Clinical experience with the European Ankylosing Spondylitis Infliximab Cohort (EASIC): long-term extension over 7 years with focus on clinical efficacy and safety

F. Heldmann[1], X. Baraliakos[1], U. Kiltz[1], J. Brandt[2], I.E. van der Horst-Bruinsma[3], R. Landewé[4], J. Sieper[5], G.R. Burmester[6], F. van den Bosch[7], K. de Vlam[8], H. Gaston[9], M. Gruenke[10], M. Witt[10], T. Appelboom[11], P. Emery[12], M. Dougados[13], M. Leirisalo-Repo[14], M. Breban[15], J. Braun[1]

[1]Rheumazentrum Ruhrgebiet, Herne, Germany; [2]Rheumapraxis-Steglitz/Charité, Berlin, Germany; [3]VU Medical Center, Amsterdam, the Netherlands; [4]Department of Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam, the Netherlands; [5]Charité Campus Benjamin Franklin, Berlin, Germany; [6]Charité University Medicine Berlin, Germany; [7]Universitair Ziekenhuis Ghent, Belgium; [8]University Hospital Leuven, Belgium; [9]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, Leeds, NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK; [10]Klinikum der Universität München, Germany; [11]Hopital Erasme Brussels, Belgium; [12]University of Leeds, UK; [13]Hopital Cochin Paris, France; [14]Helsinki University Central Hospital, Helsinki, Finland; [15]Hopital Ambroise Paré, Boulogne, France.

Abstract

Objective

Knowledge on the long-term effects of anti-TNF therapy in patients with ankylosing spondylitis (AS) is still limited. Our objective was to study the long-term efficacy and safety of anti-TNF therapy in AS.

Methods

After having completed the first part of the EASIC trial a total of 71 patients were enrolled into this 96-week extension study. Patients were treated with the same dosages and dosing intervals of infliximab as in the EASIC core study. Efficacy was assessed by using standardised assessment tools such as BASDAI, BASFI, BASMI, patient global assessment, CRP levels and the proportion of patients without any sign of enthesitis or arthritis. Long-term safety was assessed by documenting adverse events (AE), serious adverse events (SAE) and reasons for dropping out.

Results

Of the 71 patients included, 64 (90.1%) completed the trial , and 7 discontinued: one was lost to follow-up, 3 withdrew informed consent and in 3 patients therapy was stopped for different reasons: secondary loss of response, recurrent infections and basal cell carcinoma of the skin. The completers showed rather stable low scores of BASDAI (mean 2.4, median 2.52), BASFI (mean 3.1, median 2.76) and BASMI (mean 3.2, median 3) as well as patients global assessment and CRP. The vast majority of patients did not have enthesitis or arthritis. A total of 476 AE were observed, 13 of which were SAE. The majority of these were infections and most of them affected the respiratory tract. Two malignancies occurred: one basal cell carcinoma and one malignant melanoma. These were the only SAE judged to be possibly related to the study drug.

Conclusion

Anti-TNF treatment with infliximab is efficacious over long periods of time in patients with AS. The observation of two skin related malignancies, including one melanoma, during the whole study period of 7 years is in line with reports from previous large AS data sets.

Key words

ankylosing spondylitis, anti-TNF, infliximab

Frank Heldmann, Xenofon Baraliakos, Uta Kiltz, Jan Brandt, Irene E. van der Horst-Bruinsma, Robert Landewé, Joachim Sieper, Gert Rüdiger Burmester, Filip van den Bosch, Kurt de Vlam, Hill Gaston, Mathias Gruenke, Mathias Witt, Thierry Appelboom, Paul Emery, Maxime Dougados, Marjatta Leirisalo-Repo, Maxime Breban, Jürgen Braun.

Please address correspondence to: Dr Frank Heldmann, Rheumazentrum Ruhrgebiet, Landgrafenstrasse 15, 44652 Herne, Germany. E-mail: frank.heldmann@ediacon.de

Received on November 23, 2014; accepted in revised form on May 4, 2015.

Funding: Centocor provided financial support for the conduction of this investigator-initiated study.

Competing interests: F. Heldmann has received honoraria and grant support from Abbvie, Amgen, BMS, Centocor, Janssen-Cilag, Pfizer, Roche, and UCB; X. Baraliakos has received honoraria and grant support from Abbvie, BMS, Boeringer-Inghelheim, Celgene, Centocor, Chugai, Janssen Biologics, Novartis, Pfizer, Sandoz, and UCB; R. Landewé has received honoraria and/or grants and/or payments for consultancies from Abbvie, Amgen, Augurex, BMS, Celgene, Centocor, GSK, Novartis, Pfizer, Merck, Roche, Schering, TiGenix, and UCB; J. Sieper has received honoraria and/or speaker fees from Merck; G.R. Burmester has received honoraria for consultancies and lectures from MSD Germany; F. van den Bosch has received consultancy and/or speaker fees from Abbvie, Celgene, Janssen, Merck, Novartis, Pfizer, and UCB; M. Leirisalo-Repo has received honoraria for consultancies and lectures from Abbvie, BMS, Boeringer-Inghelheim, MSD, Pfizer, Roche and Regeneron; P. Emery has undertaken clinical trials and provided expert advice to Abbvie, BMS, Lilly, MSD, Novartis, Pfizer, Roche, Samsung, and Takeda; M. Gruenke has received speaker fees from Centocor; J. Braun has received honoraria and grants from Abbott, Centocor, Celltrion, Janssen, MSD, Schering-Plough, Pfizer, and UCB. All the other authors declare that they have no financial competing interests associated with this research.

Introduction

Ankylosing spondylitis (AS), the main subtype of the spondyloarthritides (SpA), is a chronic inflammatory rheumatic disease that affects about 0.5% of the adult Caucasian population (1), and usually starts in early adulthood (2). AS is clinically characterised by inflammatory back pain due to sacroiliac and/or spinal inflammation which may eventually lead to an increase in new bone formation. In addition, AS patients may have peripheral arthritis, enthesitis and uveitis (3).

Non-steroidal anti-inflammatory drugs (NSAIDs) are considered as first line pharmacological therapy for AS, while other pharmacological treatments such as conventional disease-modifying anti-rheumatic drugs (DMARDs) and corticosteroids only play a limited role, in contrast to treatment of rheumatoid arthritis (4). However, international recommendations stressed use of TNF blockers for patients with AS who have persistently high disease activity despite conventional treatment (4), with a recent recommendation that for a definition of inefficacy the treatment duration with NSAIDs before starting anti-TNF therapy does not need to exceed 4 weeks (5).

Several recent trials have shown that treatment with infliximab is efficacious in patients with active AS (6-10), confirming the findings of the pivotal ASSERT trial with 279 patients (11, 12). Magnetic resonance imaging (MRI) revealed a significant decrease in spinal inflammation in this study (13). Whether TNF blockers slow or inhibit structural damage in AS is still a matter of debate (14-16), but no inhibition of radiographic progression was seen in comparison to the historical OASIS cohort over a period of 2 years (17-19). Long-term data on the clinical efficacy and safety of anti-TNF therapy in AS are still limited (20-24). However, long-term data are critical for appropriate economic analyses related to anti-TNF therapy (25, 26).

Therefore, the EASIC cohort was initiated by a group of European rheumatologists several years ago. EASIC is an open label investigator-driven international multicentre trial with patients who had received infliximab for 2 years as part of ASSERT (11). The results of the first two years of the EASIC study have been recently published (22). Here we present the results of the extension of this study which represents a total treatment period of more than 7 years.

Material and methods

All European patients (n=149) who participated in ASSERT were invited to take part in the 2-year extension trial named EASIC. Altogether, 103 patients consented to take part in this study (69.1%). Patients were subdivided into 3 subgroups according to the treatment they received in the 1.3±0.9 years between the end of ASSERT and the start of EASIC: group 1a (no infliximab treatment between trials, flare before the start of EASIC, reintroduction of infliximab, n=9), group 1b (no infliximab treatment between trials, sustained remission, follow-up until flare during EASIC, n=5 patients) and group 2 (continuous infliximab treatment between ASSERT and EASIC, n=89 patients). All 81 patients who completed the 96 weeks of EASIC were asked to become part of the extension of EASIC. All patients received infliximab in the same dosages and dosing intervals as in EASIC core study, no subgroups were defined.

The study design for the entire study period with ASSERT, EASIC, EASIC extension and the interval between ASSERT and EASIC is summarised in Figure 1. The EASIC extension is an open-label long-term observational study. The study protocol was designed on the basis of current clinical practice. Inclusion and exclusion criteria and the management of concomitant medications were similar to the EASIC core study.

The study protocol was reviewed and approved by the respective institutional review boards or independent ethics committees at each site and regulatory authorities in each country. All participating patients provided written informed consent prior to any trial associated procedure.

Efficacy analysis

Analyses include secondary endpoints of EASIC that address: long-term

clinical effectiveness after 7 years of therapy, as assessed by standard assessment tools. The ASAS response criteria (ASAS 20, 40, ASAS 5/6 and the ASAS partial remission rates) (27) are not very informative in long-term outcome studies because they refer to the baseline values (28). Therefore we focussed on status rather than on change scores, and outcome assessments that are capable of showing long-term benefits such as low disease activity, good functional status, good spinal mobility and favourable judgement of patients and physicians as well as lack of arthritis or enthesitis. For this purpose we chose as outcome parameters the Bath AS disease activity index (BASDAI), (29), Bath AS functional index (BASFI), (30), Bath AS metrology index (BASMI), (31), and patient global assessments on a visual analogue scale (VAS), MASES enthesitis index, and the 44-swollen joint count. C-reactive protein levels were measured at the discretion of the investigators, but were collected in a high proportion (95%) of patients. Although there is evidence that the 10-step and linear definitions of the BASMI perform better with regard to sensitivity to change and feasibility of BASMI in computer evaluations (32), we used the 2-step definition of the BASMI in order to allow comparisons with baseline values of EASIC and ASSERT where the 2-step definition was used.

The predefined primary endpoint of EASIC extension was the change of radiographic progression after more than 7 years of infliximab treatment. Spinal inflammation as assessed by MRI was a secondary outcome. These analyses will be presented separately.

Safety analysis

The safety of infliximab was analysed on the basis of documented (serious) adverse events. The number of adverse events (AE), serious adverse events (SAE), infections, and infusion reactions was recorded. The opinion of the investigator whether an AE was possibly related to the study medication or not was collected. The number of drop-outs possibly related to adverse events was documented.

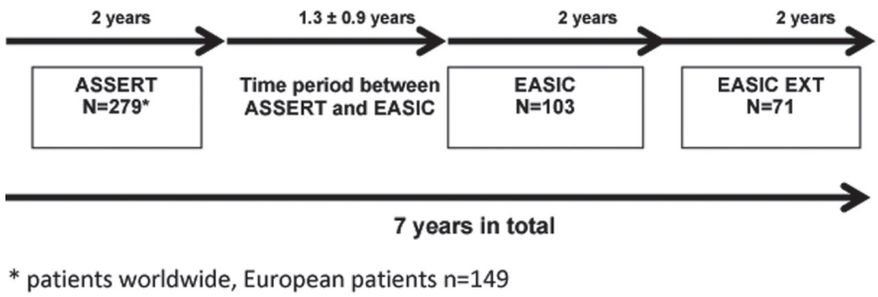

Fig. 1. Study design of EASIC and EASIC extension.

Statistical analysis

Our statistical analyses are descriptive statistics and include mean values and standard deviations for the variables mentioned above. We describe the proportion of patients with BASDAI levels <4 and <3 respectively indicative for low disease activity (28) and the proportion of patients showing no enthesitis or arthritis at the end of the study. We do not report ASAS response criteria such as ASAS 20 response because responses as compared to baseline are not as meaningful for long-term studies. Since all patients received the drug, the main objective of the study was to determine how many patients report low disease activity or are free of symptoms (28). We used the Mann-Whitney U-Test to analyse differences of BASDAI, BASFI and BASMI between NSAID-users and NSAID-non-users.

Results

A total of 71 patients were included in this 96-week open label extension of EASIC, 60 of whom were male (84.5%). The baseline characteristics of the EASIC patients are described elsewhere (22). Ten patients discontinued for logistic reasons. The characteristics of the patients who took part in this study are summarised in Table I.

The transition between EASIC and EASIC extension was continuous, therefore the participating patients generally continued with the same dosages and dosing intervals as in the EASIC core study. The patients received a mean dosage of infliximab of 410±81mg (5mg/kg) per infusion; 50 patients (70.4%) were treated every 6 weeks and 21 (29.6%) every 8 weeks.

Of the 103 European patients who had been enrolled into EASIC, 64 completed the EASIC extension (62.1%). However, of the 71 patients who started the EASIC extension 64 completed (90.1%). Of 7 patients who discontinued, 3 were withdrawn by the investigator; one due to secondary loss of response, one had recurrent infections which were neither serious nor opportunistic and the third patient stopped because of a basal cell carcinoma of the skin. Another patient was lost to follow-up and the remaining three patients withdrew their informed consent.

Efficacy

The efficacy data are based on a completer analysis after 96 weeks of the extension (192 weeks of EASIC). The mean BASDAI at this time point was 2.4±1.7 (median 2.52), the mean BASFI 3.1±2.0 (median 2.76), the mean BASMI (median 3) was 3.2±2.0, and the mean CRP

Table I. Baseline characteristics of the patients included in the EASIC extension study.

Number of patients	71
Proportion of male patients	60 (84.5%)
Mean age at baseline	45.8 ± 10.2 years
Mean body weight at baseline	81.9 ± 13 kg
Mean BASDAI at baseline	2.4 ± 1.6
Mean BASFI at baseline	3.1 ± 2.2
Mean BASMI at baseline	3.3 ± 2.2
Number of patients without enthesitis	63
Number of patients without arthritis	58

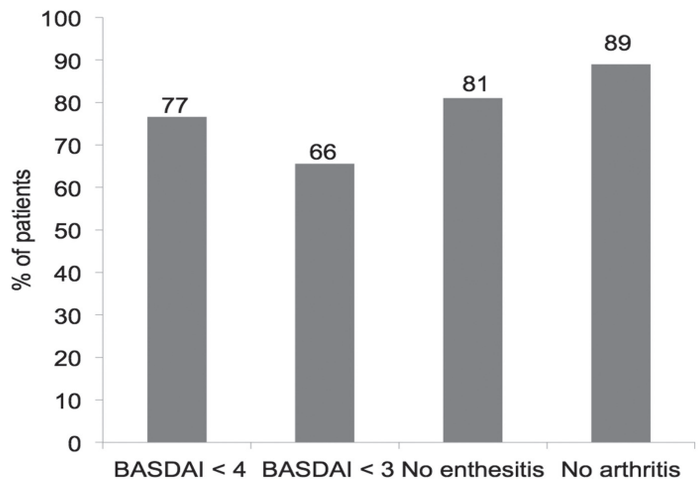

Fig. 2A. Clinical outcomes after 96 weeks of EASIC extension.

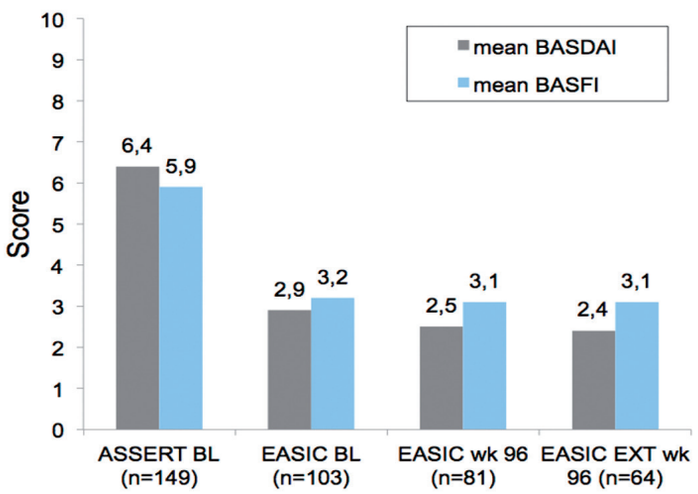

Fig. 2B. Chronology of outcome parameters during the whole observation period.

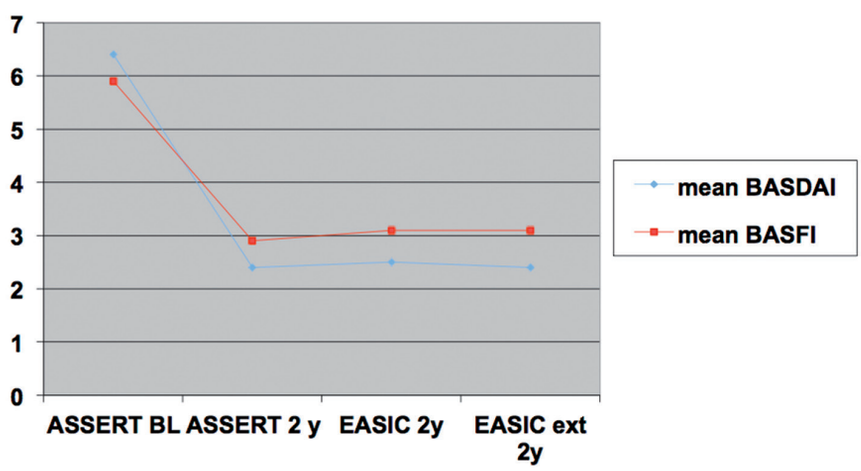

Fig. 2C. Chronology of BASDAI and BASFI during the whole observation period.

serum level was 4.9±5.9 mg/l (CRP levels available for 61 patients).

At week 192, 49/64 patients (76.6%) had BASDAI levels <4, and 42/64 showed BASDAI levels even <3 (65.6%) indicating low disease activity (Fig. 2A). The majority of patients (81%) did not show any enthesitis and 89% (57/64) of patients were free of peripheral arthritis. Patient global assessment was 1.2±1.3 cm on a 10 cm VAS scale (n=61) at this timepoint.

The clinical efficacy results after 192 weeks of EASIC (the entire study period) with all timepoints including ASSERT and EASIC at baseline, at the end of the core study and at the end of the EASIC extension are presented in Table II and Figures 2A-B-C. Including the period of 1.3 years between ASSERT and EASIC the patients were treated for more than 7 years. The higher value of the mean BASDAI at EASIC baseline as compared to the end of EASIC and EASIC extension is explained by the fact that some patients (group 1) did not receive infliximab between ASSERT and EASIC (22). The mean BASMI did not change in the EASIC extension study, the baseline BASMI for those patients who actually entered the extension study was 3.2.

Of interest, concomitant NSAIDs were used by 35/71 patients (49.3%) during the study, and 15 used analgesics in addition (21.1%). If NSAID use had an impact on radiographic progression scores, will be analysed separately. DMARDs and systemic steroids were only used by 2 and 3 patients, respectively. No significant differences between NSAID-users *vs*. NSAID-non-users were found for BASDAI (3.04 *vs*. 2.16, p=0.078), BASFI (3.54 *vs*. 2.9, p=0,34) and BASMI (3.44 *vs*. 3.2, p=0.51). There was no distinction between NSAID-users on demand and continuous NSAID-users in the EASIC study.

Safety

The safety data are summarised in Tables IIIA and IIIB.

A total of 476 adverse events (AE) were observed in 63 patients during the EASIC extension. More than one AE was reported by 96.8% of the patients. The most frequent reports were infections which contributed to 35.1% of all AEs. There were 116 infections (69.5%) that affected the respiratory tract, 25 (14.9%) the skin, 12 (7.2%) the gastrointestinal and 7 (4.2%) the urogenital tract. None of the 5 minor infusion reactions led to discontinuation of the study. An elevation of liver enzymes was noted in 7 cases. Non-infectious skin AEs occurred 36 times.

Of interest, 5 cases of psoriasis in 4 patients, 3 cases of relapsing inflammatory

Table II. Clinical efficacy data of the EASIC project.

Trial	ASSERT	ASSERT	EASIC	EASIC	EASIC extension
Time point	Baseline	2 years	Week 0	Week 96	Week 192
Efficacy parameter					
BASDAI (mean)	6.4	2.4	2.9*	2.5*	2.4*
BASFI (mean)	5.9	2.9	3.2*	3.1*	3.1*
BASMI (mean)	4.0	2.7	2.1*	2.2* +	3.2
Patient global assessment (VAS)	7.0	2.7	3.3*	2.8*	1.2*
CRP (mg/dl)	2.9	0.6	0.7*	0.5*	0.49*
Arthritis free patients (%)	NA	81.6	74.3	78.4	89

*p<0.0001 in comparison with ASSERT baseline data. +the mean BASMI of the 71 patients who were finally included in the EASIC extension study was 3.2.

bowel disease (IBD) and 2 cases of anterior uveitis were noted. Only one patient had a history of psoriasis, and he experienced flares of psoriasis twice. The 3 other cases were new onset of disease.

A diagnosis of IBD was already established in 2 patients who both flared during the study. A history of anterior uveitis was present in one patient who flared and one had a new onset.

There were 2 malignancies of the skin, one malignant melanoma and one case of basal cell skin carcinoma as mentioned above. The patient with malignant melanoma refused to discontinue the study. These two malignacies were the only 2 SAE out of a total of 13 SAE that were considered to be possibly related with the study drug by the investigator. The other AEs that fulfilled the criteria for seriousness were one case of nephrolithiasis, one patient who reported worsening of AS, one patient with left-sided hip pain and a new diagnosis of osteoarthritis of the right hip. One case of duodenal ulcer and one case of depression were reported. One patient fathered a healthy child. Another patient was hospitalised with a hematopneumothorax and rib fractures after an accident. There was one case of arterial hypertension and one of chest pain. Another patient suffered from a relapsing intervertebral disc prolapse in the lumbar spine which led to 5 episodes of hospitalisation during the entire study period and two SAE during the extension study. No opportunistic infections including tuberculosis occurred during EASIC extension.

Discussion

The EASIC cohort is currently one of the largest cohorts of patients with AS receiving anti-TNF therapy for an extended period of time. Our study provides prospective data on patients who received treatment with infliximab over more than 7 years. The clinical (22) and radiographic data of the EASIC core study (33) have been published elsewhere. The radiographic analysis after 7 years is currently ongoing.

These data confirm the findings of another recent study from our group with a smaller number of patients which showed that long-term anti-TNF therapy is effective and safe over many years (21).

The 90.1% retention rate of infliximab in the EASIC extension study was remarkably high. Even though the retention rate within the 4 years of EASIC was less at 62%, this rate is still in line with other studies (23) and it is higher than the 48% rate for our other infliximab cohort (21). Although the transition between EASIC core and the extension was continuous, 10 patients were lost between the trials – mainly for logistic (long distance from home to study site etc.) rather than drug related reasons. In addition, 6 patients were discontinued right at the beginning of the EASIC core study for similar reasons (22). Therefore, the 62% retention rate reflects study design rather than a medication related problem such as safety or efficacy issues.

The importance of low disease activity levels, preferably lower than 3, and the clinical relevance of low BASFI and BASMI levels has been well recognised (28, 34). Close examination of the clinical efficacy data shows that disease activity and physical function levels have been very stable with low BASDAI, BASFI and BASMI levels over time. The significance of these findings is consistent with the global assessment of the completing patients (1.2 on a 0–10 cm scale). The patient reported outcome results strongly support the sustained efficacy of treatment with infliximab.

The small decline in mean BASMI levels within 4 years of observation has to be interpreted as a statistical phenomenon, because, when only those patients who were finally included into the extension phase were analysed there was no difference in the mean BASMI between baseline and week 96. The good functional and patient global data view support a lack of decline (35). Long-term impairments of function and spinal mobility may be due to inflammation and/or radiographic progression which is similar to new bone formation (36, 37). The data of this study suggest that neither were occuring to a significant extent. However, some radiographic progression has been reported after 5 years of anti-TNF therapy (33). Osteodestructive changes, as indicated by worsening of hip osteoarthritis, have only been reported in one patient, and it is not clear whether this was due to AS related inflammation (38-40). Moreover, the proportion of patients without enthesitis or arthritis remained at a stable low level over the study period of more than 7 years.

Despite the mean low disease activity observed in this study, almost half of the patients received concomitant NSAID therapy similar to other studies (20-24). This may be related to insufficient control of inflammation and pain due to AS or osteoarthritis. The reported positive effects of NSAIDs on radiographic progression may have contributed to some patients continuing this medication (41, 42). Of interest there was no difference with regard to disease activity, function and spinal mobility between patients who used NSAIDs and those who did not in our cohort.

Long-term treatment of AS patients with infliximab has been safe in this and other long-term studies (20-24). As expected for patients treated with TNF blockers, the most common adverse events were

Table III. Adverse events in EASIC extension.

A. Overview of all adverse events (AE)

	Number of AEs (% of all AEs)
Total	476
Infections	167 (35.1)
SAE	13 (2.2)
SAE: Infections	0
Opportunistic infections including Tb	0
Infusion reactions /allergic reactions	5 (1.0)
Malignancies	2 (0.4)
Elevation of liver enzymes	7 (1.5)
Worsening of AS	17 (3.6)
Other	278 (58.4)

Tb: tuberculosis.

B. Overview of all infections.

	Number of infections (% of all infections)
Total	167
Upper respiratory infections (including ear infections)	116 (69.5)
Gastrointestinal infections	12 (7.2)
Urogenital infections	7 (4.2)
Skin infections	25 (14.9)
Other infections	7 (4.2)

infections, the majority of which affected the upper repiratory tract (43, 44). No cases of tuberculosis or opportunistic infections were reported in this study. Two malignancies of the skin, including one melanoma, were documented during the 7 year study period. This incidence is in line with previous results for anti-TNF therapy (45, 46). No patient developed lymphoma during the entire study period; this is also in line with the increased relative risk of lymphoma which is reported for RA (47), but not for AS (48). The observed infusion reactions were minor and did not lead to study discontinuation. There were 5 adverse reactions in 984 infusions (0.5%), this is very low. In the EASIC core study the substantially higher rate of infusion reactions was likely a result of the 1.3 year-drug free interval between the studies (22). Infusion reactions have also been rarely observed in other studies with patients on long-term therapy with infliximab (49).

Skin, gut and eye manifestations are known to occur in patients with spondyloarthritis (3). The paradoxical occurrence of flares, and even new onset of IBD, psoriasis and anterior uveitis has also been reported (50), even though anti-TNF therapy is effective in these diseases (51). The incidence of these adverse events was low in this study (52-54); 5 cases of psoriasis, 3 of inflammatory bowel disease and 3 of acute anterior uveitis occurred. All patients with psoriasis chose to remain in the trial.

One limitation of this EASIC extension study is its inclusion of volunteering patients who are doing well under infliximab therapy in EASIC, as evidenced by the low baseline BASDAI. Still in summary, patients treated with infliximab in EASIC extension showed favourable responses to long-term anti-TNF therapy. They reported stable levels of low disease activity, preserved function and spinal mobility. Long-term efficacy data have also been favourable for other anti-TNF agents (23, 24, 55).

Importantly, therapy with infliximab appears to be safe over many years, with regard to infections and malignancies.

Key messages

- Anti-TNF therapy with infliximab provides long-term symptomatic benefit in patients with ankylosing spondylitis over more than 7 years. Physical function and spinal mobility remain stable during prolonged treatment.
- Long-term therapy with infliximab shows a favourable safety profile for patients with ankylosing spondylitis.

References

1. BRAUN J, VAN DER HEIJDE D: Novel approaches in the treatment of ankylosing spondylitis and other spondyloarthritides. *Expert Opin Invest Drugs* 2003; 12: 1097-109.
2. BRAUN J, BOLLOW M, REMLINGER G *et al*.: Prevalence of spondyloarthropathies in HLA B27 positive and negative blood donors. *Arthritis Rheum* 1998; 41: 58-67.
3. SIEPER J, BRAUN J, RUDWALEIT M, BOONEN A, ZINK A: Ankylosing spondylitis: an overview. *Ann Rheum Dis* 2002; 61 (Suppl. 3): iii8-18.
4. BRAUN J, VAN DEN BERG R, BARALIAKOS X *et al*.: 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2011; 70: 896-904.
5. VAN DER HEIJDE D, SIEPER J, MAKSYMOVYCH WP *et al*.: Assessment of SpondyloArthritis International Society: 2010 Update of the International ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann Rheum Dis* 2011; 70: 905-8.
6. BRAUN J, BRANDT J, LISTING J *et al*.: Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet* 2002; 359: 1187-93.
7. BRANDT J, HAIBEL H, CORNELY D *et al*.: Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. *Arthritis Rheum* 2000; 43: 1346-52.
8. BRANDT J, HAIBEL H, SIEPER J, REDDIG J, BRAUN J: Infliximab treatment of severe ankylosing spondylitis: one-year follow-up (letter). *Arthritis Rheum* 2001; 45: 2936-7.
9. BREBAN M, VIGNON E, CLAUDEPIERRE P *et al*.: Efficacy of infliximab in refractory ankylosing spondylitis: results of a six-month open-label study. *Rheumatology* 2002; 41: 1280-5.
10. BRAUN J, BRANDT J, LISTING J *et al*.: Long-term efficacy and safety of infliximab in the treatment of ankylosing spondylitis: an open-label, observational extension study of a three-month, randomized, placebo-controlled trial. *Arthritis Rheum* 2003; 48: 2224-33.
11. VAN DER HEIJDE D, DIJKMANS B, GEUSENS P *et al*.; AND THE ANKYLOSING SPONDYLITIS STUDY FOR THE EVALUATION OF RECOMBINANT INFLIXIMAB THERAPY STUDY GROUP: Efficacy and safety of infliximab in patients with Ankylosing Spondylitis. Results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum* 2005; 52: 582-91.
12. BRAUN J, DEODHAR A, DIJKMANS B *et al*.; ANKYLOSING SPONDYLITS STUDY FOR THE EVALUATION OF RECOMBINANT INFLIXIMAB THERAPY STUDY GROUP: Efficacy and safety of infliximab in patients with ankylosing spondylitis over a two-year period. *Arthritis Rheum* 2008; 59: 1270-8.
13. BRAUN J, LANDEWÉ R, HERMANN KG *et al*.; ASSERT STUDY GROUP: Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. *Arthritis Rheum* 2006; 54: 1646-52.
14. BARALIAKOS X, LISTING J, BRANDT J *et al*.: Radiographic progression in patients with ankylosing spondylitis after 4 yrs of treatment

with the TNF-alpha antibody infliximab. *Rheumatology* 2007; 46: 1450-3.
15. BARALIAKOS X, LISTING J, RUDWALEIT M, BRANDT J, SIEPER J, BRAUN J: Radiographic progression in patients with ankylosing spondylitis after 2 years of treatment with the tumour necrosis factor alpha antibody infliximab. *Ann Rheum Dis* 2005; 64: 1462-6.
16. BRAUN J, KALDEN JR: Biologics in the treatment of rheumatoid arthritis and ankylosing spondylitis. *Clin Exp Rheumatol* 2009; 27 (Suppl. 55): S164-7.
17. VAN DER HEIJDE D, LANDEWÉ R, EINSTEIN S *et al*.: Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. *Arthritis Rheum* 2008; 58: 1324-31.
18. VAN DER HEIJDE D, LANDEWÉ R, BARALIAKOS X *et al*.: Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group: *Arthritis Rheum* 2008; 58: 3063-70.
19. VAN DER HEIJDE D, LANDEWÉ R, MAKSYMOVYCH W *et al*.: Adalimumab (Humira) Therapy for Ankylosing Spondylitis over 2 years does not demonstrate inhibition of radiographic progression compared with a historical control group. Abstract 670; ACR 2008.
20. BRAUN J, BARALIAKOS X, LISTING J *et al*.: Persistent clinical efficacy and safety of anti-tumour necrosis factor α therapy with infliximab in patients with ankylosing spondylitis over 5 years: evidence for different types of response. *Ann Rheum Dis* 2008; 67: 340-5.
21. BARALIAKOS X, LISTING J, FRITZ C *et al*.: Persistent clinical efficacy and safety of infliximab in ankylosing spondylitis-early clinical repsonse predicts long-term outcome. *Rheumatology* 2011; 50: 1690-9.
22. HELDMANN F, BRANDT J, VAN DER HORST-BRUINSMA IE *et al*.: The European Ankylosing Spondylitis Infliximab Cohort (EASIC): a European multicentre study of long-term outcomes in patients with ankylosing spondylitis treated with infliximab. *Clin Exp Rheumatol* 2011; 29: 672-80.
23. SAOUGOU I, MARKATSELI TE, VOULGARI PV, DROSOS AA: Maintained clinical response of infliximab treatment in ankylosing spondylitis: a 6-year long-term study. *Joint Bone Spine* 2010; 77: 325-9.
24. MARTIN-MOLA E, SIEPER J, LEIRISALO-REPO M *et al*.: Sustained efficacy and safety, including patient-reported outcomes, with etanercept treatment over 5 years in patients with ankylosing spondylitis. *Clin Exp Rheumatol* 2010; 28: 238-45.
25. BOONEN A, MAU W: The economic burden of disease: comparison between rheumatoid arthritis and ankylosing spondylitis. *Clin Exp Rheumatol* 2009; 27 (Suppl. 55): S112-7.
26. FRANKE LC, AMENT AJ, VAN DE LAAR MA, BOONEN A, SEVERENS JL: Cost-of-illness of rheumatoid arthritis and ankylosing spondylitis. *Clin Exp Rheumatol* 2009; 27 (Suppl . 55), S118-23.
27. VAN DER HEIJDE D, DOUGADOS M, DAVIS J *et al*.: ASsessment in Ankylosing Spondylitis International Working Group/Spondylitis Association of America recommendations for conducting clinical trials in ankylosing spondylitis. *Arthritis Rheum* 2005; 52: 386-94.
28. ZOCHLING J, BRAUN J: Remission in ankylosing spondylitis. *Clin Exp Rheumatol* 2006; 24 (Suppl. 43): S88-92.
29. GARRETT S, JENKINSON T, KENNEDY LG, WHITELOCK H, GAISFORD P, CALIN A: A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994; 21: 2286-91.
30. CALIN A, GARRETT S, WHITELOCK H *et al*.: A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 1994; 21: 2281-5.
3. JENKINSON TR, MALLORIE PA, WHITELOCK HC, KENNEDY LG, GARRETT SL, CALIN A: Defining spinal mobility in ankylosing spondylitis (AS): the Bath AS Metrology Index. *J Rheumatol* 1994; 21: 1694-8.
32. VAN DER HEIJDE D, LANDEWÉ R, FELDTKELLER E: Proposal of a linear definition of the Bath Ankylosing Spondylitis Metrology Index (BASMI) and comparison with the 2-step and 10-step definitions. *Ann Rheum Dis* 2008; 67: 489-93.
33. BARALIAKOS X, HELDMANN F, VAN DER HEIJDE D *et al*.: Radigraphic findings after 5 years of infliximab treatment in patients with ankylosing spondylitis. *ACR* 2010.
34. BRAUN J, SIEPER J: What is the most important outcome parameter in ankylosing spondylitis? *Rheumatology* 2008; 47: 1738-40.
35. VESOVIC-POTIC V, MUSTUR D, STANISAVLJEVIC D, ILLE T, ILLE M: Relationship betweeen spinal mobility measures and quality of life in patients with ankylosing spondylitis. *Rheumatol Int* 2009; 29: 879-84.
36. MACHADO P, LANDEWÉ R, BRAUN J, HERMANN KG, BAKER D, VAN DER HEIJDE D: Both structural damage and inflammation of the spine contribute to impairment of spinal mobility in patients with ankylosing spondylitis. *Ann Rheum Dis* 2010; 69: 1465-70.
37. WANDERS A, LANDEWÉ R, DOUGADOS M, MIELANTS H, VAN DER LINDEN S, VAN DER HEIJDE D: Association between radiographic damage of the spine and spinal mobility for individual patients with ankylosing spondylitis: can assessment of spinal mobility be a proxy for radiographic evaluation? *Ann Rheum Dis* 2005; 64: 988-94.
38. CHEN HA, CHEN CH, LIAO HT *et al*.: Factors associated with radiographic spinal involvement and hip involvement in ankylosing spondylitis. *Semin Arthritis Rheum* 2011; 40: 552-8.
39. VANDER CRUYSSEN B, MUNOZ-GOMARIZ E, FONT P *et al*.; ASPECT-REGISPONSER-RESPONDIA WORKING GROUP: Hip involvement in ankylosing spondylitis: epidemiology and risk factors associated with hip replacement surgery. *Rheumatology* 2010; 49: 73-81.
40. BARALIAKOS X, BRAUN J: Hip involvement in ankylosing spondylitis: what is the verdict? *Rheumatology* 2010; 49: 3-4.
41. PODDUBNYY D, RUDWALEIT M, HAIBEL H *et al*.: Effect of non-steroidal anti-inflammatory drugs on radiographic spinal progression in patients with axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. *Ann Rheum Dis* 2012; 71: 1616-22.
42. WANDERS A, VAN DER HEIJDE D, LANDEWÉ R *et al*.: Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. *Arthritis Rheum* 2005; 52: 1756-65.
43. LISTING J, STRANGFELD A, KARY S *et al*.: Infections in patients with rheumatoid arthritis treated with biologic agents. *Arthritis Rheum* 2005; 52: 3403-12.
44. ZINK A, ASKLING J, DIXON WG, KLARESKOG L, SILMAN AJ, SYMMONS DP: European Biologics Registers- Methodology, selected results, and perspectives. *Ann Rheum Dis* 2009; 68: 1240-6.
45 STRANGFELD A, HIERSE F, RAU R *et al*.: Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. *Arthritis Res Ther* 2010; 12: R5.
46. BURMESTER GR, PANACCIONE R, GORDON KB, MCILRAITH MJ, LACERDA AP: Adalimumab: long-term safety in 23458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis and Crohn's disease. *Ann Rheum Dis* 2012 Epub ahead of print
47. ASKLING J, BAECKLUND E, GRANATH F *et al*.: Anti-tumor necrosis factor therapy in rheumatoid arthritis and risk of malignant lymphomas: relative risks and time trends in the Swedish Biologics Register. *Ann Rheum Dis* 2009; 68: 648-53.
48. ASKLING J, KLARESKOG L, BLOMQVIST P, FORED M, FELTELIUS N: Risk for malignant lymphoma in ankylosing spondylitis: a nationwide Swedish case-control study. *Ann Rheum Dis* 2006; 65: 1184-7.
49. BARALIAKOS X, LISTING J, RUDWALEIT M *et al*.: Safety and efficacy of readministration of infliximab after longterm continuous therapy and withdrawal in patients with ankylosing spondylitis. *J Rheumatol* 2007; 34: 510-5.
50. KO JM, GOTTLIEB AB, KERBLESKI JF: Induction and exacerbation of psoriasis with TNF-blockade therapy: *J Dermatol Treat* 2009; 20: 100-8.
51. KIRCIK LH, DEL ROSSO JQ: Anti-TNF agents for the treatment of psoriasis. *J Drugs Dermatol* 2009; 8: 546-59.
52. DER HEIJDE D, HAIBEL H, RUDWALEIT M, SIEPER J: Differences in the incidence of flares or new onset of inflammatory bowel diseases in patients with ankylosing spondylitis exposed to therapy with anti-tumor necrosis factor α agents. *Arthritis Rheum* 2007; 57: 639-47.
53. LIM LL, FRAUNFELDER FW, ROSENBAUM JT: Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. *Arthritis Rheum* 2007; 56: 3248-52.
54. BRAUN J, BARALIAKOS X, LISTING J, SIEPER J: Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. *Arthritis Rheum* 2005; 52: 2447-51.
55. VAN DER HEIJDE DM, REVICKI DA, GOOCH KL *et al*.; ATLAS STUDY GROUP: Physical function, disease activity, and health-related quality-of-life outcomes after 3 years of adalimumab treatment in patients with ankylosing spondylitis. *Arthritis Res Ther* 2009; 11: R124.