Evaluation of clinical outcome, treatment compliance and tolerability of adalimumab in patients with active rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis in Hungary: results from EviraEast, a multi-country, multi-center post marketing observational study

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In Hungary, limited amount of published data exist on real-life setting clinical outcome, treatment compliance and tolerability of adalimumab therapy.

EviraEast, a multi-country post marketing observational study assessed clinical outcomes of adalimumab treatment in adult patients with active rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis during a 13-month follow-up.

In Hungary, 315 patients were enrolled; the mean duration of disease at baseline was 8.0 years, and the majority of RA and AS patients had high disease activity (DAS28>5.1). The mean duration of adalimumab treatment was 48.0 weeks with 23.2% dropout rate. High compliance rate (93.6%) was observed and the majority (93.6%) of patients accepted self-injection. Positive clinical outcome (decrease of DAS28≥1.2) at 3 months was achieved by more than 50% of patients. At the end of study, remission (DAS28<2.6) rate in RA was 34.3%, whilst BASDAI 50 response rates were observed 68.5% of AS and 76.9% of PsA patients. Improved physical function in and good tolerability with adalimumab therapy was documented. Overall adverse event rate was 18.2%.

The results confirmed well established effectiveness and safety profile of adalimumab in routine clinical practice in the approved rheumatic indications.

KEYWORDS: Adalimumab, Psoriatic arthritis, Rheumatoid arthritis, Ankylosing spondylitis, Effectiveness, Observational

AZ ADALIMUMABBAL KEZELT RHEUMATOID ARTHRITISES, ARTHRITIS PSORIATICÁS ÉS SPONDYLITIS ANKYLOPOETICÁS BETEGEK KLINIKAI EREDMÉNYEINEK, A BETEGEK EGYÜTTMŰKÖDÉSÉNEK ÉS A GYÓGYSZER TOLERÁLHATÓSÁGÁNAK VIZSGÁLATA MAGYARORSZÁGON: EviraEast, TÖBB ORSZÁGBAN VÉGZETT MULTICENTRIKUS POSZTMARKETING, MEGFIGYELÉSEN ALAPULÓ VIZSGÁLAT

Magyarországon kevés publikált adat áll rendelkezésre a valós életből az adalimumab-terápia klinikai eredményeivel, a betegegyüttműködéssel és tolerálhatósággal kapcsolatban.

Az EviraEast 13 hónapos utánkövetéses posztmarketing, több országra kiterjedő, multicentrikus, megfigyelésen alapuló vizsgálat, mely felnőtt, aktív rheumatoid arthritises (RA), arthritis psoriaticás (PsA) és spondylitis ankylopoeticás (SPA) betegek klinikai eredményeit vizsgálta adalimumab-terápiát követően.

Magyarországon 315 beteg vett részt a vizsgálatban, induláskor a betegség fennállásának átlagos időtartama 8,0 év volt, és a RA-es és a SPA-s betegek többségének magas aktivitású volt a betegsége (DAS28>5,1). Az adalimumab-kezelés átlagos időtartama 48 hét volt, 23,2%-os lemorzsolódással. A betegegyüttműködési arány magas volt (93,6%), és a betegek többsége (93,6%) elfogadta az öninjekciózást. A betegek több mint 50%-ánál 3 hónap után klinikai javulás (DAS28>1,2 csökkenése) volt megfigyelhető. A vizsgálat végén a remisszió (DAS28<2,6) aránya 34,3% volt RA-ben, míg a BASDAI 50 válaszaránya 68,5% volt SPA-ban és 76,9% PsA-ban. Az adalimumab-terápia jól tolerálható volt és fizikai funkciójavulást is dokumentáltak. A nem kívánt reakciók aránya összességében 18,2% volt.

Az eredmények igazolták, hogy az engedélyezett reumatológiai indikációkban az adalimumab a rutin klinikai gyakorlatban megalapozott hatékonysággal, és biztonságossági profillal rendelkezik.

KULCSSZAVAK: adalimumab, arthritis psoriatica, rheumatoid arthritis, spondylitis ankylopoetica, hatékonyság, megfigyelésen alapuló

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Introduction

Inflammatory rheumatic disorders such as rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) carry significant disease burden requiring effective medical interventions and treatment strategies.

RA is characterized as a progressive inflammatory synovitis with joint swelling affecting approximately 1% of the adult population. As the disease progresses structural joint damage develops and joint function deteriorates. In RA, joint damage and physical disability are the major adverse outcomes associated with reduction in quality of life and premature mortality. PsA is a heterogeneous condition with prevalence of 0.1%, characterized by its broad spectrum of phenotypes of joint involvement, skin and extra-articular manifestations involving multiple organs. PsA can develop at any time, but for most people, it appears between the ages of 30 and 50, affecting men and women equally [1]. Left untreated, PsA can be a progressively disabling disease. AS is a chronic inflammatory rheumatic disease with a prevalence of 0.2%. AS mostly affects the spine and sacro-iliac (SI) joints but it is also frequently accompanied with peripheral and extraarticular manifestations [2]. AS can cause pain and limited range of motion in the lower back, hips or neck. Fatigue and continuous pain are debilitating, and decrease the quality of life. The inflammation is frequently accompanied with ankylosis which might cause the joints and bones to fuse causing deformity and disability [3]. Biologic response modifiers like tumor necrosis factor (TNF) inhibitors have become established therapies for active RA, AS and PsA in recent years in Hungary.

In many areas of medicine, such as diabetes care or cardiology, clear therapeutic targets are available. More recently, in 2010, a treatment target has also been advocated for RA, namely remission or low disease activity. This recommendation is based on data from various clinical trials showing a good correlation with these clinical outcomes and long term functional improvement and damage progression control, as revealed by systematic literature reviews [4]. Much less information on the value of defining therapeutic targets for ankylosing spondylitis or psoriatic arthritis was available until 2013.

Recently, an international task force was set forth with the aim of improving management of RA in clinical practice, thus providing guidance for treatment to target ('T2T'). To achieve optimal therapeutic outcomes in RA, the treatment aim was defined as clinical remission, being disease activity an alternative goal in patients with long-standing disease. Regular follow-up (every 1-3 months during active disease) with appropriate therapeutic adjustment to reach the desired condition within 3 to a maximum of 6 months was recommended [4]. In Hungary, the most commonly used measure of remission is DAS28 score < 2.6. However, the establishment of remission should not be based on a single time point measurement, but rather for a longer time-period to avoid disease progression during intercurrent phases of increased disease activity. Furthermore, radiological progression is currently not assessed routinely, but is the key to monitor long-term disability [5]. Recent data indicated that the level of remission as well as the length of being in remission affects subsequent progression of radiographic damage in RA. Long-term remission induced by intensive, short-term treatment selected by biomarker profiles is the ultimate goal in the management of RA [6]. In 2010, the same year as the 'Treating rheumatoid arthritis to target' consensus paper was published, recommendations for the management of rheumatoid arthritis by EULAR also appeared in a separate paper [6]. The EULAR recommendations which have just been updated [24] complement with the 'T2T' outcomes in general principles, but are more specific in providing guidance for the use of individual drugs or drug classes.

T2T recommendations were also published for spondyloarthritis (SpA). In 2013, a task force was formed to discuss and develop a consensus on recommendations aimed at defining a treatment target for axial and peripheral SpA, thus improving the management these diseases in clinical practice [7]. Overarching principles and nine of the statements address SpA in general, and two more statements relate specifically to axial SpA, peripheral SpA and PsA. The main treatment target, which should be based on a shared decision with the patient, was defined as remission, or low disease activity as an alternative target for those patients who did not reach remission. Additional recommendations relate to extra-articular and extra-axial aspects and other important factors, such as comorbidity. T2T SpA recommendations can inform various stakeholders about expert opinion that aims for reaching optimal outcomes of SpA.

Treatment strategies of PsA have been changed significantly in the past few years, with emerging data demonstrating the benefits of conventional synthetic Disease Modifying Anti-Rheumatic Drugs (csDMARD) and tumor necrosis factor alpha (TNFα) inhibitors. EULAR recommendations have been recently developed to provide clinicians with concise, easy-to-follow guidance on optimal use of available therapies and with clear PsA treatment strategies [8]. Ten recommendations were developed for treatment from NSAIDs through csDMARDs to biological agents, accounting for articular and extra-articular manifestations of PsA. The best evidence for efficacy is available for three csDMARDs (methotrexate, leflunomide, and sulfasalazine) and four TNF inhibitors (adalimumab, etanercept, golimumab and infliximab). According to the 2010 EULAR recommendations,

TNF inhibitors should be considered in patients with active arthritis and an inadequate response to at least one csDMARD, such as methotrexate [8].

The key recommendations for axial SpA including AS are those recommended by ASAS/EULAR in 2010 [9]. NSAIDs are first-line therapy for patients with axial SpA, and should be given continuously in patients with persistent active, symptomatic disease. Some evidence exists that continuous NSAID treatment may decrease radiographic progression; however, this finding is still controversial and NSAIDs also have significant side effects. csDMARDs, including methotrexate and sulfasalazine, are not effective in axial SpA and are not recommended for use in treatment of axial manifestations. ASAS recently published updated recommendations for anti-TNF use in AS, based on ASAS classification criteria [10]. The updated consensus for use of anti-TNFs recommends treatment with at least two NSAIDs over a 4-week period before use of anti-TNF agents. In axial SpA, therapy with an anti-TNF agent is recommended when therapy with NSAIDs have failed. Anti-TNFs improve the signs and symptoms of axial SpA, reduce disease activity, reduce inflammation in SI joints and spine, and improve health related quality of life. Recent evidence suggests that TNF inhibitors appear to reduce radiographic progression in AS, especially with early initiation and longer duration of follow up [11].The appropriate use of medication and treatment adherence are central to the successful management of long term conditions such as RA, PsA and AS as these are characterized by fluctuating and usually progressive disease courses and a need for lifetime medical management. Although biological DMARDs (bDMARDs) revolutionized the treatment of inflammatory rheumatic diseases, compliance with and adherence to these treatment modalities is a major issue like in other chronic diseases, since poor compliance to biologics can undermine the effectiveness of these expensive medications.

Adalimumab is a fully human anti-TNF monoclonal antibody with established efficacy and safety profile and indicated for the treatment of the above-mentioned types of inflammatory arthritis [12]. In Hungary, limited amount of published data exist which characterize patient populations treated by adalimumab in SpA. Further, it is important to establish in real-life setting the clinical outcome and tolerability of adalimumab therapy in Hungarian patients, as well as their treatment compliance.

EviraEast was a non-interventional, post-marketing, multi-country, multi-center, prospective, single-arm, observational study conducted between 2009 and 2011 in 6 Central and Eastern European countries including Hungary, and Israel. Of the 809 patients enrolled in total, current analysis evaluates the results of patients from Hungary with main focus on achievement of treatment targets.

Methods

EviraEast (Evaluation of clinical outcome, treatment compliance and tolerability of HumIRA® (adalimumab) in patients with active Rheumatoid Arthritis, Psoriatic Arthritis and Ankylosing Spondylitis in EASTern European countries) aimed for assessing clinical outcomes, treatment compliance and tolerability of adalimumab in adult patients with active RA, PsA and AS during a maximum of 13-month follow-up. As a post-marketing observational study, EviraEast included patients that were eligible to adalimumab therapy according to the local product label and prescription/reimbursement guidelines. The investigational sites were medical centers experienced in biologic treatment. No additional procedures (other than standard of care) were applied to the patients. This study was conducted in accordance with requirements for monitoring, notification/submission of a post-marketing observational study of the Hungarian ethics committee and relevant regulations.

Patients

Adult patients with active RA, PsA (both with axial and peripheral symptoms) or AS were enrolled. The involved patients were either naive to adalimumab therapy (prior exposure to infliximab or etanercept treatment was allowed) or completed AbbVie sponsored interventional clinical trials and were continuing treatment with commercial adalimumab thereafter. The assignment of the patient to adalimumab was not decided in advance by this protocol as per the observational nature of the study, but fell within the current practice, and the prescription of adalimumab was clearly separated from the decision to include the patient in this study. Patients were excluded from the study if they were already treated (or were planned to be treated) with drugs of known interactions with adalimumab, if they were participating in another clinical trial and if they had a diagnosis of active infection. Written informed consent for participation was obtained prior to enrolment in the study according to the Hungarian regulation.

Study design and conduct

EviraEast was conducted in a prospective, single-arm format. As this study was observational in nature, patients' follow-up schedule was left to the judgment of their physicians within the 14–17 months period of the study (including latent tuberculosis (TB) screening and prophylaxis, if indicated). The TB screening period per patient was 1–4 weeks and, when required, the TB prophylactic treatment period before adalimumab administration was in accordance with Hungarian guidelines [13]. According to the study protocol each patient was to be observed during his/her adalimumab treatment for a period of maximum 13 months.

The study duration allowed approximately 7 patient visits in the following recommended order: screening visit, followed by TB prophylaxis, if indicated; baseline visit and introduction of adalimumab therapy; follow-up visit approx. 1 month after introduction of adalimumab therapy; subsequent follow-up visits approx. 3 months after the previous visit. The number and date of the visits were scheduled according to the decision of the physician so failure to meet the recommended dates did not constitute a breach of the protocol. If the physician decided to permanently discontinue adalimumab before the end of the planned observational period of 13 months, the reason for discontinuation and the new treatment regimen prescribed, if applicable, was documented. The next routine follow-up visit was the termination visit for this patient. If treatment with adalimumab was discontinued, the physician was requested to see the patient after a period of 70 days or 5 half-lives following the administration of the last dose adalimumab treatment.

During the screening visit, the following patient characteristics and medical history data were documented: demographics and social background (education, profession), rheumatic disease: severity and duration, relevant medical history, including TB history and screening procedures for the presence of active or latent TB and TB prophylaxis (if applicable). During Baseline visit, patients were introduced to adalimumab therapy and baseline values were recorded. Throughout the Follow-up visits, disease specific treatment history (csDMARDs and bDMARDs) and current disease specific medications (csDMARDs, non-selective NSAIDS, cox-2 inhibitors, steroids) were recorded. DAS28 [14] for RA patients, BASDAI [15] for PsA and AS patients, HAQ-DI [16] and laboratory values (ESR or CRP) for all patients were also documented at each Follow-up visit. The date of patient training for self-injection of adalimumab was also documented. The main objectives during the follow-up visits were to evaluate the clinical outcome and tolerability of adalimumab treatment by tracking the change in DAS28 score for RA patients, BASDAI score for PsA and AS patients, HAQ-DI score and laboratory values (ESR, CRP). Patient acceptance of self-injection was evaluated based on the investigator's opinion on the patient's ability to appropriately execute self-injection after initial training in the medical center and documentation of necessity of re-training. Compliance was evaluated based on injections missed or delayed by more than 7 days based on patients self-report. Changes in disease specific treatment were recorded at each visit.

Adverse events and serious adverse events were also recorded as per patient reports. Special attention was paid to opportunistic infections including TB, other serious infections, new malignancies, lupus/lupus-like syndrome, demyelinating disorders and congestive heart failure. Physicians rated the severity of any adverse event being collected as a data point in the study and for all serious adverse events as mild, moderate or severe. For serious adverse events, causality was also provided by the physician. Adverse events were coded according to MedDRA version 14.1, disease specific and prophylactic tuberculosis treatments were coded according to WHO-ATC English Version 2011.

Study endpoints

The primary endpoint for RA patients was the proportion of patients with positive clinical outcome defined as a DAS28 decrease by 1.2 or more after 3 months of adalimumab treatment compared to baseline. For PsA and AS patients, the proportion of patients with 50% or higher decrease in BASDAI index after 3 months of adalimumab treatment relative to baseline served as primary endpoint (e.g. positive outcome). Secondary end points were: mean HAQ-DI score decrease after 4, 7 and 13 months of adalimumab therapy compared to baseline; number and type of adverse events and serious adverse events; the duration of treatment with adalimumab; patient acceptability of self-injection (as detailed in section *Study design and conduct*).

Data processing and statistical analysis

The electronic data capture system webTrial (a.f.m. logic Völp, Göbel GbR) was utilized for data entry. All data have been entered into electronic case report forms (eCRFs). Case report forms were checked for consistency of data and inconsistent data were queried. Statistical analysis was performed by SAS® 9.2 for Windows.

The analysis of this observational study used only descriptive statistics, i.e. no statistical tests were performed. Qualitative data are presented by means of frequency distributions. For quantitative data the number of analyzed values (n), mean, standard deviation (SD), minimum, 25% quartile, median, 75% quartile and maximum are provided. Generally no imputation of missing values was performed. The time course of repeatedly measured parameters makes use of all available data assigned to the respective visit. In addition, a time point 'end of study' (EOS) was analyzed using the last observed value during the follow-up period (visits 3–7) and serves as 'last-observation-carried-forward' analysis. However, patient visits dated after the discontinuation of adalimumab therapy were not analyzed. As a general principle, baseline values were defined as the assessments performed at Visit 2, irrespective of the start date of adalimumab therapy. The complete analysis was performed for each primary diagnosis of the rheumatic disease separately.

Discontinuation of adalimumab treatment and reason for discontinuation was also documented (with more than 1 discontinuation reason could be specified per patient).

The incidence of adverse events (AE) and serious adverse events (SAEs) is presented, displaying the number and percentages of affected patients.

The use of anti-rheumatic medication history and concomitant anti-rheumatic treatment is also reported here.

One major analysis dataset named statistical evaluation dataset (SES) was considered for the statistical analysis, which consisted of all patients whose primary diagnosis of rheumatic disease was specified and who were treated with adalimumab as it was documented on the eCRF. For the analysis of clinical outcome, a clinical outcome analysis dataset (COS) was utilized which included all patients of the SES, who had a non-missing assessment of clinical outcome at baseline and at least one follow-up visit (Visit 3–7) with an assessment of clinical outcome. In addition, patients with unclear visit schedules were also excluded from the COS.

Results

In total, 809 patients were enrolled (440 patients/54.4% with RA, 129 patients/15.9% with PsA and 238 patients/29.4% with AS, 2 patients/0.2% without primary diagnosis) in 6 different Eastern European countries (Croatia, Hungary, Poland, Romania, Slovakia, and Ukraine) and Israel. The first documented study visit in Hungary was on April 2nd, 2009; the last documented visit of a patient took place on July 15th, 2011. In Hungary, 315 patients were enrolled by 72 investigators: 193 patients (61.3%) with RA, 39 patients (12.7%) with PsA and 82 patients (26.0%) with AS. Out of these, 314 patients (99.6%) were evaluable for statistical analysis (statistical evaluation set, SES). Furthermore, 252 patients of the SES (80.2%) were eligible for the primary analyses of clinical outcome (COS, which includes all patients of the SES, who have a non-missing assessment of clinical outcome at baseline and not less than one follow-up visit with a non-missing assessment of clinical outcome and in addition, patients with unclear visit schedules were also excluded from the COS). SES dataset was used for safety evaluations.

Investigational sites were 13 biological therapy centers in Budapest, Székesfehérvár, Debrecen, Kecskemét, Szeged, Gyula, Nyíregyháza, Szombathely, Veszprém, Miskolc, Pécs, Hévíz, Esztergom, the number of enrolled patients ranged from 2 to 92. The average duration of adalimumab therapy was 48 weeks.

Patient characteristics are shown in *Table I*. The mean age in SES was 53.5, 50.1 and 45.5 years for RA, PsA and AS patients, respectively. The gender distribution was consistent with known demographic characteristics of the respective diseases: 84.5% of females among RA patients, 61.0% of males among AS patients, and almost balanced (48.7% of males and 51.3% of females) among PsA patients. As shown in *Table I*, positive result of latent TB screening was documented very rarely in the study population.

In the following sections, efficacy data are analyzed and described by diagnostic groups.

Rheumatoid arthritis patients

The total number of RA patients enrolled in the study in Hungary was 193. Of those, 166 patients could be included into clinical outcome evaluation analyses. At the study end, the number of evaluable RA patients was 127 (65.8% of enrolled RA subjects), corresponding to a dropout rate of 34.2% throughout the study. Based on the observed data, the dropout started after the third visit. The mean age of RA patients was 53.5 (SD 12.0), the majority of them were female (*Table I*). The mean duration of RA at study start was 8.2 years. The percentages of patients with early disease (< 1 year from diagnosis) was low, only 4.1%. (It should be noted that diagnosis within 1 years of study start does not necessary mean an early disease.) Education level is depicted in *Table I*.

At baseline, 83.4% (n=161) of RA patients had high, 11.4% (n=22) moderate and 0.5% (n=1) low disease activity as indicated by the respective DAS28 values (≥5.1, between 5.1 and 3.2 and <3.2). None of the patients were in remission at the beginning of the study.

A patient could have more than one type of anti-rheumatic medication prior to and during adalimumab therapy. At baseline, 186 (96.4%) of the 193 RA patients were on any kind of anti-rheumatic drug treatment. Most of the patients were being treated with csDMARDs (n=179; 92.7%), 79 (40.9%) with steroids and 34 (17.6%) with bDMARDs. The most commonly used csDMARDs were methotrexate (n=153; 79.3%), sulfasalazine (n=86; 44.6%) and leflunomide (n=84, 43.5%). Almost half (46.1%) of RA patients received at least two csDMARDs prior to initiation of anti-TNF treatments, in line with local prescribing guidelines.

During the follow up period on adalimumab therapy, 93.3% (n=180) of enrolled RA patients had concomitant anti-rheumatic treatment, the most common were csDMARDs (n=173; 89.6%) and steroids (n=87; 45.1%). Twenty-nine (15%) RA patients had non-selective NSAIDs, 11 (5.7%) biological DMARDs, 10 (5.2%) cox-2 inhibitors, 4 (2.1%) pain killers and 5 (2.6%) other drug therapies. The most commonly used concomitant drugs were methotrexate (n=115; 59.6%), methylprednisolone (n=83; 43%), leflunomide (n=59, 30.6%) and sulfasalazine (n=53; 27.5%). One-hundred and ninety (98.4%) patients were treated with 40 mg of adalimumab every other week. There were only 2 patients (1%) who were administered 40 mg adalimumab every week.

The mean duration of observed adalimumab therapy was 48.4 weeks (SD=13.5) in RA. Forty-

		RA N=193	PsA N=39	AS N=82
Age (±SD)	Mean	53.5 (±12)	50.1(±11.6)	45.5(±13.1)
Female	%	84.5%	51.3%	39.0%
Educational background				
No professional education	n	46	11	17
	%	23.8%	28.2%	20.7%
Completed professional education	n	117	18	50
	%	60.6%	46.2%	61.0%
Education/ apprenticeship	n	30	10	13
	%	15.5%	25.6%	15.9%
Board-certified university degree or higher	n	30	19	50
	%	15.5%	48.7%	61.0%
Ongoing professional education (student)	n	163	20	32
	%	84.5%	51.3%	39.0%
Disease duration (years, ±SD)	Mean	8.2(±7.6)	10.2(±9.7)	6.4(±7.1)
Disease activity by DAS28 score				
Missing	n	9	NA	
	%	4.7		
Remission (<2.6)	n	0		
	%	0		
Low disease activity (2.6 to 3.2)	n	1		
	%	0.5		
Moderate disease activity (3.2 to 5.1)	n	22		
	%	11.4		
High disease activity (>5.1)	n	161		
	%	83.4		
Disease activity by BASDAI				
Missing	n	NA	24	3
	%		61.5	3.7
BASDAI <4	n		1	5
	%		2.6	6.1
BASDAI ≥4	n		14	74
	%		35.9	90.2
Functional status by HAQ-DI	Mean	1.5	0.9	0.9

NA=not applicable

Table I. Demographic and baseline disease characteristics

three (22.3%) out of 193 enrolled RA patients discontinued the therapy during the study: majority of them (27/14%) due to the investigator's decision, 12 patients (6.2%) because of lack of efficacy, 8 patients due to adverse events, 4 patients (2.1%) due to the patient's personal request, whilst 2 and 3 patients had unknown reasons or other reasons (1% and 1.6%, respectively). 43 RA patients who discontinued therapy spent an average of 31.8 weeks on adalimumab therapy (SD=18.1). 175 (91.1%) RA patients were able to use the self-injection and found it convenient. Twelve patients (6.3%) were not able to self-inject adalimumab because of their disease condition. There were 4 patients who could use

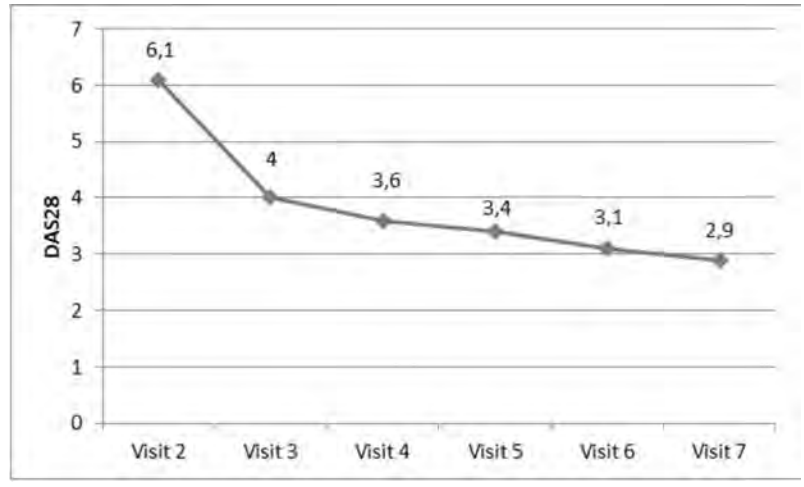
the self-injection but assessed it as inconvenient. Regarding the treatment compliance, 93.2% (n=179) of RA patients didn't miss any of the injection during the observation period.

With regards to primary efficacy endpoints ("positive clinical outcome"), a DAS28 score decrease by at least 1.2 after 3 months was observed in 68.7% (n= 114 out of 166) of RA patients whilst this positive outcome could not be reached only in 11.4% (19/166) of patients. 33 patients (19.9%) could not be evaluated due to lack of data. At visit 7, positive clinical outcome was achieved by 89% of the patients, whereas at the end of the study, 81.9% of them had positive clinical outcome. The mean DAS28 score decreased from 6.1 to 2.9 by the study end as illustrated in *Figure 1*.

At the end of the study 34.3% (n=57) of RA patients were in remission (DAS28<2.6), 21.1% (n=35) had low (DAS28 between 2.6 and 3.2), 28.9% (n=48) had moderate (DAS28 between 3.2 and 5.1) and 15.7% (n=26) had high (DAS28>5.1) disease activity. Overall, 47.6% of the 166 evaluable patients reached the state of remission during the observation. Twenty-seven patients (16.3%) reached remission at 3 months, 12% (n=20) between 3 and 6 months, 15.7% (n=26) between 6 and 12 months and 3.6% (n=6) after 12 months. Fifty-four (32.7%) patients did not reach the state of low disease activity. Forty-three (26.1%) patients reached it at 3 months, thirty-two (19.4%) patients between 3 and 6 months, 28 (17%) patients between 6 and 12 months and 8 (4.8%) patients after 12 months.

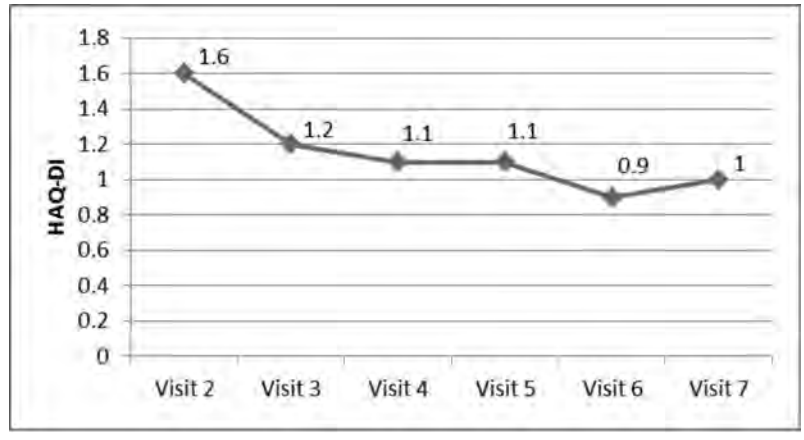
The physical function, assessed by HAQ-DI, improved during adalimumab therapy. The mean HAQ-ID score decreased from 1.6 (SD=0.6) to 1 (SD=0.7) by the end of the study (see *Figure 2*). The mean change in HAQ-DI was -0.6 (SD=0.6) in RA patients at the end of the study compared to the baseline (V2).

The mean value of the ESR was 35.7 mm/hour (range: 2.0 to 104.0) at visit 1 and 24.2 mm/hour (range: 0.0 to 120.0) at the end of the study, whereas the mean CRP value decreased from 20.8 mg/l (SD=26) at the baseline to 10.9 mg/l (SD=18.4) at the end of the study.



Number of evaluated patients: V2=166; V3=109; V4=128; V5=129; V6=125; V7=100

Figure 1. The mean value of DAS28 by visit – RA patients, as observed



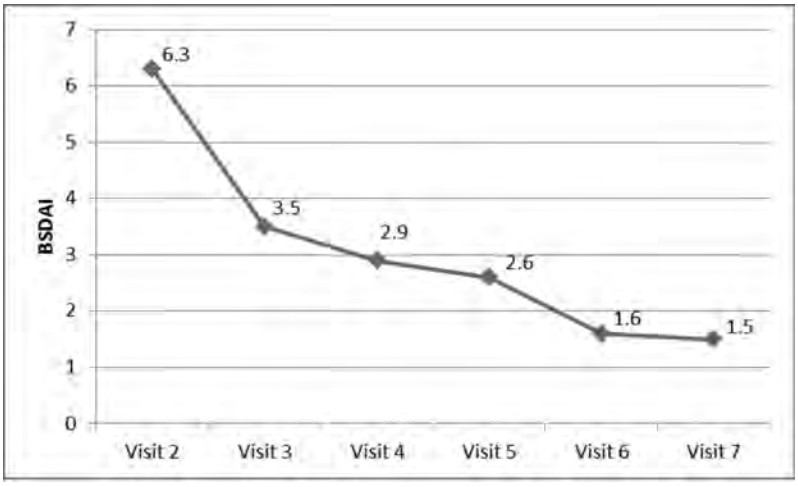
Number of evaluated patients: V2=123; V3=90; V4=88; V5=91; V6=81; V7=72

Figure 2. Mean HAQ-DI by visit- in RA patients, as observed

Psoriatic arthritis patients

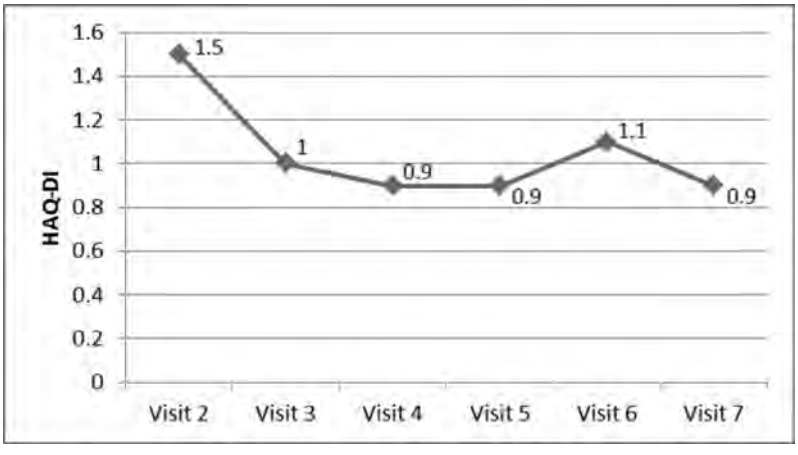
The total number of PsA patients enrolled in the study in Hungary was 40 and 39 were included in SES analysis. Of those, 13 patients could be included into clinical outcome evaluation analyses. At the study end, the number of evaluable PsA patients was 28 (71.8% of enrolled PsA subjects), corresponding to a dropout rate of 20.5% throughout the study. As mentioned before, patients with both axial and peripheral symptoms could be enrolled. The mean age was 50.1 years and approximately half of the patients were female (51%). Other socio-demographic parameters are detailed in *Table I*.

The mean disease duration at baseline was 10.2 (SD=9.7) years representing an established PsA population. Only 2.6% of patients had early disease. At baseline, 61.5% (n=24) of PSA patients had severe and 38.5% (n=15) moderate disease. Regarding the



Number of evaluated patients: V2=13; V3=13; V4=11; V5=11; V6=9; V7=9

Figure 3. Mean BASDAI value by visits – PsA patients, as observed



Number of evaluated patients: V2=18; V3=14; V4=15; V5=11; V6=11; V7=10

Figure 4. Mean HAQ-DI by visit- in PsA patients, as observed

activity of axial symptoms, the BASDAI index score was ≥4 in 35.9% (n=14) and was <4 in 2.6% (n=1) of the patients. There were 24 patients whose baseline BADSAI score was not available, most likely due to the absence of axial manifestations.

Prior to the enrollment in the study, 92.3% (n=36) of all PsA patients (n=39) received any type of anti-rheumatic drug treatment. The majority, 71.8% of patients (n=28) patients had prior csDMARD therapy, 28.2% (n=11) non-selective NSAID 23.1% (n=9) bDMARD and 10.3% (n=4) steroid treatment. Most PsA patients (38.5% of all enrolled PsA subjects) received only 1 csDMARD prior to adalimumab treatment. During the study, 71.8% (n=28) of PSA patients reported concomitant usage of other drugs, most of them (n=23, 59%) were on DMARD therapy, 23.1% (n=9) on non-selective NSAID, 10.3% (n=4) on steroid and 5.1% (n=2) on other drug treatment. Majority (92.8%) of PsA patients were administered 40 mg adalimumab every other week.

The mean duration of patients' adalimumab treatment was 48.2 weeks (SD=14) in PsA. 8 (20.5%) of the 39 patients (100%) discontinued adalimumab treatment prior to the study end: 4 (10.3%) patients due to the investigator's decision, 4 (10.3%) patients due to lack of efficacy, 3 (7.7%) patients due to adverse event, 1 (2.6%) patient due to own personal request and 1 (2.6%) patient due to other reasons. The mean duration of treatment of those who discontinued adalimumab therapy was 27.8 weeks (SD= 15.5 weeks). Most PsA patients (97.4%) were able of self-injection of adalimumab and found it convenient. Almost all patients had all prescribed injections during the study except only one patient (2.6%) who missed 3 or more injections.

Regarding the primary endpoint, 8 (61.5%) of the total 13 evaluable PsA patients had positive clinical outcome after 3 months of adalimumab therapy in the study (defined by a 50% or higher decrease in BASDAI score relative to baseline), whereas at the end of the study 10 (76.9%) patients had positive clinical outcome. The mean BASDAI value of PSA patients was 6.3 at visit 2 and it decreased to the value of 1.5 till Visit 7 (*Figure 3*) and 2.4 till the end of the study. Mean HAQ-ID score decreased from 1.5 (SD=0.5) at baseline to 0.9 (SD=0.5) at the end of the study and Visit 7 with mean absolute change of -0.7 (SD=0.8) (*Figure 4*).

The mean CRP value was 13.7 mg/l (SD=12.7) at the baseline and 7.4 mg/l (SD=11.8) at the end of the study.

Ankylosing spondylitis patients

There were 82 AS patients enrolled in this study with mean age of 45.5 (SD 13.1) years and predominant male representation. Of those, 73 patients could be included into clinical outcome evaluation analyses. At the study end, the number of evaluable AS patients was 51 (62.2% of enrolled AS subjects), corresponding to a dropout rate of 26.8% throughout the study. Additional socio-demographic data are presented in *Table I*. Most of the patients had established disease with mean disease duration of 6.4 (SD=7.19) years, and 23.2% of early disease (disease duration less than 1 year).

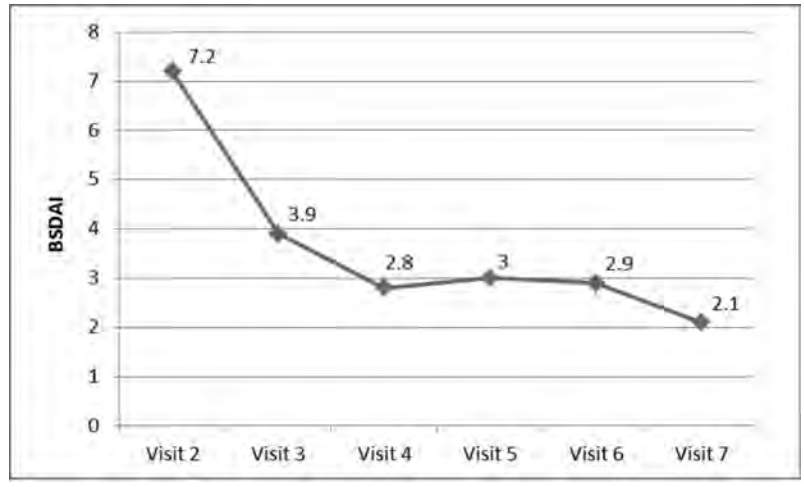
Regarding baseline disease activity, 90.2% (n=74) of the patients had high disease activity (BASDAI score ≥4) and only 6.1% (n=5) had a BASDAI <4, with missing data about 3.7% (n=3).

As expected, majority (63/82 or 76.8%) of AS patients received prior anti-rheumatic therapy: only approximately a half of patients (n=45; 54.9%) were treated with prior non-selective NSAID, and 28% (n=23) with DMARDs (23.3% received only 1 DMARD prior to adalimumab treatment). During the study, 67.1% (n=55) of the AS patient had concomitant medication. Thirty-eight patients (46.3%) were treated with non-selective NSAIDs, 24.4% (n=20) with DMARDs. Vast majority of AS patients (96.3% or 79 patients) were treated with 40 mg of adalimumab every other week and only 2 patients (2.4%) received adalimumab on a weekly basis.

The mean duration of adalimumab treatment was 46.9 weeks (SD=14.2). in the analysed AS population Twenty-two (26.8%) of the 82 AS patients discontinued adalimumab treatment during the study: again, majority of them (14 patients/7.1%) due to the investigator's decision 7 patients (8.5%) due to lack of efficacy, 4 subjects (4.9%) due to adverse events and 4 patients (4.9%) due to personal request. The mean duration of the treatment of AS patient who discontinued adalimumab therapy was 27.8 weeks (SD= 11.8 weeks). All AS patients were able to self-inject adalimumab, only two of them (2.5%) assessed the process as inconvenient. Similar to RA and PsA patients, the compliance was as high as 92.6% with 95 subjects taking all injection during the observational period.

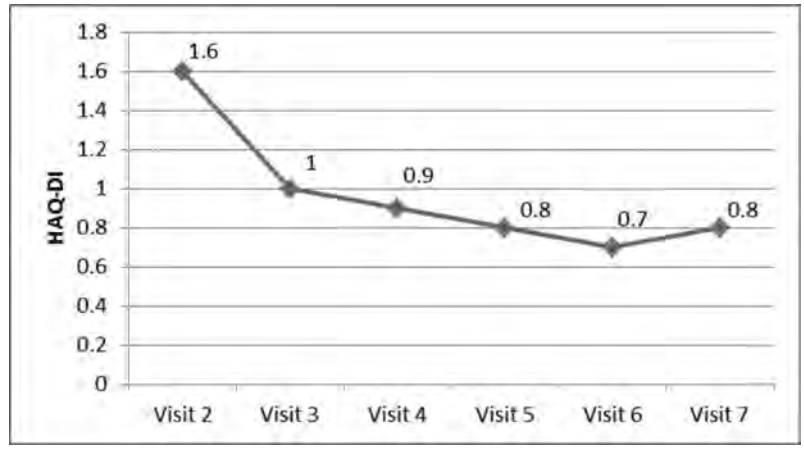
With regards to the primary endpoint, 61.6% (n=45) of patients reached primary endpoint after 3 months. At the end of the study, 50 (68.5%) patients had BASDAI 50 response out of 73 evaluable subjects. The mean BASDAI score decreased from baseline 7.2 (SD=1.9) to 2.1 SD=2.1) by Visit 7, corresponding to 67.1% mean decrease change (SD=29.5) (*Figure 5*). The mean HAQ-ID score was 1.6 (SD=0.6) at baseline and 0.8 (SD=0.6) at Visit 7 (*Figure 6*).

Regarding inflammatory laboratory parameters, mean CRP value decreased from 15.7 mg/l (SD=18) at baseline to 6.2 mg/l (SD=10.6) by the end of the study.



Number of evaluated patients: V2=73; V3=60; V4=64; V5=63; V6=54; V7=45

Figure 5. Mean BASDAI value by visits – AS patients, as observed



Number of evaluated patients: V2=14; V3=8; V4=9; V5=9; V6=6; V7=5

Figure 6. Mean HAQ-DI by visit- in AS patients, as observed

Safety

Positive TB screening was documented in 6 patients out of all patients who have started adalimumab therapy at maximum 31 days before, at or after the baseline visit (n=294), all of them received prophylaxis according to the local guidelines. It should be noted that due to local immunization practices, around half of the patients (45.9% of above population) were immunized against TB.

In general, adalimumab was well tolerated in the routine clinical practice. In total, 101 adverse events (AEs) occurred in total of 57 patients corresponding to 18.2% adverse event rate. The majority of the events (87.3%) were deemed mild or moderate by the physicians. The rates of adverse events, serious adverse events, adverse events leading to discontinuation and adverse events of interest are presented in *Table II*. No malignancies, lupus-like

Adverse event category	RA N=193	PsA N=39	AS N=82	Total N=314
Adverse event	30 (15.5)	10 (25.6)	17 (20.7)	57 (18.2)
Serious adverse event	5 (2.6)	2 (5.1)	1 (1.2)	8 (2.5)
Adverse event leading to discontinuation	15 (7.8)	4 (10.3)	7 (8.5)	26 (8.3)
Infection	9 (4.7)	5 (12.8)	5 (6.1)	19 (6.1)
Serious infection	1 (0.5)	1 (2.6)	0 (0.0)	2 (0.8)
Demyelinating disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lupus-like syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malignancies (excluding lymphoma and NMSC)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NMSC	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	1 (1.2)*	1 (0.3)
Injection site reaction / dermatitis	3 (1.5)	0 (0.0)	0 (0.0)	3 (0.9)

Note: n (%) = number (percentage) of patients with at least one event. A patient could experience more than 1 different term of adverse event
* Sudden cardiac death

Table II. Overview of adverse events

syndrome and demyelinating disorder occurred during the observation period. For a female RA patient, TB immunization was documented at screening visit. TB screening at baseline was negative. However, a positive TB screening was reported at Visit 6, eleven months after start of adalimumab therapy) with positive signs of currently active TB in chest X-ray. Adalimumab therapy was terminated at Visit 6. There was one death, in the AS group: a 63-year-old man experienced sudden cardiac death due to acute myocardial infarct; this patient had a history of ischemic heart disease, cardiac infarct, and right bundle branch block. The event was evaluated by the treating physician as non-related to adalimumab therapy.

The overall adverse event (AE) rate in the RA group was 15.5% (out of 193 patients), majority of them (66.7%) were deemed as not related to adalimumab treatment. The most frequent adalimumab related AEs were in the Skin and subcutaneous tissue disorders (Alopecia, Drug eruption, Dry skin, Pruritus, Skin disorder, Skin reaction and Urticaria) (4.7%), Infections and infestations (Asymptomatic bacteriuria, Bronchitis, Herpes virus infection, Staphylococcal sepsis, Upper respiratory tract infection and Viral upper respiratory tract infection) (4.7%) and General disorders and administration site condition (Injection site reaction, Injection site dermatitis and Edema peripheral) (2.1%) system organ classes as coded in MedDRA. In the RA group, 5 subjects (2.6%) experienced any serious events (a total of 9 events): two patients had vascular disorder (Hypertension and Thrombophlebitis); one patient experienced cardiac disorder (Atrial fibrillation), one had gastrointestinal disorder (Gastritis erosive), one had nervous system disorder (Cerebral ischemia and Paraesthesia), another patient suffered a staphylococcal sepsis, and one experienced peripheral edema. The overall adverse event (AE) rate leading to discontinuation in the RA group was 7.8%.

The adverse event rate in the PsA group was higher (25.6%) than in RA (10 out of 39 subjects), and majority of the adverse events were deemed possibly related to adalimumab treatment (66.7%). The most common AEs reported were infections (Bronchitis, Pneumonia primary atypical, Sinusitis and Urinary tract infection) (12.8%), gastrointestinal disorders (Abdominal pain, Vomiting, and Dyspepsia) (5.1%) and hepatobiliary disorders (Cholecystitis, Cholelithiasis, Hepatic steatosis and Hepatotoxicity) (7.7%). During the study, 2 PsA patients suffered from serious adverse events: one hepatobiliary disorder (Cholecystitis and Cholelithiasis) and one infection (Urinary tract infection) were reported. The adverse event rate leading to discontinuation in the PsA group was 10.3% (4/39), mostly due to infections (5.1%), gastrointestinal disorders and hepatobiliary disorders (2.6% each).

Approximately one-fifth (20.7%) of the AS patients (n=82) experienced any adverse events. However, most of the events were deemed as “not related” to adalimumab (64.3%). Skin and subcutaneous tissue disorders occurred in 4 patients (Erythema, Rash and Pruritus) (4.9%), gastrointestinal disorders occurred in 4 patients (Diarhhoea, Gastritis erosive, Heamorrhoids and Vomiting) (4.9%), infections and infestations (Influenza, Erythema induratum,

Pneumonia, Sinusitis and Rhinitis) in 6.1%, nervous system disorders occurred both in 2 patients (2.4%, Headache and Cerebral ischeamia). As mentioned earlier, one patient had serious adverse event in the AS group: a fatal acute myocardial infarction resulting in sudden cardiac death. Like in the RA and PsA group, discontinuation rates due to AEs were less than 10%: 8.5% of the AS patients had any adverse events leading to discontinuation (skin and subcutaneous tissue disorder and infections, in 2 patients (2.4%) each).

Discussion

EviraEast was the first and largest real-life data on adalimumab assessing clinical outcomes, treatment compliance and tolerability of adalimumab in adult patients with active rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) in Hungary in routine clinical practice. As a non-interventional study, EviraEast included patients that were eligible to adalimumab therapy according to the local product label and prescription/reimbursement guidelines in Hungary. Involved patients were middle aged in general, and the gender distribution was consistent with the known demographic characteristics of the respective diseases, and their characteristics seem to be similar to other EU populations. Notably, the mean duration of rheumatic disease at the beginning of the study was 8.0 years for the total enrolled population. Interestingly, both the shortest disease duration and the highest representation of early disease was observed in the AS cohort. Adalimumab initiation reflect local practices and access to the medication in Hungary, which is to patients with established disease and failure to one or multiple conventional treatments: due to local prescription and reimbursement regulations, patients with high disease activity and nonresponsive to several traditional treatment courses were enrolled into the study, therefore this population represents a high activity difficult-to-treat group.

As expected, most RA and PsA patients received multiple csDMARDs previously; the selection of prior csDMARDs reflected the local treatment practices that are in line with latest local and international treatment recommendations: methotrexate was most common in RA, followed by sulfasalazine, leflunomide and chloroquine. Almost half of RA patients received ≥2 prior csDMARDs, while less PsA and AS patients received only 1 csDMARD prior to adalimumab, only partly reflecting the local treatment and reimbursement guidelines. There were also biologically experienced patients included in the study. By the end of study, mean DAS28 score reduced significantly and more than half of the RA patients achieved at least low disease activity (LDA), and these good results may be in part due to the higher use of concomitant csDMARDs. According to T2T recommendations, LDA is an acceptable treatment goal for longstanding RA represented by the majority of the enrolled patient. Our data are in line with a recent systematic review and meta-analysis of remission rates in randomized clinical trials and observational studies showing these treatment goals cannot be easily achieved [2]. In 20 randomized controlled trials, involving 4290 patients on either csDMARD monotherapy or combination csDMARD therapy, DAS remission occurred in 26% of patients on monotherapy and 42% of patients on combination therapy. In 17 observational studies, including 4762 patients either on DMARD monotherapy or DMARD combinations, remission was achieved in 27% of the patients, 33% by DAS criteria and 17% by ACR criteria [2]. Moreover, in DREAM registry that involved mainly long lasting RA patients treated with TNF-inhibitors, DAS28 remission was achieved by 27% of the patients after 6 months of treatment [17]. In a previous observational study with adalimumab called ReAct [18] – which was the largest observational study of a TNF-antagonist and was designed as an open-label trial to mimic routine care of patients with RA – it was found that good EULAR response (DAS28 decrease by 1.2) was achieved in 33% and 56% after 3 months and 1 year, respectively. EULAR response rates were even higher in EviraEast at 3 months, most likely because of the high baseline disease activity. ReAct also showed that adalimumab was also effective when used as the second and third TNF antagonist. Similarly, in EviraEast, biologic experienced patients were also represented in 15.6%; however, no separate analysis was done for this biological therapy experienced subpopulation due to small sample size.

With regards to SpAs, by the study end, the mean BASDAI decreased substantially. It should be noted again that BASDAI evaluates axial symptoms and the percentage of PsA patients achieving a primary endpoint might have been higher if a peripheral measure of disease activity had been used These AS results are in line with previous results of a multinational 12 week open label observational study (RHAPSODY) conducted with adalimumab reported by Rudwaleit et al. [19]. More than half of patients with active AS, receiving adalimumab 40 mg every other week achieved a BASDAI 50 or ASAS40 response. Similar response rates were seen during the first 6 months in DANBIO and BSRBR registry [20, 21], where 63% and 52% of AS patients treated with TNF-inhibitors experienced clinical response (defined as BASDAI 50% response) during the first 6 months of therapy. These data are in line with our observations in this study.

In case of PsA, no observational study with adalimumab has assessed the severity of axial symptoms so far. Therefore data in this very small patient population are valuable, though one must bear in mind that lack of assessment of peripheral symptoms in PsA population is a major limitation of the study. In

the recent ACCLAIM study, the effectiveness and safety of adalimumab was evaluated in patients with active psoriatic arthritis (PsA) who had inadequately responded to prior therapy [22]. Results of this study showed that adalimumab-treated patients achieved significant improvements in both skin and joint manifestations of PsA, as well as in physical function and work status.

Altogether, the clinical outcome results are deemed satisfying and consistent with other real-life data.

In EviraEast, physical function was assessed by using HAQ-DI in all diagnostic groups and the mean HAQ-DI improved substantially. However, employing BASFI index in diseases with axial manifestations, i.e. in AS and PsA, would have provided more precise insight on improvement of physical function.

Good compliance with the adalimumab administration schedule meaning no missed injection was observed in 93.6% of patients. Regarding drug survival, the proportion of discontinued adalimumab therapies ranged from 20.5% in PsA patients, through 22.3% in RA patients to 26.8% in AS patients. Adalimumab was most frequently discontinued due to investigator's decision (14.3%) or lack of efficacy (7.3%), and in 4.8% of patients due to adverse events. A premature termination of adalimumab therapy occurred on average after 30.2 weeks of treatment. These data show somewhat better compliance and persistence rates compared to recently published data [23]: according to the systematic literature review, compliance rates with biological DMARDs in RA are between 63 and 90%, and persistence rates decrease steeply over time. According to the data, greater compliance was seen with infliximab infusion than with etanercept and adalimumab self-administration, because patients may miss courses of self-injection whereas intravenous administration makes compliance easier to control. Interestingly, our data show that treatment modalities with self-injection not necessarily lead to lower compliance compared to infusion treatments.

In general, adalimumab was well tolerated in this study. 14 serious adverse events were reported in 8 patients (2.5%); 9 (64.3%) of these events were considered as not related to adalimumab. Sudden cardiac death occurred in 1 patient with AS. No cases of malignancies, lupus-like syndrome, demyelinating disorder or tuberculosis were reported, therefore it can be concluded that safety in local real-life setting is similar to randomized controlled trails, open –label extensions and registries with regards to adverse event profile and event rates.

In summary, EviraEast PMOS evaluated clinical outcomes, safety, treatment compliance and tolerability of adalimumab therapy in adult patients with active, long-standing RA, PsA and AS in routine clinical practice in Hungary. No special demographic, disease and disease specific treatment characteristics were observed in the EviraEast patient population, as compared with patients generally eligible to biologic therapy. The results of the study confirmed the well-established effectiveness and safety profile of adalimumab in RA, PsA and AS patients treated in routine clinical practice. In addition, good tolerability and excellent compliance with adalimumab therapy were documented.

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Dr. Drescher served as a consultant for AbbVie.
Dr. Juhász has nothing to declare.
Dr. Keszthelyi has nothing to declare.
Dr. Kovács has served as a consultant for AbbVie, MSD, Pfizer, UCB, Novartis, and has received research funding from Abbott Laboratories and UCB, and speaker fees from Roche, Sager Pharma, UCB and MSD.
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Dr. Varga has nothing to declare.
Dr. Nagy, Dr. Ruzicska and Dr. Schnaider are employees of AbbVie, and may own AbbVie Stock.

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