eastern Europe (CEE). This 1-year observational study was undertaken to evaluate the effectiveness and safety of adalimumab in routine clinical practice in CEE and to obtain region-specific data on the impact of adalimumab therapy on healthcare resource utilization, sick leave, and work status.

Methods

Study design and population

This observational study was performed in a multi-country, multi-centre, single-arm format in five CEE countries (Croatia, Czech Republic, Hungary, Romania, and Russia) between October 2012 and October 2014. The study was approved by the local ethics committees of the participating countries according to local laws and regulations. The study was conducted according to the Declaration of Helsinki for all human or animal experimental investigations. The study is registered at ClinicalTrials.gov (ClinicalTrials.gov identifier NCT01754727).[20]

Patients older than 18 years with active AS and fulfilling the modified New York Criteria[21] were eligible for the study. All patients were assigned treatment with originator adalimumab (hereafter referred to as adalimumab) and were prescribed adalimumab for ≤1 month before study enrolment and independent of study inclusion. A negative screening test result for tuberculosis (TB) or TB prophylaxis as per local guidelines was required. Patients had to be willing to authorize the use and disclosure of personal and health data and to provide written informed consent to participate in the study.

Patients were treated with adalimumab 40 mg subcutaneously every other week throughout the 12-month follow-up period. Patients with dose modifications were not excluded from the study per protocol. Assessments were performed at enrolment (baseline) and then prospectively at 3 (Visit 1), 6 (Visit 2), 9 (Visit 3), and 12 (Visit 4) months of treatment, though the actual number and timing of follow-up visits were at the investigator's discretion. In the event of premature discontinuation of adalimumab treatment before study end, the patient's next routine follow-up visit was the study termination visit.

Assessments

Patient sociodemographic characteristics and AS-specific medical history were recorded at baseline.

Disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS). BASDAI scores range on a numerical scale from 0 (no symptoms) to 10 (very severe symptoms).[22] Treatment response was defined as a 50% reduction from baseline in the BASDAI score,[22] and it is expressed as BASDAI-50 response. Remission (inactive disease) was defined as ASDAS score <1.3; low disease activity by scores between 1.3 and <2.1; high disease activity by scores between 2.1 and 3.5; and very high disease activity by scores >3.5. Clinically important improvement was defined as an ASDAS change of ≥1.1 units, and major improvement was defined as a change of ≥2.0 units.[23,24] Functionality was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI) score on a numerical scale from 0 to 10.[22]

Data on AS-related healthcare resource utilization and sick leave during treatment with adalimumab were recorded prospectively by a systematic interview with the patient at each study visit. The number of admissions to hospital, number of hospital inpatient days, number of visits to various healthcare providers (e.g. general practitioner, rheumatologist, other specialists, physiotherapist, and rheumatology nurse), number of episodes of sick leave, and number of sick leave days were recorded. These same data on AS-related healthcare resource utilization and sick leave in the 3-month period preceding the start of adalimumab therapy were also recorded at baseline. Retrospective data were collected by medical chart review and supplemented by patient interview. The 3-month data were multiplied by a factor of 4 for comparison with the prospective 12-month data collected during adalimumab therapy. This approach was used to limit memory bias.[25,26]

Changes in healthcare resource utilization and sick leave in the 12 months before and after the start of adalimumab treatment were compared between treatment responders and non-responders defined by achieving or not achieving a BASDAI-50 response.

At each visit, data on AS-specific systemic medication and information on work status were also recorded. Serious adverse events (SAEs) were reported based on the Medical Dictionary for Regulatory Activities (version 18.1, English) system organ class and preferred term.

Statistical analyses

Statistical analyses were conducted using SAS® version 9.2 (SAS Institute, Cary, NC, USA). The total effectiveness population consists of all patients who received at least one dose of adalimumab in the course of the study. In this observational study, no hypothesis testing was performed; results are summarized by descriptive statistics. Continuous parameters are described as mean ± standard deviation (SD). Categorical data are described using absolute and relative (%) frequency distributions. For assessments over time, the observed case analysis by visit (Visits 1 to 4) is used. For disease activity and functionality measures, the observed case analysis is complemented by an analysis according to the last observation carried forward (LOCF) principle at final visit (Visit 4). The last evaluable score was used for the analysis, and the respective value for the corresponding visit is expressed as Visit 4-LOCF. A descriptive subgroup analysis was performed to compare the results of healthcare resource utilization and sick leaves stratified by treatment response (as defined by BASDAI-50 response). The study was not powered for statistical comparison between subgroups.

Results

Patient disposition

A total of 452 patients were enrolled in the study: 148 (32.7%) in Hungary, 121 (26.8%) in Romania, 90 (19.9%) in Russia, 62 (13.7%) in the Czech Republic, and 31 (6.9%) in Croatia. As two enrolled patients did not receive adalimumab treatment, the total effectiveness population comprised 450 patients.

In total, 109 patients dropped out of the study before study end. For 87 of these patients, reasons for study discontinuation were investigator decision (n=49), lost to follow-up (n=15), patient request (n=11), adverse event (n=11), and SAE (n=1). The remaining 22 patients were lost to follow-up without a documented reason.

Mean study follow-up was 318.3±102.3 days.

Almost all patients with valid data (>98.4%) received adalimumab at the recommended dose of 40 mg subcutaneously every other week over the study course. During the 12-month observational period, eight patients had one dosage change and four patients had two dosage changes. The proportion of patients who received 40 mg every week was 0.7% (n=3, Visit 0), 0.7% (n=3, Visit 1), 0.5% (n=2, Visit 2), 1.1% (n=4, Visit 3), and 0.3% (n=1, Visit 4).

Baseline demographics and clinical characteristics

The baseline demographic and clinical characteristics of the 450 patients in the total effectiveness population are summarized in Table 1. Mean age ± SD was 42.9±12.1 years, and 68.7% of patients were men. Mean duration from diagnosis was 7.7±8.7 years. At study inclusion, 62.7% of patients (n=282) were employed full-time, 10% (n=45) were retired, and 18.2% (n=82) were unemployed due to disability, mainly relating to AS. AS-related EAMs (past or present) at the time of enrolment included uveitis (n=86; 19.1%), inflammatory bowel disease (n=42; 9.3%), and psoriasis (n=29; 6.4%); 38.9% of patients (n=175) had peripheral arthritis. Previous use of conventional synthetic disease-modifying antirheumatic drugs (csDMARD) or biological DMARD (bDMARD) medications was documented for 42.9% of patients (n=193). The most frequently used csDMARD was sulfasalazine (n=127; 28.2%), and 14.2% of patients had previously been exposed to bDMARDs (etanercept, infliximab, or golimumab). At study inclusion, 293 patients (65.1%) were receiving AS-specific medications, mainly non-steroidal anti-inflammatory agents (NSAIDs), including cyclo-oxygenase-2 (COX-2) inhibitors (n=214; 47.6%), and 82 patients (18.2%) were taking sulfasalazine. Baseline BASDAI (6.3±2.1), ASDAS (4.0±1.1), and BASFI (6.2±2.3) scores indicated high levels of disease activity and functional impairment.

Table 1. Baseline demographics and clinical characteristics of patients in the total effectiveness population (n=450).

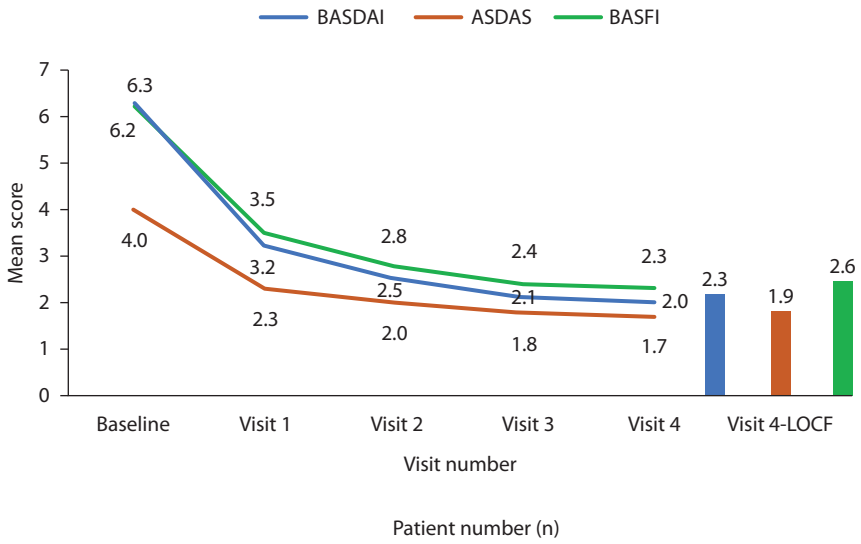
Characteristics	Value
Age (years), mean ± SD	42.9±12.1
Male:female ratio, n (%)	309 (68.7%):141 (31.3%)
Time from AS diagnosis (years), mean ± SD	7.7±8.7
Positive TB screening, n (%)	37 (8.2)
Working full-time (paid), n (%)	282 (62.7)
Peripheral arthritis, n (%)	175 (38.9)
Extra-articular manifestations, n (%)	
Uveitis	86 (19.1)
Inflammatory bowel disease	42 (9.3)
Psoriasis	29 (6.4)
BASDAI (0–10), mean ± SD	6.3±2.1
ASDAS, mean ± SD	4.0±1.1
BASFI (0–10), mean ± SD	6.2±2.3

AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; SD, standard deviation; TB, tuberculosis.

Improvements in disease activity, physical function, and work status during adalimumab treatment

Remarkable improvements in disease activity and physical function were observed by the first visit at 3 months, followed

Figure 1. Disease activity and physical functioning at baseline, month 3 (Visit 1), month 6 (Visit 2), month 9 (Visit 3), month 12 (Visit 4), and month 12 LOCF (Visit 4-LOCF).



Patient number (n)

	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 4-LOCF
BASDAI	443	426	396	368	352	430
ASDAS	443	425	394	365	350	429
BASFI	436	420	387	363	345	429

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; LOCF, last observation carried forward.

by more gradual but continued improvements through to study end. Mean ± SD BASDAI, ASDAS, and BASFI scores at the last study visit as observed were 2.0±1.6, 1.7±1.0, and 2.3±2.0, respectively (Figure 1). Compared with baseline, BASDAI-50 response was achieved by 78.9% of patients at study end, and ASDAS major improvement was shown by 64.8% of patients (observed data).

The proportion of patients actively working for payment during the study increased slightly from 62.7% at baseline (n=282) to 67.6% at month 12 (n=244).

Reduction in healthcare resource utilization and sick leave

Improvements were observed across all parameters used to compare healthcare resource utilization before and after the start of adalimumab treatment.

Reductions by study end (12-month visit) versus the 12-month period prior to adalimumab therapy were as follows (all observed data): mean number of hospital admissions from 2.8±3.9 (n=404) to 0.9±2.8 (n=392), a decrease of 67.9%; mean number of inpatient days from 23.0±40.8 (n=395) to 3.9±17.7 (n=388), a decrease of 83.0%; mean number of visits to healthcare providers from 25.7±22.8 (n=422) to 13.8±11.3 (n=411), a decrease of 46.3%, which was mainly due to fewer visits to rheumatologists (−4.4 visits) and general practitioners (−4.3 visits).

Data on sick leave were analysed for employed patients (i.e. those with a 'working for payment' status at baseline and at least once during follow-up). Reductions by study end (12-month visit) versus the 12-month period prior to adalimumab therapy were as follows (all observed data): mean number of sick leave episodes from 3.2±8.8 (n=246) to 1.1±5.6 (n=249), a decrease of 65.6%; mean number of sick leave days from 32.2±69.2 (n=243) to 5.1±24.5 (n=249), a decrease of 81.4%.

In a subgroup analysis stratified by the BASDAI-50 treatment response, reductions in the numbers of hospital admissions, inpatient days, sick leave episodes, and sick leave days were numerically larger in treatment responders compared with treatment non-responders; the only parameter showing no difference was the number of visits to various healthcare providers (Table 2).

Safety outcomes

A total of 29 SAEs, most frequently infections and infestations, were reported in 19 patients (4.2% of the effectiveness

Table 2. Changes in healthcare resource utilization and sick leave in the 12 months before and after the start of adalimumab treatment according to treatment response defined by BASDAI-50.

	Responders	Non-responders
Number of hospital admissions, mean ± SD	–2.4±4.5 (n=263)	–0.8±4.3 (n=104)
Number of inpatient days, mean ± SD	–21.7±38.2 (n=255)	–16.0±60.1 (n=101)
Number of visits to different healthcare providers, mean ± SD	–11.6±20.8 (n=284)	–12.4±26.7 (n=109)
Number of sick leave episodes, mean ± SD	–2.6±5.9 (n=173)	–0.7±3.4 (n=57)
Number of sick leave days, mean ± SD	–29.2±64.7 (n=172)	–18.4±66.7 (n=56)

BASDAI-50, ≥50% improvement from baseline in the Bath Ankylosing Spondylitis Disease Activity Index score; SD, standard deviation.

population); 27 of these events (93.1%) were classified as mild or moderate in severity. Seventeen SAEs (58.6% of the total SAEs) were considered to be related to adalimumab with reasonable possibility; the remaining events were assessed as unrelated. All events were within the scope of the known safety profile of adalimumab. No new safety signals were detected.

Discussion

As treatment with bDMARDs is considerably more expensive than that with conventional systemic agents, reductions in the utilization of healthcare resources as well as benefits in functional status and work productivity outcomes are of particular socioeconomic interest.

In this cohort of patients with AS from five participating CEE countries, marked improvements were observed in clinical disease activity and physical function under adalimumab therapy, as well as decreases in healthcare resource utilization and number of sick leave episodes and sick leave days, compared with the period prior to starting adalimumab therapy. These findings are consistent with other studies reporting reductions in hospital admissions and sick leave in AS patients during treatment with anti-TNF agents.[27–29] As shown previously with infliximab, cost savings generated by fewer hospital admissions and sick leave days can contribute substantially towards reducing the direct and indirect costs of AS,[27] offering a range of benefits for healthcare systems, employers, and patients. Moreover, economic assessments conducted in the UK showed that adalimumab[19] and other anti-TNF agents[30] were cost effective compared with conventional therapy for treating patients with AS and non-radiographic axial SpA.

Reductions in the various parameters of healthcare resource utilizations were considerable in our study, especially for number of sick leave days. Despite the relatively short observational period of 12 months, an increase in the proportion of patients who could work for payment was also noted. These findings are in line with the sizeable improvements observed in clinical outcomes: despite the lengthy average disease duration, at the end of the study, mean ASDAS was in the range of low disease activity (<2.1)[23] and mean BASFI was in the range of normal physical function (<3.0).[31,32] It has been shown previously that the capability of AS patients to work correlates directly with the physical consequences associated with their condition.[33,34] Further, even though improvements with adalimumab therapy were observed amongst both responders and non-responders as defined by the BASDAI-50 response, it was shown clearly in our study that reductions in healthcare resource utilization were much larger amongst clinical responders. The only parameter showing no difference between responders and non-responders was the number of outpatient visits. A possible explanation for this finding may be that the majority of patients, irrespective of the main clinical disease activity, may have had comorbidities requiring regular medical checks.

Specific measures to assess workability, such as the Work Productivity and Activity Impairment-Specific Health Problem Questionnaire (WPAI-SHP),[33] were not employed in our study. In a previous observational study of adalimumab in CEE countries, presenteeism (percentage of impairment while working) decreased from 56.7 to 20.1%, absenteeism (percentage of work time missed) decreased from 15.6 to 6.4%, and total work productivity impairment decreased from 59.9 to 22.1% during treatment for 1 year.[18]

In general, the data presented in this study agree with previous global[10–14] and regional[18] clinical trials investigating the effectiveness, cost-effectiveness,[19] and safety[35] of adalimumab in AS. No new safety findings were identified outside of the well-established safety profile of adalimumab.[35]

The study is limited by its observational design, which provides a lower level of evidence than randomized controlled trials; however, real-world data better reflect the standard of care received by patients with AS. As a reasonable proportion of patients (65%) were using AS-specific medications in addition to adalimumab and there were no restrictions in changing concomitant medication, the outcomes observed may not be solely attributable to adalimumab. The calculation method and retrospective-prospective manner in which patient charts and

patient interviews were used to determine healthcare resource utilization and sick leave may have introduced recall and seasonal bias. Lastly, retrospective data for healthcare resource utilization and sick leave may have been overestimated by extrapolating data reported for the 3 months immediately before the start of adalimumab treatment (when disease activity may have been higher) across a 12-month period.

Conclusion

Treatment with originator adalimumab in routine clinical practice in five participating CEE countries was associated with clinically meaningful improvements in disease activity and physical function as well as sizeable reductions in healthcare resource utilization and sick leave.

Contributions: The design and study conduct for the clinical trial were provided by AbbVie. DOB, MH, and ON contributed substantially to the conception and design of the work. DOB, SFE, SG, LS, MH, ON, and SS contributed substantially to the acquisition, analysis, and interpretation of data for the work. DOB, SFE, SG, LS, MH, ON, DM, and SS contributed substantially to drafting of the manuscript and revising it critically for important intellectual content. DOB, SFE, SG, LS, MH, ON, DM, and SS provided final approval of the version to be published.

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